Transplantation - Epidemiology

OR10-001

Will they donate? Predictors of non-donation and withdrawal in a UK multicentre prospective cohort study of potential living kidney donors

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Preferred Presentation Method: Oral or Poster

Introduction: NHS Blood and Transplant performs an annual potential deceased donor audit, examining the donor variables associated with organ donation after death. No national data are collected on potential living kidney donors, those who start assessment for living donation. Little is known, therefore, about what sociodemographic factors influence progression to donation or withdrawal.

Objectives: This UK multicentre prospective potential living donor cohort study investigated the sociodemographic predictors of living kidney donation, and of non-donation, in particular, of potential donor withdrawal.

Methods: Data were prospectively collected on all individuals who presented to seven UK renal units (Bristol, Cambridge, Cardiff, Newcastle, Stoke-on-Trent, Swansea and Preston) for living kidney donor assessment between 01/08/14 and 31/1/16. Multivariable logistic regression models were used to explore the relationship between potential donor sociodemographic variables and likelihood of living kidney donation.

Results: 805 individuals presented for directed donation, linked to 498 possible recipients. Potential donors had a median age of 45.0 years (Interquartile range (IQR) 21.0), 55.8% were women and 93.8% were of white ethnicity. Median body mass index (BMI) was 26.7kg/m^2 (IQR 6.2). 26.9% of potential donors had a BMI ≥30kg/m^2.

70 individuals remained in work-up at the end of the study. Of the 735 potential donors who completed work-up 84.8% did not donate. 24.8% did not donate because an alternative donor for the same intended recipient was selected to proceed. 17.8% were deemed medically, surgically or psychologically unsuitable. 15.0% withdrew from work-up.

Higher BMI was associated with a lower likelihood of donation (Odds Ratio (OR) per +1kg/m^2 0.92 (95% Confidence Interval (CI) 0.88-0.96) p<0.001)). Potential donors for female recipients were less likely to donate than those for men (OR 0.60 (95% CI 0.38-0.94) p=0.03). Individuals were also less likely to actually donate if they were intending to donate to a friend rather than a relative (OR 0.18 (95% CI 0.05-0.60) p=0.01). Potential donors whose recipients had renal failure due to a systemic disease were less likely to donate (OR 0.41 (95% CI 0.21-0.80) p=0.01), due to a greater likelihood of their intended recipient being unfit for transplantation. Those in the greatest socioeconomic deprivation quintile were less likely to donate compared to those in the least deprived group (OR 0.49 (95% CI 0.24-1.00) p=0.05), but the overall trend with deprivation was consistent with chance (p=0.12).

Younger potential donors (OR per +1 year 0.97 (95% CI 0.95-0.98) p<0.001), those of non-white ethnicity (OR 2.98 (95% CI 1.05-8.44) p=0.04) and friend donors (OR 2.43 (95% CI 1.31-4.51) p=0.01) were more likely to drop out of work-up. Socioeconomic deprivation was not associated with an increased likelihood of withdrawal after adjustment for donor age.

Conclusion: This is the first UK multicentre prospective study of potential living kidney donors. It has described predictors of potential living kidney donors not progressing through to donation, and predictors of withdrawal from the assessment process. Qualitative work with individuals who withdraw might identify possible ways of supporting those who wish to donate but experience difficulties doing so.

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Keywords: Epidemiology, Living donor, Renal transplant

Transplantation - Outcomes

OR10-002

Recipient Age is a Significant Factor in Immunological and Infective Complications Following Kidney Transplantation

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Preferred Presentation Method: Oral or Poster

Introduction: In recent years, there has been a marked increase in the number of older patients (>65 years) undergoing kidney transplantation. While there is increasing evidence that the ageing immune system is characterised by immunosenescence, many centres do not have age-specific protocols for immunosuppression.

Objectives: In this study, we sought to examine the effect of recipient age on the development of complications of over- and under-immunosuppression post-transplantation.

Methods: We investigated the outcomes of 90 kidney transplants performed in our centre between April 2009-March 2016 in recipients aged >65, 42 of whom were >70; these patients were compared to 57 controls matched for number of HLA mismatches and divided into groups according to age at transplantation (18-34, 35-49 & 50-64).Recorded variables included rejection, development of de novo donor-specific anti-HLA antibodies (DSA), development of CMV or BK viraemia and death post-transplantation.

Results: There were significant differences in the mean %cRF pre-transplant across the groups: 18-34, 17.75%; 35-49,29.65%; 50-64, 36.29%; 65-69, 17.1%; and >70, 8.4%; p=0.008. Episodes of rejection were highest in the youngest groups (31.3% & 20% of patients aged 18-34 & 35-49, respectively) with a marked decrease in the older groups (9.5%, 10.4% & 11.9% in those aged 50-64, 65-69 & >70, respectively). Rates of de novo Class IDSA were also significantly higher in the younger age groups (18.8%, 0% & 23.8% in patients aged 18-34, 35-49 & 50-64, compared to 4.2% & 7.1% in recipients aged 65-69 & >70, respectively; p=0.025), while thedevelopment of de novo Class II DSA followed a similar trend (6.3%, 20% & 14.3% in patients aged 18-34, 35-49 & 50-64, versus 2.1% & 4.8% in recipients aged 65-69 & >70, respectively; p=0.077). Conversely, the ratesof CMV viraemia were strikingly elevated in recipients aged 60-69 (77.1%) and >70 years (73.8%) compared to those <65 (50.9%).

Conclusion: These data indicate that older recipient age is associated with reduced rates of rejection and de novo DSA but significantly increased infectious complications post-transplantation. Given the significant morbidity consequent to over-immunosuppression, consideration should be given to the development of age-specific protocols for immunosuppression.

Disclosure of Interest: None Declared

Keywords: Transplant IS, Transplant outcome

Glomerular Pathobiology

OR1-001

New therapeutic targets in proteinase-3 induced granuloma formation in granulomatosis with polyangiitis

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Preferred Presentation Method: Oral or Poster

Introduction: Anti-neutrophil cytoplasm antibodies (ANCA) are associated with a severe form of small vessel systemic vasculitis, in which they target two specific auto-antigens, proteinase-3 (PR3) and myeloperoxidase (MPO) found within neutrophils and monocytes. Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) are the main clinical syndromes, both characterised by kidney and lung disease, but granulomatous inflammation is almost exclusively found in GPA, and unlike other manifestations, remains difficult to treat. In GPA patients, PR3 is the predominant ANCA auto-antigen and neutrophil membrane PR3 expression is increased.

Objectives: There has been limited understanding of why granulomata are restricted to this patient subgroup. We investigated the role of PR3 in driving giant cell and granuloma formation using a novel *in vitro* model in an attempt to identify new therapeutic targets.

Methods: PBMCs were isolated from healthy controls (HC) (n=16), GPA (n=16) and MPA (n=16) patients and stimulated for 72 hours with or without PR3 (1µg/ml or 10µg/ml). Cells were stained and analysed by Bright field, confocal immunofluorescence and scanning electron microscopy (SEM) to demonstrate aggregation and fusion. Cytokine production was quantified by CBA and ELISA.

Results: PR3 induced both giant cell and granuloma formation using GPA patients' cells. Monocytes fused and PBMCs formed tight aggregates suggesting giant cell and granuloma formation respectively. GPA patients showed a greater rate of PBMC aggregation both spontaneously ($p<0.001$) and in the presence of PR3 compared to MPA patients ($p<0.0002$) and HC (<0.0001). Fused monocytes and T-cells, orientated into classical granuloma-like structures demonstrated by confocal microscopy. Specific pro-inflammatory cytokine profiles were found uniquely in GPA patients, supporting the notion of PR3-mediated monocyte activation, and fusion with additional T cell aggregation.

Conclusion: Persistent PR3 auto-antigen exposure stimulates unique cytokine profiles from monocytes that drive giant cell and granuloma formation in this novel *in vitro* model and have suggested novel therapeutic targets.

Disclosure of Interest: None Declared

Keywords: ANCA, Glomerulonephritis, Monocyte

Glomerular Pathobiology

OR1-002

Podocyte glycogen synthase kinase 3 (GSK3) is an evolutionarily conserved master regulator of glomerular/excretory function controlling podocyte differentiation and cell cycling.

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Preferred Presentation Method: Oral or Poster

Introduction: Glycogen synthase kinase 3 (GSK3) is a multi-functional enzyme existing as two structurally related isoforms (α and β) in mammals coded by different genes; but exists as a single gene in *Drosophila* called Shaggy. There are several recent publications suggesting that inhibiting mammalian podocyte GSK3 is beneficial in a number of disease settings. They suggest these effects are mediated by the β isoform, however there are no GSK3β specific pharmacological inhibitors and they all also inhibit GSK3α.

Objectives: This study set out to define the evolutionary importance of GSK3 in the mammalian podocyte and *Drosophila* nephrocyte and to elucidate the mechanisms through which this enzyme works.

Methods: We have studied the role of GSK3 in the glomerular podocyte using transgenic mice and additionally a *Drosophila* nephrocyte-specific gene knockout model. We have also developed an *in vitro* system using conditionally immortalised podocytes derived from GSK3α/β floxed mice transduced with a lentivirus expressing cre recombinase to induce gene excision.

Results: Developmental deletion of both GSK3 isoforms in the mouse podocyte results in death at postnatal day 10-16 with massive albuminuria, renal failure and acidosis. However, deleting 3 out of 4 alleles of GSK3α/β causes no phenotype demonstrating a high level of compensation within this system. The evolutionary importance of GSK3 in podocyte development is further supported with the observation that nephrocyte-specific loss of the *Drosophila* GSK3 orthologue, Shaggy, results in a complete lack of nephrocytes, the closest invertebrate model of mammalian podocytes. Mechanistically we thought that this detrimental phenotype would be driven by wnt signalling through activation of β-catenin. However this was not the case as contemporaneous transgenic podocyte-specific deletion of β-catenin together with GSK3α/β did not improve the phenotype of these mice. Non-biased proteomic analysis of GSK3α/β knockout podocytes revealed that mechanistically these cells enter re-enter the cell cycle but do not proliferate. Instead they progress to mitotic catastrophe and lose their differentiation markers.

Conclusion: Podocyte GSK3 is a critical enzyme for renal function and inhibiting both isoforms too much is highly detrimental. Care must therefore be taken when considering therapeutic pharmacological inhibition of this enzyme.

Disclosure of Interest: None Declared

Keywords: Animal model, Glomerular function, Podocyte

Cystic Diseases

OR1-004

Human Urine Derived Renal Tubular Epithelial Cells (HURECs) reveal a novel ciliary phenotype for CEP290 ciliopathies and serve as readout for identification of novel therapies for nephronophthisis

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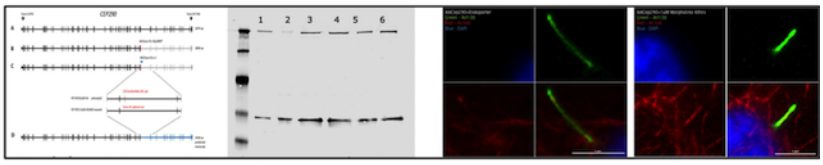
Preferred Presentation Method: Oral or Poster

Introduction: Nephronophthisis (NPHP) is a ciliopathy and a childhood cystic kidney disease that is a leading genetic cause of pediatric renal failure requiring renal replacement therapy.CEP290 localizes at the transition zone of the primary cilia and is a vital protein for morphologically and functionally normal primary cilium.Mutations in *CEP290* cause ciliopathy syndromes. CEP290 is expressed in centrosomes and at the transition zone of the cilia; mutations are thought to affect the structure and function of the cilia. Over 130 different mutations have been described within *CEP290*.

Objectives: We characterised cilia defects in an affected boy aged 13 years with a Joubert syndrome phenotype and explored rescue therapies.

Methods: Mutation analysis revealed a *CEP290* homozygous nonsense mutation in exon 41 c.5668G>T (p.Gly1890X). Using HUREC from the patient we examined cilia structure. We used pharmacological means and targeted exon-skipping to rescue the phenotype.

Image:



A. B. C.

Figure: A) Morpholino induced exon skipping of Exon 41 leads to a shorter transcript of 2438 amino acids B) Western blot demonstrating CEP290 protein in response to exon skipping at 24 hrs (ln-3),48 hrs(ln-4), 72 hrs(ln-5) & 96hrs(ln-6). Ln-1 is WT protein and ln-2 is mutant protein. GAPDH is loading control. C) Immunofluorescence microscopy demonstrates rescue of ciliary phenotype after anti-sense oligonucleotide mediated exon skipping of exon 41. Scale bar 5μm.

Results: In HuRECs derived from the patient we demonstrate loss of CEP290 protein and abnormalities in ciliary structure. Specifically, we see elongated cilia (6.98 mm vs 4.70 mm in wild type controls) under scanning electron microscopy (SEM) and under immunofluorescence. This ciliary phenotype could be recapitulated by siRNA mediated knockdown of *CEP290* and Sonic Hedgehog pathway inhibition in WT cells. The ciliary abnormality could be rescued by treatment with the Hedgehog (Hh) agonist purmorphamine (2 mM) for 24 h. As an alternative means of rescue we used a targeted morpholino oligonucleotide towards the intron-exon splice junction of exon 41. Using this approach we show, using RT-PCR, exon skipping and a rescue of expression of a near full-length CEP290 protein. Phenotypic rescue of elongated cilia was also confirmed. We demonstrate that the effect of exon skipping persists for over 96 hours in cell culture models (Figure 1)

Conclusion: In a patient with a homozygous truncating *CEP290* mutation, we have modelled the ciliary defect using HUREC. The abnormal ciliary phenotype which included elongated cilia with abnormal. axonemal acetylation was rescued by both Hh agonist treatment and targeted exon-skipping. This individualised approach offers new therapeutic options for the treatment of ciliopathies.

Disclosure of Interest: None Declared

Keywords: Cystic kidney disease, Development, Tubular epithelial cell

Diabetic Nephropathy

OR1-006

Increasing insulin receptor number protects podocytes from ER stress

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Preferred Presentation Method: Oral or Poster

Introduction: Diabetic nephropathy is the major cause of end-stage renal disease. It has a variety of characteristics, including endoplasmic reticulum (ER) stress and podocyte loss leading to proteinuria. A functional ER stress pathway enables healthy cells to respond quickly to errors in the synthesis and folding of nascent proteins, but an overwhelmed ER stress response triggering apoptosis is associated with diabetic conditions.

Objectives: To develop a high throughput assay which would enable us to monitor ER stress in podocytes under diabetic conditions, and to determine whether manipulation of insulin signalling could protect podocytes from ER stress.

Methods: Our high content imaging assay uses an antibody to detect upregulation of ER stress-inducible transcription factor C/EBP homology protein (CHOP) in the nucleus of single immortalized podocytes. Experiments are performed in 96-well plates and subjected to automated fluorescence microscopy using the InCell Analyzer system. We have compared the CHOP response in wild-type cells to podocytes stably over-expressing the insulin receptor, or shRNA stable knock-down of PTEN (phosphatase and tensin homolog), or following treatment with the insulin sensitizer, Rosiglitazone. Cells were treated with insulin resistance-inducing media (high glucose, high insulin, TNFα, IL-6) to recapitulate diabetic conditions for 14 days and/or 10^{-5}-10^{-3} M palmitate (free fatty acids) for 24hrs.

Results: Incubating podocytes in insulin resistance-inducing media caused a significant ($p < 0.0001$) increase in CHOP expression, and a dose-dependent increase was also observed for palmitate ($p < 0.0001$), which was additive ($p = 0.0330$). Conversely, cells stably over-expressing the insulin receptor experienced a significantly reduced CHOP induction ($p < 0.0001$), and over-expression of the insulin receptor mitigated the CHOP upregulation caused by insulin resistance-inducing media. Since the insulin receptor signals primarily through phosphatidylinositol (PI) 3-kinase activation of Protein kinase B (PKB)/Akt, we hypothesized that by removing a negative regulator of this pathway, PTEN, we could effectively increase insulin signalling through Akt and therefore also reduce ER stress. However, PTEN knock-down had the opposite effect, significantly increasing CHOP induction ($p < 0.0001$) in untreated and palmitate-treated cells, but no further increase in CHOP was seen when PTEN knockdown cells were treated with insulin resistance-inducing media. Treatment with the insulin sensitizer Rosiglitazone moderately protected cells ($p = 0.009$) from ER stress induced by insulin resistance-inducing media or palmitate.

Conclusion: Whereas enhancing insulin signalling in podocytes through over-expression of the insulin receptor or treatment with Rosiglitazone protects cells from ER stress, removal of a negative regulator of insulin signalling, PTEN, has the opposite effect, increasing ER stress. This highlights the complexity of insulin signalling and especially the importance of its modulation by a negative regulator. Here we also report a robust high throughput assay, amenable to screening large numbers of patient samples or compounds for evaluating novel treatments for diabetic nephropathy.

Disclosure of Interest: None Declared

Keywords: Imaging, Lipids, Podocyte

Glomerular Pathobiology

OR1-007

Connective Tissue Growth Factor (CTGF) is a Critical Mediator of Cryoglobulinaemic Vasculitis (CV) and a novel target for therapy

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Preferred Presentation Method: Oral or Poster

Introduction: Introduction

Through a serendipitous discovery we found that ren1-CTGF transgenic mice develop cryoglobulinaemic glomerulonephritis(CGN). CTGF, is a matricellular protein involved in cell proliferation and differentiation with pleotropic effects. We previously demonstrated elevated serum CTGF levels in patients with HCV induced- and Mixed Essential-CV.

Objectives: To confirm these findings and investigate the therapeutic potential of targeting CTGF we used of the thymic stromal lymphopoeitin (TSLP) Tg mice that develop CV and CGN and targeted CTGF with antisense oligonucleotides (ASO).

Methods: CTGF levels were measured in TSLP mice and WT littermates. TSLP Tg mice were treated with weekly CTGF control ASO therapy or vehicle alone for 10-14 weeks.

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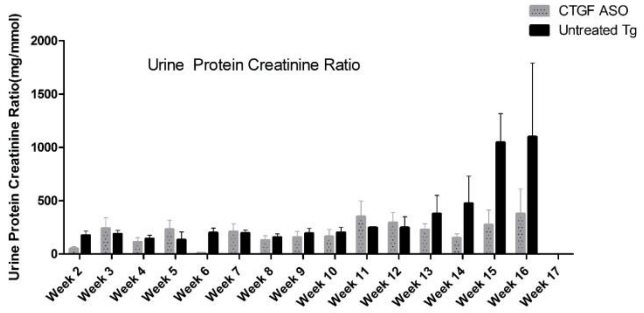

Results: TSLP Tg mice show an age dependent increase in serum CTGF levels (median 1128pg/ml and 45360 at 6 and 17 weeks respectively). With CTGF ASO this was suppressed to levels comparable to WT littermates(4112 pg/ml). The incidence of ulcerative ear and neck lesions was 50% lower in the CTGF ASO group (p=0.0549). Mice that received CTGF ASO developed significantly lower proteinuria compared with untreated Tg animals (p<0.001).There was less severe histological injury in the CTGF ASO cohort (mean mesangial expansion score 1.456±SD 0.310 vs. 2.078 ± SD 1.038, p=0.0159). WT mice had preserved glomerular podocyte density that was unaffected by ASO therapy (CTGF ASO treated 288.3 +/- 67 vs control ASO treated 285+/- 73 podocytes/10^6 μm^3), while TSLP-Tg control ASO mice had significantly reduced podocyte density which was significantly ameliorated by CTGF ASO treatment (control ASO treated 164.8 +/- 57 vs CTGF ASO treated 218 +/- 35 podocytes/10^6 μm^3). The podocyte CTGF expression was also significantly lower in CTGF ASO treated mice compared with untreated Tg mice (proportion glomeruli with CTGF expression 0.3333 ± 0.5164 vs 0.8333 ± 0.4082, p=0.0462 respectively).

Conclusion: This study demonstrates that CTGF is an important mediator of CV and CGN, and its antagonism provides a novel therapeutic target. The link between TSLP and CTGF is under investigation, but of interest is the finding that elevated TSLP levels are found in HCV patients with cryoglobulinaemia, suggesting that our animal data may accurately recapitulate findings in patients.

Disclosure of Interest: None Declared

Keywords: Glomerulonephritis

Glomerular Pathobiology

OR1-008

Th17 Cells and Podocyte Crosstalk

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Preferred Presentation Method: Oral or Poster

Introduction: There is increasing evidence that a subset of T helper (Th17) cells can survive steroid treatment and may be driving steroid resistant inflammatory conditions such as uveitis, ulcerative colitis and asthma. Additionally there is evidence to suggest a role for a circulating factor(s) released by T cells in idiopathic nephrotic syndrome. Work published previously by our group demonstrated that an unknown factor present in the plasma of nephrotic patients in relapse is capable of stimulating VASP signalling in the podocyte and increasing podocyte motility. This factor signals via the PAR-1 receptor. We hypothesised that the Th17 cells are capable of signalling to the podocyte and that this signalling occurs via the PAR-1 receptor.

Objectives: To investigate the capability of Th17 cells to signal to the podocyte and to define the signalling and behaviuoral changes elicited by such crosstalk. We also looked at the number of Th17 cells in patients who relapse compared to those who suffer no relapse.

Methods: Th17 cells were cultured and their culture supernatants were retrieved and applied to conditionally immortalised wild-type human podocytes. Protein was extracted and used in western blotting experiments to investigate intracellular signalling. Scratch assays were performed to look at podocyte motility. A Par-1 agonist containing the sequence of the tethered ligand was used to look at the effect of PAR-1 stimulation on the podocyte. PBMCs taken from relapsing and non-relapsing patients were isolated and FACS sorted. The frequency of Th17 cells were determined by gating IL-17 and RORγt double positive cells.

Results: Th17 cell culture supernatant treatment of the podocytes stimulated p38 MAPK and JNK signalling pathways. p38 MAPK and JNK both have target phosphorylation sites on paxillin. Only the JNK target site (S178) was phosphorylated in response to Th17 cell culture supernatant treatment. Th17 cell culture treatment also significantly increased podocyte motility. This effect was blocked by both JNK inhibition and Protease inhibition. Suggesting that the effector molecule in the Th17 cell culture supernatant is a protease that acts via JNK. PAR-1 agonist treatment of podocytes stimulated the same signalling events. The PAR-1 agonist treatment had such a large effect on adhesion that motility could not be measured. Additionally relapsing patients had significantly more circulating Th17 cells.
The frequency of Th17 cells were determined by gating IL-17 and RORγt
double positive cells.

Conclusion: This work suggests that there is a hitherto unknown protease present in Th17 cell culture supernatant that signals via the PAR-1 receptor on the podocyte and via JNK and Paxillin phosphorylation affects podocyte motility and/or adhesion. Further inhibitor studies are required to confirm this pathway. However, if shown to be correct, this work provide multiple therapeutic targets that could be used to protect the podocyte against the circulating factor. Given the significant increase in Th17 cells in the circulation of relapsing patients, it is clear that Th17 cells could be the source of an unknown permeability factor.

Disclosure of Interest: None Declared

Keywords: Nephrotic syndrome, Podocyte

Regenerative Medicine
OR1-009
Systemic administration of stem cells via the left heart ventricle enables their efficient delivery to the kidneys.

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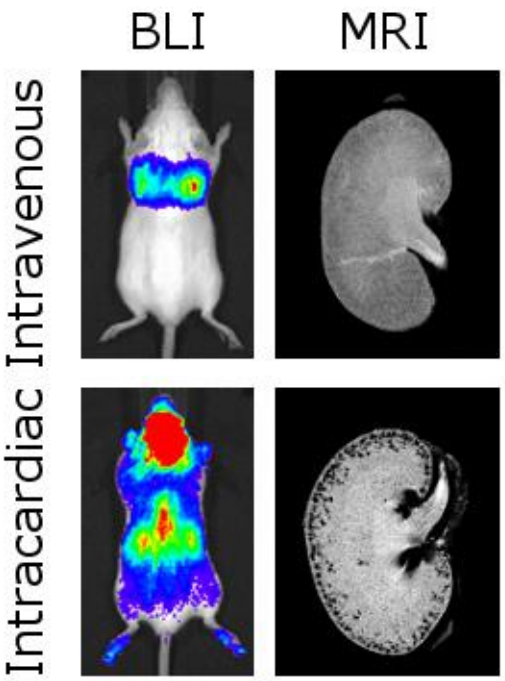
Preferred Presentation Method: Oral
Introduction: A roadblock associated with regenerative medicine therapies involving stem cells is the pulmonary first-pass effect, where cells administered intravenously are trapped in lung capillaries before they can reach their target organs, limiting the therapy's full potential. Systemic administration via other routes could potentially overcome this barrier, but are seldom investigated. Here, we administer stem cells via the left-ventricle of the heart with the aim of delivering them to the kidneys.
Objectives: To assess stem cell delivery to the kidneys after administration via the intravenous or left heart ventricle route using a combination of *in vivo* imaging modalities.

Methods: Mouse mesenchymal stem cells (MSCs) were genetically tagged with a green fluorescent protein (ZsGreen), firefly luciferase and labelled with superparamagnetic iron oxide nanoparticles (SPIONs). These cells were then injected into a mouse model of chronic kidney disease intravenously via the tail vein or, intracardially, via the left ventricle. Animals were then imaged via bioluminescence imaging (BLI, Perkin Elmer IVIS Spectrum) and magnetic resonance imaging (MRI, Bruker 9.4 T Avance III HD) to assess cell biodistribution after which they were culled and the organs harvested for ex-vivo imaging and histology.
Image:



Results: Tail vein administration of cells resulted in their entrapment in the lungs, with no evidence for cells reaching any other organs. In contrast, intracardiac administration resulted in a whole-body distribution of cells, with strong bioluminescence originating from regions around the kidney and head (Fig. 1, BLI). *Ex vivo* BLI imaging revealed that all organs that were harvested for imaging (heart, kidneys, brain, liver, spleen and lungs) contained cells when these were administered intracardially, but not when administered via the tail vein, where only the lungs displayed a signal. The use of SPIONs enabled highly spatially resolved *in vivo* imaging of cell trafficking via MR, and scans of the abdomen revealed hypointense contrast in the periphery of the kidneys. High resolution *ex vivo* scans confirmed these results with contrast observed in the form of discrete spots in the renal cortex (Fig. 1, MRI). Histological analysis confirmed MSCs accumulate predominantly in the glomeruli, supporting the pattern observed via MRI.
Conclusion: The pulmonary first-pass effect can be partially overcome by systemic delivery via the left ventricle of the heart, allowing stem cells to reach the kidneys. With the use of appropriate labels, cell trafficking can be successfully imaged non-invasively at different resolutions using a combination of BLI and MRI. Importantly, BLI allows the confirmation of cell viability, whereas MRI allows the highly spatially resolved identification of the cell localisation within the kidneys. Our data suggests that when the use of stem cell therapies is considered, the route of administration needs to carefully assessed if their delivery to organs other than the lungs is required.

Disclosure of Interest: None Declared

Keywords: Animal model, Imaging, Stem cell

Regenerative Medicine

OR1-010

Human kidney-derived cells ameliorate acute kidney injury without engrafting into renal tissue

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Preferred Presentation Method: Oral

Introduction: Renal progenitor cells (RPCs) have been proposed as a possible therapy for treating patients with kidney disease. CD133 has been suggested as a specific marker for human RPCs isolated from kidney biopsies since CD133+ cells have been reported to integrate into damaged renal tissue and improve renal health when administered to mice with kidney disease. However, the effect of the cells on renal function has not previously been assessed in detail.

Objectives: Our objectives were to: i) evaluate the impact of $CD133^+$ and $CD133^-$ human kidney cells on glomerular filtration rate (GFR) following intravenous administration (IV) into immunodeficient rats with cisplatin (CP)-induced injury; and ii) determine whether the cells can integrate into damaged kidneys in the CP rat model.

Methods: Acute kidney injury was induced by injecting cisplatin (7mg/100g, IP) in immunodeficient athymic rats. 1 million CD133+GFP+PKH26+ or CD133-GFP+PKH26+ were injected intravenously (IV) at day 2 and 7 and the rats were culled at day 14. Serum biomarkers and the transcutaneous assessment of the clearance of FITC-sinistrin were used to monitor the renal function over time. Histological analysis (H&E, Masson's Trichrome) was performed to investigate the effects of the cells on renal structure. Immunofluorescence-based analysis were also carried out to identify the human cells in kidneys and lungs. A biodistribution in vivo study was also performed to investigate the fate of the human cells 1, 6 and 24 hours after injection.

Results: Both $CD133^+$ and $CD133^-$ cells were found to improve renal function as determined by transcutaneous GFR measurements and serum biomarkers. However, the amelioration was not associated with the engraftment of the cells in the kidneys. Instead, the cells were found in the lungs soon after IV administration, and disappeared within 24 hours. Moreover, we report an accumulation of phagocytic cells in the lungs that might be involved in the disappearance of the cells from the lungs.

Conclusion: Taken together, our data indicate that (i) CD133 expression has no relevance for the *in vivo* therapeutic potential of human kidney cells, and (ii) the mechanism of amelioration is based on paracrine factors, not on integration of administered cells.

References: Santeramo I et al, Human kidney-derived cells ameliorate acute kidney injury without engrafting into renal tissue, Stem cells translational medicine, in press.

Disclosure of Interest: None Declared

Keywords: AKI, GFR, Stem cell

Regenerative Medicine

OR1-011

Proof that mesothelial cells directly contribute to peritoneal scars in vivo

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Preferred Presentation Method: Oral or Poster

Introduction: Fibrosis leading to scarring, and thus ultrafiltration failure, is a major complication of long-term peritoneal dialysis. Mesothelial cells (MCs) line the peritoneal walls, and injured adult MCs can clearly transdifferentiate to myofibroblasts in culture. We have previously discovered that embryonic MCs normally undergo mesothelial-mesenchymal transition (MMT) *in vivo*, contributing to underlying vasculature.

Nevertheless, it has yet to be definitively proven whether mature MCs can undergo MMT and generate myofibroblasts in living animals.

Objectives: Our objective was to demonstrate that MCs, after localised peritoneal injury, are major contributors of peritoneal scar formation, using a mesothelium-specific genetic lineage tracing system.

Methods: To follow the fate of MCs expressing Wilms tumour protein 1 (Wt1), we used an inducible genetic lineage tracing system in adult mice, which labelled MCs to express β-Galactosidase or EGFP. After MC labelling, peritoneal adhesions between the caecum and peritoneal wall were generated by surgical trauma to the serosa. Adhesions and control tissues were analysed at various time points after surgery and the mechanisms of MC contribution to the scars analysed using X-Gal staining, histology and immunofluorescence.

Results: In the abdominal cavities of healthy adult mice, labelled cells were only detected in MCs covering the viscera and lining the body wall. In striking contrast, labelled cells derived from the mesothelial layer made a major contribution to scar tissue. Within 7 days after injury, vividly labelled cells were found within the perimeter of the abdominal wound and inside the scar. By 14 days, these cells had contributed to a meshwork of elongated myrofibroblast-like cells. Furthermore, our data reveal that the MCs underwent mesothelial-mesenchymal transition (MMT) towards a migratory and mesenchymal phenotype.

Conclusion: To our knowledge, this is the first definitive genetic proof that injured mature MCs retain their normal embryonic ability to undergo MMT *in vivo*. Critically, these insights also place MCs centre stage in the pathobiology of tissue fibrosis that follows peritoneal injury. Prevention of MMT is thus a logical target to prevent peritoneal fibrosis.

Disclosure of Interest: T. Wilm Conflict with: MRC, S. Namvar Conflict with: MRC, A. Woolf Conflict with: MRC, S. Herrick Conflict with: MRC, B. Wilm Conflict with: MRC

Keywords: Animal model, Fibrosis, Peritoneal inflammation

Peritoneal Dialysis

OR1-012

MicroRNA-200c Inhibits TGF-β1-induced Epithelial-to-mesenchymal Transition and Fibrogenesis in Human Peritoneal Mesothelial Cells

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Preferred Presentation Method: Oral or Poster

Introduction: Progressive peritoneal fibrosis is a common complication that limits the effectiveness of long-term peritoneal dialysis (PD). Mesothelial cells line the peritoneal cavity and constitute the first line of defence against chemical and bacterial insults. Epithelial-to-mesenchymal transition (EMT) of mesothelial cells and mesothelial denudation are commonly observed in long-term PD, but the underlying mechanisms remain to be elucidated. MicroRNA-200c (miR-200c) has been reported to regulate EMT in various cells, but its role in peritoneal fibrosis has not been explored.

Objectives: We investigated the role of microRNA-200c (miRNA-200c) in EMT and fibrogenesis in a murine PD model and cultured peritoneal mesothelial cells.

Methods: Male C57BL/6N mice were administered PBS or glucose-based PD fluid twice daily by intra-peritoneal injection for up to 30 days. Parietal peritoneum was obtained and miRNA-200c expression examined using locked nucleic acid in-situ hybridization. Cultured human peritoneal mesothelial cells were stimulated with exogenous TGF-β1 and the expression of miRNA-200c and EMT markers was investigated by qPCR and Western blot analysis. In separate studies, miRNA-200c was overexpressed in cultured mesothelial cells to investigate its effect on fibrogenesis.

Results: PD fluid, but not PBS, given intraperitoneally to C57BL/6N mice resulted in a significant reduction of peritoneal miRNA-200c expression which was sustained for 1 month. Decreased miRNA-200c expression was associated with mesothelial cell detachment and increased submesothelial matrix protein deposition. Exogenous TGF-β1 significantly decreased miRNA-200c and E-cadherin expression in mesothelial cells in a dose-dependent manner, and this was accompanied by increased SNAIL, ZEB2, fibroblast-specific protein-1, fibronectin and collagen I synthesis. Over-expression of miRNA-200c ameliorated the pro-fibrotic effect of TGF-β1.

Conclusion: Our data demonstrate that miRNA-200c regulates EMT and fibrogenesis in peritoneal mesothelial cells, and decreased peritoneal miRNA-200c expression is associated with peritoneal fibrosis during PD.

Disclosure of Interest: None Declared

Keywords: Extracellular matrix, Fibrosis, Peritoneal dialysis

Peritoneal Dialysis

OR1-013

microRNA Regulation of Macrophage Phenotype in Peritoneal Fibrosis

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Preferred Presentation Method: Oral

Introduction: Peritoneal fibrosis is a major cause of treatment failure in peritoneal dialysis and linked to repeat episodes of infection-driven inflammation. Macrophages (MØ) are a heterogeneous population of immune cells essential for immune surveillance, response to infection and inflammation. Distinct subpopulations of MØ are implicated in tissue repair and fibrosis. microRNAs (miRs) are epigenetic regulators and fundamental to the control of cellular phenotype. However, the role of miR regulation of MØ phenotype in peritoneal fibrosis has not been examined.
Objectives: The objective was to perform an *in vivo* study of miR regulation of resident and inflammatory MØ phenotype in peritoneal fibrosis.
Methods: We utilized a well-established *murine* model of peritoneal fibrosis, flow cytometry sorted MØ subpopulations, RNA-sequencing, RT-qPCR, lentiviral mediated miR expression, and Ingenuity Pathway Analysis for bioinformatics.
Results: A single episode of acute peritoneal inflammation is self-limiting with restoration of tissue homeostasis, whereas repeat episodes initiate the development of fibrosis. In response to acute inflammation two distinct MØ lineage branches are evident – tissue resident and inflammatory MØ. We employed RNA-sequencing to determine the miR expression profiles of resident and inflammatory MØ and identify differentially regulated miRs. We identified miR-146b as abundantly expressed in resident and inflammatory MØ, and upregulated following repeat episodes of acute inflammation and at time of fibrosis. To determine the precise functions of miR-146b we cloned the pre-miR transcript into a lentiviral mediated expression vector and achieved increase expression 100-fold *in vitro* and 10-fold *in vivo*. Efficacy of miR-146b expression was confirmed by repression of known mRNA transcripts Traf6 and Irak1/2 leading to decreased TNF-alpha production. The potential of miRs to target multiple mRNA transcripts enables a single miR to influence multiple processes. We aimed to identify *bona fide* miR-146b target mRNA transcripts and define the impacted physiological processes in resident MØ. We expressed miR-146b in resident MØ *in vivo* followed by RNA-sequencing of the whole transcriptome. We identified numerous differentially regulated mRNA transcripts, including 2-5A synthetase 3 and heat shock 70kDa protein 1B. Ingenuity Pathway Analysis identified the top regulated canonical pathways relevant to inflammation and fibrosis including reactive oxygen generation by MØ, and STAT3 and interferon signaling.
Conclusion: MØ are a heterogeneous population of cells tailored by their microenvironment and tissue-specific functions. We have determined the miR expression profiles of resident and inflammatory MØ and defined dysregulated miRs, thus providing potential therapeutic targets in peritoneal fibrosis.

Disclosure of Interest: None Declared

Keywords: Fibrosis, Macrophage, Peritoneal inflammation

Medicines Management

OR11-001

Screening for adrenal insufficiency prior to withdrawal of corticosteroid treatment for renal conditions: an audit cycle at a tertiary centre

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Preferred Presentation Method: Oral or Poster

Introduction: Corticosteroids are a common and effective treatment for a variety of inflammatory renal disorders. However, due to a considerable number of significant adverse effects maintenance doses should be kept as low as possible and cessation considered in patients with stable remission. Clinical practice in many centres is to taper prednisolone gradually and discontinue without formally testing for adrenal insufficiency but our experience indicated that a proportion of patients on low dose Prednisolone exhibited biochemical adrenal insufficiency but were not symptomatic.

Objectives: For the past few years, we have routinely undertaken Short Synacthen Tests (SST) prior to stopping steroid treatment >3 months. In an initial audit in 2014 we demonstrated that 46% (19/41) of patients had adrenal insufficiency. To facilitate safe withdrawal we made the recommendation to involve Endocrinology in those identified to have adrenal insufficiency and carried out this re-audit 2 years later.

Methods: We studied all patients on Prednisolone therapy for renal conditions who had an initial SST conducted between 1st September 2015 and 31st August 2016. Data was collected retrospectively using our electronic system.

Results: 46 (27 females, 19 males) SSTs were conducted. The average patient age was 54 years (range 22-83). Patients were on corticosteroids for a variety of conditions including vasculitis (21/46), lupus nephritis (12/46) and glomerulonephritis (10/46). The average duration, where available, of corticosteroid use was 30.3 months (range 4 – 181). The majority of patients were on Prednisolone 5mg daily at the time of testing (39/46).

Fifty-six percent (26/46) of patients failed the SST (30 minute cortisol <450 nmol/l). 21 of 26 patients were referred to Endocrinology. Of those who were not referred 4/5 had indications to continue on Prednisolone. 16/26 patients that failed the test were switched to Hydrocortisone. Baseline cortisol ranged from <20 to 643 nmol/l (Median 211 nmol/l). The positive predictive value of passing the SST with a baseline >350 nmol/l was 100% making it legitimate to use this as a cut-off for 9am cortisol testing. Standard of care is to repeat SST at 6-12 months from conversion to hydrocortisone. To date, 7 patients have been re-tested of which 3 have passed and stopped steroids. 16 of the 20 patients that passed the SST stopped taking steroids at once rather than through conventional tapering.

Conclusion: We have confirmed that biochemical adrenal insufficiency is common in this cohort of patients. Identification is relevant as it aims to protect patients from adrenal crisis when subjected to stress. Endocrinology involvement has facilitated safe withdrawal through conversion to hydrocortisone, scheduled re-testing and patient education of dose adjustment during intercurrent illness.

Disclosure of Interest: None Declared

Keywords: Audit, Clinical quality improvement, Corticosteroids

Transplantation - Immunosuppression

OR11-002

A Phase-Two, Randomised, Placebo-Controlled Trial: Belimumab in Renal Transplantation Targets Naïve and Activated Memory B Cells Whilst Sparing Regulatory B Cells

G. Banham [1,*], A. Gibson [2], J. Chadwick [2], K. Foster [2], N. Torpey [3], S. Flint [2], M. Clatworthy [1], R. Henderson [2] on behalf of BEL114424 Study Group

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Preferred Presentation Method: Oral or Poster

Introduction: Alloantibody production by terminally differentiated B cells negatively affects kidney transplant outcomes but regulatory B cells (Bregs) may promote transplant tolerance. Bregs are defined based on expression of interleukin-10 (IL-10) and a subset of Bregs display a memory phenotype. The balance of B cells secreting pro-inflammatory (e.g. interleukin-6 (IL-6)) and anti-inflammatory cytokines (e.g. IL-10) provides a broader assessment of B cell derived cytokines that contribute to immune regulation. B lymphocyte stimulator (BLyS; also know as BAFF) is a cytokine that enhances B cell survival and proliferation. In renal transplant recipients elevated serum BLyS is associated with de-novo donor specific antibodies and an increased frequency of antibody mediated rejection

Objectives: We tested the hypothesis that inhibition of BLyS in renal transplantation would result in a beneficial alteration in B cell phenotype, favouring Bregs and reducing activated B cells using data from the first clinical study of belimumab (an anti-BLyS antibody) in renal transplantation (BEL114424; ClinicalTrials.gov number NCT01536379; EudraCT number 2011-006215-56).

Methods: Patients were randomised to intravenous belimumab 10mg/kg (n=14), or placebo (n=14) on the day of renal transplant and at weeks 2, 4, 8, 12, 16 and 20, in addition to standard of care immunosuppression (basiliximab, mycophenolate mofetil, tacrolimus and prednisolone). Detailed immunophenotyping of peripheral blood mononucear cells (PBMC) was performed including staining for intracellular IL-10 and IL-6 following in vitro stimulation. Follow-up in vitro studies were performed to further characterise the effect of BLyS on memory B cell cytokine release using healthy volunteers.

Results: Belimumab effectively neutralised serum free BLyS. In belimumab treated patients we observed a reduced proportion of naïve B cells with a concomitant increase in circulating CD27+ memory B cells. Within this subset there were fewer activated (CD95+) memory B cells and a post hoc analysis demonstrated a marked downregulation of TACI, a receptor for BLyS. On in vitro stimulation, there were more B cells from belimumab treated subjects producing IL-10 compared to IL-6, consistent with a more regulatory B cell phenotype. In contrast, follow-up experiments using CD27+ memory B-cells enriched from healthy volunteers found that the ratio of cells producing IL-10 versus cells producing IL-6 was reduced when cells were stimulated in the presence of recombinant BLyS.

Conclusion: BLyS appears important in controlling the balance of pro and anti-inflammatory cytokine production by memory B cells and inhibition of BLyS with belimumab therapy may achieve the difficult therapeutic remit of suppressing B cell activation whilst augmenting Bregs.

GlaxoSmithKline funded this study.

Disclosure of Interest: G. Banham Conflict with: GlaxoSmithKline, A. Gibson Conflict with: GlaxoSmithKline, J. Chadwick Conflict with: GlaxoSmithKline, K. Foster Conflict with: GlaxoSmithKline, N. Torpey Conflict with: Astellas Pharma; Alexion Pharmaceuticals, S. Flint Conflict with: GlaxoSmithKline, M. Clatworthy Conflict with: GlaxoSmithKline; Sandoz, R. Henderson Conflict with: GlaxoSmithKline

Keywords: B cell, Clinical trial, Immunosuppression

Conservative/End of Life Care

OR12-001

Quality of life in frail older people with end stage renal disease – How does dialysis compare with conservative kidney care?

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Preferred Presentation Method: Oral or Poster

Introduction: Older people represent the majority of patients with ESRD. The presence of frailty, cognitive impairment and falls adds to the potential burden of dialysis in this cohort. Some studies have reported that QoL is better preserved in patients receiving conservative kidney care (CC) compared with those on dialysis. However, little is known about these outcomes in frail older patients.

Objectives: The Frail and Elderly Patients on Dialysis (FEPOD) study has demonstrated that quality of life (QoL) outcomes do not differ between older patients receiving in-centre haemodialysis (HD) and assisted peritoneal dialysis (PD).This cross sectional analysis aims to compare QoL between older patients on HD, assisted PD and CC.

Methods: The FEPOD study was extended to allow the recruitment of CC patients. These patients were receiving CC, > 60 years old with an estimated GFR ≤ 10ml/min. 28 recruited patients were retrospectively matched to HD and assisted PD patients by age, gender, ethnicity, diabetes status and index of deprivation. The SF12, HADS depression score, symptom score, illness intrusiveness rating scale (IIRS), RTSQ and Barthel score were the outcomes of interest. Frailty was assessed using the clinical frailty scale. Generalised linear modelling was used to assess the impact of treatment modality (CC, HD and PD) on QoL outcomes, adjusting for baseline characteristics.

Results: 84 (28 CC, 28 HD, 28 PD) patients were included in the analysis. The median age for the cohort was 82 (79 – 88) years. There were no differences in baseline characteristics between the 3 groups except for the prevalence of peripheral vascular disease. This was lower in the CC group compared to the other modalities (CC - 3.6%, HD - 21.4%, PD - 28.6%, p = 0.04). After multivariate analysis, CC was associated with lower SF12 PCS [0.83 (0.69 - 1.00), p = 0.05) and higher symptom scores [Exp B =1.61 (1.12 – 2.31), p =0.01) compared with assisted PD. There were no differences in other measures of QoL. Worsening frailty was associated with higher depression scores [Exp B = 2.59 (1.45 – 4.62), p <0.01], IIRS [Exp B = 1.20 (1.12 – 1.28), p < 0.01) and lower SF12 PCS [Exp B = 0.87 (0.83 – 0.93), p < 0.01).

Conclusion: Certain dimensions of QoL (SF12 PCS, IIRS and symptom burden) were poorer in CC patients compared with those on PD. Otherwise, QoL outcomes were no different. As in the primary study, frailty was associated with adverse QoL outcomes. These findings require corroboration in larger longitudinal studies. They highlight the need for an individualised approach to the management of ESRD in older people where all options are carefully explored, including CC.

Disclosure of Interest: None Declared

Keywords: Conservative kidney care, Dialysis, Frailty

Peritoneal Dialysis

OR12-002

Peritoneal Inflammation Increases Over Time, with Subsequent Increases in Plasma IL-6: Results From the Global Fluid Study

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Preferred Presentation Method: Oral

Introduction: Local peritoneal inflammation is a feature of peritoneal dialysis (PD) treatment and high concentrations of dialysate IL-6 (dIL6) are a strong determinant of solute transport. Solute transport increases during long term PD but it is unknown whether dialysate IL-6 rises. Plasma IL-6 (pIL6) is an independent predictor of patient survival but whether dialysate IL-6 contributes to plasma levels is unknown.

Objectives: We tested the hypotheses that dIL6 increases with time and that pIL6 rises due to diffusion from the dialysate.

Methods: We conducted a longitudinal analysis of the Global Fluid study, a multinational cohort study from UK, Canada and Korea with repeat measures. All incident patients with 3 or more paired dialysate/plasma samples were assayed for IL-6 by electrochemiluminescence. A linear mixed model with random intercept/slopes was used to assess associations with pIL6. Covariates included time on PD, centre, dIL6, gender, baseline age, comorbidity score and urine volume in an adjusted model with backwards selection. pIL6 and dIL6 were log transformed. Cox regression using time-varying covariates was used for all-cause mortality with 68 events.

Table:

Results: There were 223 patients with 1310 measurements, with a median follow up time of 2.2 years from 6 centres. Over time there is a significant increase in dIL6 (1.17 pg/ml/year 95% CI 1.11 to 1.24 p<0.001) and pIL6 (1.08 pg/ml/year per year 95% CI 1.02 to 2.24 p=0.001). In the multivariate model pIL6 was significantly positively associated with dIL6 (coeff=0.096 95% CI 0.061 to 0.131 p<0.001 Figure 1), centre ($\chi 2$=15.1, d.f.=4, p=0.005) and age (coeff= 0.0042 p<0.001, and negatively associated with urine volume (coeff=-0.066 95% CI -0.093 to -0.0062 p<0.001). There was no significant association with gender or baseline comorbidity score in this selected cohort. The rise in time was mostly predicted by changes in dil6 and RRF (coeff for time=0.11 95% CI -0.002 to 0.2 p=0.11). Random effects demonstrated that higher initial pIL-6 was associated with less increase over time (covariance -0.0067 95% CI -0.11 to -0.0026). Time varying pIL6 was negatively associated with survival (HR 2.15 per log10 order, 95% CI 1.05 to 4.47) after adjustment for age and comorbidity.

Conclusion: Both dialysate and plasma IL-6 levels increase with duration of PD. The increase in pIL6 over time is associated with both increasing dIL6, decreasing residual renal function and reduced survival.

Disclosure of Interest: None Declared

Keywords: Peritoneal dialysis, Survival

Transplantation - Outcomes

OR13-002

Clinical relevance of complement activating donor specific antibodies in highly sensitised patients: Two centre retrospective study

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Preferred Presentation Method: Oral

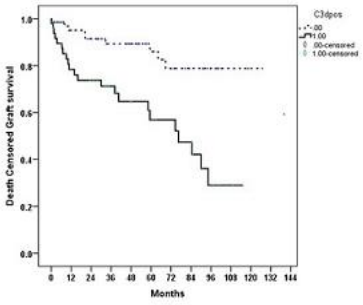
Introduction: Complement activating characteristics of donor specific antibodies (DSA) may be an important factor that predicts long term renal allograft outcome. Studies have shown that presence of complment fixing or activating donor specific antibodies at the time of rejection post transplant is associated with poor graft outcome.However, there are no similar studies looking at pre-transplant DSA and its impact on graft outcome in terms of rejection and survival, especially in highly sensitised patients who have undergone HLA antibody incompatible renal transplants.

Objectives: To study the complement activation characteristic of the donor HLA specific antibodies in a cohort of patients who have undergone HLA incompatible renal transplants.

Presence of complement activating IgG DSA as detected by C3d predicts rejection and long term renal allograft survival.

Methods: Analysed samples from two collaborating transplant centres in the United Kingdom;117 cases who were either complement dependent cytotoxicity (CDC) or Flow Crossmatch(FC) positive at pre-conditioning and underwent direct transplantation after desensitisation protocol. C3d (Immucor) assay was performed at preconditioning and the results were correlated with early antibody mediated rejection (within first 30 days post-transplantation) and death censored allograft survival. We also compared the five-year graft survival against standard transplantation at our centres. Statistical analyses performed using IBM SPSS software.

Image:



Results: C3d positive DSAs were present in 49 (42%) cases out of 117 at pre-conditioning. Median follow-up was 40 months (interquartile range = 61 months).Presence of C3d positive DSAs was not predictive of early AMR (p 0.09), although there was a trend towards that. C3d DSA presence correlated significantly with poor overall graft survival ($p = < 0.001$) (Figure). The five-year death censored graft survival was 56% in C3d positive group compared to 86% in C3d negative group.

Conclusion: Presence of pre-transplant complement activating (C3d) DSA strongly predicts renal allograft survival. In our cohort of crossmatch positive cases, survival of renal allograft in C3d negative patients is comparable to HLA non-

sensitised standard living donor transplants. This finding may enable the differentiation of IgG antibodies of varying pathogenicity and the potential role of C3d as additional biomarker in pre-transplant workup. Further sample analysis and mutivariate analysis is in progress to validate this significant finding.

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YELL, M., MUTH, B. L., KAUFMAN, D. B., DJAMALI, A. & ELLIS, T. M. 2015. C1q Binding Activity of De Novo Donor-specific HLA Antibodies in Renal Transplant Recipients With and Without Antibody-mediated Rejection. *Transplantation,* 99**,** 1151-5.

Disclosure of Interest: None Declared

Keywords: Renal transplant, Transplant immunology, Transplant outcome

Transplantation - Outcomes

OR13-012

Risk of allograft thrombosis and Use of Thrombophilia screen in high risk Kidney Transplant Recipients (KTRs) -A Single Centre Experience

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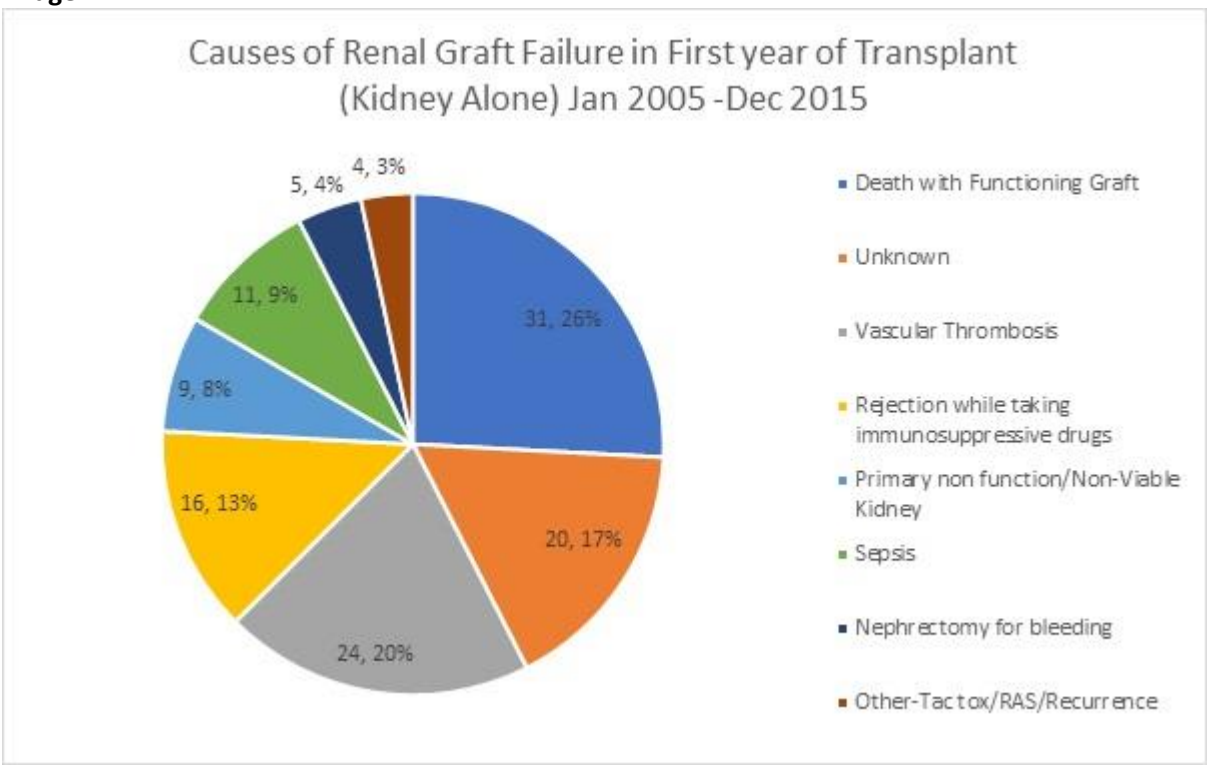
Preferred Presentation Method: Oral or Poster

Introduction: The reported incidence of vascular thrombosis following kidney transplantation leading to graft loss varies between 2-12%[1] . Thrombophilic disorders are one among several factors causing this major morbidity. Hence there is a need for an effective thrombophilic screening strategy in certain high risk Kidney Transplant Recepients (KTRs)

Objectives: To define the role of thrombophilia screening in vascular thrombosis after kidney transplantation and its utility in the pre-transplant work up of high risk KTRs

Methods: This is a retrospective observational, cross - sectional analysis of kidney transplant recipients who lost their graft in first year after transplantation between Jan 2005 and Dec 2015. High risk KTRs were defined as those patients who have had a positive family history or background history of thrombosis. Electronic and case notes were used to collect relevant study data on the recipients.

Image:



Results: Of a total of 2109 Kidney alone transplants over this 11 year period, 120 recipients (5.7%) lost their graft in the first year post-transplant. Of these 120 recipients , 24 (20 %) lost their graft due to vascular thrombosis. Other major

causes of graft loss included death with a functioning graft in 26%, unknown etiology in 17% and rejection in 13% of patients. (Fig-1)

Of the 24 patients with graft loss due to vascular thrombosis, 12 were male and 12 were female with a , median age of 36 (Range 3-64). 5 were paediatric transplants and 19 were in adults. Eleven were live donor transplants and 13 were deceased donor transplants. 3 recipients had a family history of venous thromboses and 2 recipients had previous history of venous thrombosis (recurrent fistula thrombosis/DVT). Graft Renal Vein thrombosis, Renal Artery thrombosis and dual thrombosis were identified in 13/24, 6/24 and 4/24 of the group respectively.

A Thrombophilia screen was done post operatively in 17 patients, as in the remaining 7 there were clear intraoperative causes identified for thrombosis. 6 of the 17 patients had a positive thrombophilia screen. 22 patients had Transplant Nephrectomy. 7 were commenced on warfarin postoperatively .45%(11) were successfully re-transplanted within a median time interval of 1.5 years. Eight of these 11 re-transplants had intravenous heparin anticoagulation perioperatively.

Conclusion: Allograft vascular thrombosis is responsible for 1-2% of total graft loss in our cohort similar to data in literature. The incidence of allograft thrombosis due to pre-existing thrombophilic abnormalities is small. However it would be prudent to consider a thrombophilia screen for all high-risk KTRs during pre-transplant work up,though majority of the patients with vascular thrombosis were found to have negative thrombophillia screening when checked post operatively.

During pre –transplant workup, early referral should be made to Haematology for assessing high risk kidney transplant recipients regarding anticoagulation to prevent allograft thrombosis in the view of equivocal nature of the thrombophilia screening. Further prospective studies evaluating both putative risk factors and intervention strategies are required to determine whether routine clinical screening for thrombophilic factors is justified.

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Disclosure of Interest: None Declared

Keywords: Thrombosis, Transplant outcome

Diagnostic Approaches & Interventions

OR14-001

Diagnostic accuracy of biomarkers and imaging in predicting bone turnover in advanced chronic kidney disease.

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Preferred Presentation Method: Oral

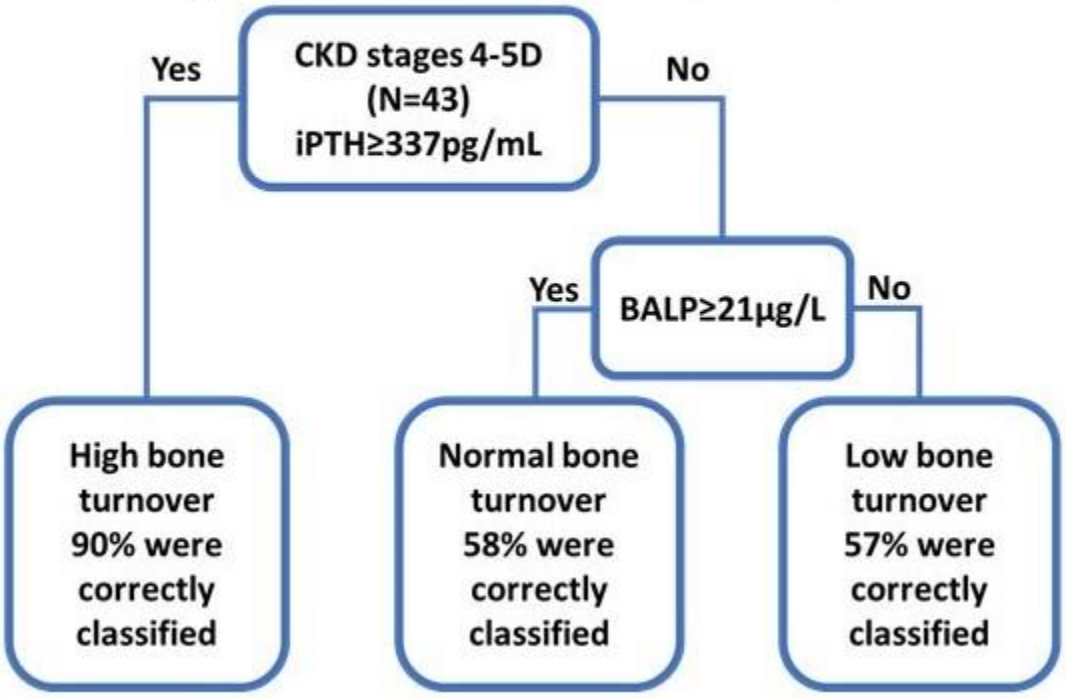
Introduction: Renal osteodystrophy is common in advanced CKD and is associated with increased fracture risk. Potential bone-specific treatment to reduce fracture risk would require characterization of bone turnover status which can only be done with bone biopsy (gold standard test) but this is rarely performed.

Objectives: To simultaneously test the diagnostic accuracy of bone turnover markers (BTMs) and high resolution peripheral quantitative computed tomography (HR-pQCT) to identify chronic kidney disease (CKD) patients' bone turnover as shown on histomorphometry.

Methods: Fasting blood samples were taken from 43 CKD stages 4-5D patients for BTMs analysis (intact parathyroid hormone [iPTH], procollagen type I N-terminal peptide [PINP], bone alkaline phosphatase [BALP], collagen type I cross-linked C-telopeptide [CTX] and tartrate-resistant acid phosphatase 5b [TRAP5b]). HR-pQCT of distal radius and tibia were performed followed by trans-iliac bone biopsy for histomorphometry.

Image:

Figure 1: Classification and Regression Tree (CART) for identifying bone turnover categories in advanced chronic kidney disease patients.



Results: All BTMs were positively correlated with bone turnover (BFR/BS) on histomorphometry (rho= 0.51 to 0.65, p≤0.001). Volumetric bone mineral density (vBMD) and micro-architecture of distal radius were negatively correlated with BFR/BS; rho= -0.35 to -0.45, p<0.05 for total and trabecular vBMD, bone volume fraction and trabecular thickness. In Receiver Operating Characteristic (ROC) analysis for identifying high bone turnover, iPTH had area under the ROC curve (AUC) of 0.76. iPTH >327pg/mL had 90% positive predictive value (PPV) for high bone turnover. In ROC analysis for identifying low bone turnover, BALP had AUC of 0.824 and BALP ≤21µg/L had 96% negative predictive value (NPV) for low bone turnover. In Classification and Regression Tree (CART) analysis using all the BTMs and imaging data, iPTH and BALP correctly identified 90%, 58% and 57% of patients with high, normal and low bone turnover respectively. CART figure is attached.
Conclusion: iPTH and BALP are good diagnostic tests for identifying bone turnover categories in advanced CKD, superior to other BTMs and HR-pQCT.

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Keywords: CKD-MBD, Imaging, Phosphate

Epidemiology & Public Health

OR14-002

The Impact of Cystatin C Based Estimates of GFR on CKD Diagnosis in Primary Care

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Preferred Presentation Method: Oral or Poster

Introduction: National and international guidelines have recommended that cystatin C based estimates of glomerular filtration rate (GFR) should be used to confirm or exclude a diagnosis of chronic kidney disease (CKD) in people with GFR 59-45ml/min/1.73m^{2}and no albuminuria. Whilst there is good evidence for cystatin C being a marker of GFR and risk in people with CKD, its use to define CKD in this manner has not been evaluated in a primary care population.

Objectives: In this analysis, we aimed to evaluate the impact of the use of cystatin C based estimates of GFR in an individually recruited, prospectively studied primary care cohort.

Methods: 1741 people with CKD stage 3 at baseline defined by two measurements of eGFR more than 90 days apart were recruited between 2008 and 2010. 1731 of these had cystatin C measurements taken at baseline. Using CKD epidemiology collaboration estimating equations, creatinine-based ($eGFR_{creat}$), cystatin-based ($eGFR_{cys}$) and combined ($eGFR_{creat\text{-}cys}$) estimating equations were compared both at baseline and over 5 years of follow-up.

Results: $eGFR_{cys}$ reclassified 7.3% of those with CKD stage 3A by $eGFR_{creat}$ as having an eGFR greater than 60 ml/min/1.73m^2. However, a much greater proportion (62.2%) of these were classified to a lower eGFR category. A similar pattern was seen using $eGFR_{creat\text{-}cys}$. Additionally, use of $eGFR_{cys}$ did not improve risk prediction models for CKD progression or all cause mortality. Change in GFR over 5 years, measured using $eGFR_{creat}$ and $eGFR_{cys}$ were weakly correlated. Independent predictors of the difference between $eGFR_{creat}$ and $eGFR_{cys}$ were smoking status, BMI, serum albumin, CRP, uACR and urate.

Conclusion: In this cohort, use of $eGFR_{cys}$ reclassified significant numbers of people as having more advanced CKD than $eGFR_{creat}$, whereas few were reclassified to an eGFR of more than 60 ml/min/1.73m^2. This suggests that use of cystatin C based estimates of GFR according to KDIGO and NICE guidelines may increase the diagnosis of CKD in those with a borderline eGFR, and may increase referral rates to secondary care services.

Disclosure of Interest: None Declared

Keywords: CKD, Cystatin, eGFR

Cardiovascular Disease

OR14-003

Subclinical cytomegalovirus reactivation drives a reversible expansion of cytotoxic endothelial homing T-cells: a novel modifiable cardiovascular disease risk factor in patients with inflammatory renal disease

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Preferred Presentation Method: Oral

Introduction: Cardiovascular disease (CVD) is a leading cause of death in inflammatory renal diseases. Traditional CVD risk factors are not over-represented in such patients. It has been suggested that inflammation and an activated immune system accelerate atherogenesis. Proinflammatory CD4+CD28- T-cells correlate with CVD in chronic kidney disease and systemic lupus erythematosus and with overall mortality in ANCA associated vasculitis (AAV). These T-cells only reach significant levels in individuals with previous exposure to cytomegalovirus (CMV). However, the mechanisms driving expansion of CD4+CD28- T-cells and the potential impact of therapies targeting this process are unknown.

Objectives: We hypothesised that low level subclinical CMV reactivation drives the expansion of CD4+CD28- T-cells, that this leads to vascular damage and that blocking CMV reactivation will prevent vascular injury. Utilising AAV as a model of inflammatory renal disease, we examined CD4+CD28- T-cell phenotype in detail, evaluated their relationship to arterial stiffness and conducted a proof of concept clinical trial.

Methods: We investigated responses to CMV lysate in peripheral blood mononuclear cells from 53 AAV patients and 30 age-matched healthy volunteers (HV) and measured their pulse wave velocity with the Vicorder device. All participants were CMV seropositive. 38 patients from the AAV cohort were randomised 1:1 to 6 months open label valaciclovir (2g QDS; reduced as per eGFR) or no additional treatment (NCT01633476). CMV reactivation (primary outcome) was tested monthly in plasma and urine. Change in CD4+CD28- T-cells (secondary outcome) and PWV were assessed at baseline, 6 and 12 months.

Results: CD4+CD28- T-cells expressed endothelial receptors CX3CR1, CD49d and CD11b and cytotoxic molecules perforin and granzymeB after CMV lysate stimulation. They also secreted IFNγ and TNFα. There was no difference in CD4+CD28- phenotype between AAV and HV, but AAV patients had a higher percentage of CD4+CD28- T-cells (11.3% vs. 6.7, p=0.022). CD4+CD28- T-cell percentage was independently associated with increased PWV in AAV after controlling for age, proteinuria, mean arterial pressure and plasma TNFa (B=0.066 [0.013, 0.119], p=0.016).

In the clinical trial, CMV reactivation was detected in control (21.1%) but not in valaciclovir-treated patients (p=0.037). Suppression of CMV reactivation led to a significant reduction in CD4+CD28- T-cell percentage at 6 months (mean reduction 23% (95% CI 3-39%; p=0.039). This effect persisted 6 months after cessation of treatment. There was no change in the control group. PWV remained stable in treated patients but increased significantly in control patients over the treatment period (p<0.01). All reactivation episodes were asymptomatic. Valaciclovir was well tolerated.

Conclusion: Our data shows for the first time that asymptomatic subclinical CMV reactivation promotes the expansion of cytotoxic, endothelial homing CD4+CD28- T-cells in AAV. Furthermore, these cells are independently associated with arterial stiffness, an established marker of cardiovascular mortality. Treatment with valaciclovir shrinks this T-cell subset and reduces progression of arterial stiffness. These findings implicate CMV infection as a potentially modifiable CVD risk factor in inflammatory renal disease, offering novel therapeutic opportunities.

Disclosure of Interest: None Declared

Keywords: cardiovascular disease, CMV, T cell

Cognitive Disorders

OR14-004

Cognitive function declines significantly over a single haemodialysis session

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Preferred Presentation Method: Oral or Poster

Introduction: Cognitive impairment (CI) is 3 times more common among haemodialysis (HD) patients compared with the general population. Cognitive function is known to decline following commencement of haemodialysis. However, the direct effect of haemodialysis remains unclear.

Objectives: We aimed to assess change in cognitive function during haemodialysis and identify any associated risk factors.

Methods: All patients ≥50 years, on haemodialysis for ≥3 months, and not known to have dementia from 2 dialysis units were selected. Cognitive function was assessed before and after a single haemodialysis session using parallel versions of the Montreal Cognitive Assessment (MOCA) tool and compared using a paired t-test. Multiple regression was used to examine factors associated with change in CI addressing potential confounding.

Results: Of 176 patients, 100 met the inclusion criteria; 82 completed both tests. Median age was 73 years (52–91), 59% male, dialysis vintage 41 months (3– 88). 62 patients (76%) had mild CI at baseline (MOCA score ≤24) with 12 (15%) severe CI (MOCA ≤17). Cognitive function declined significantly over a dialysis session (MOCA score 21±4.8 to 19.1±4.1, $p<0.001$). All domains of cognitive function were affected except visuo-spatial and naming. Age and dialysis vintage were independently associated with decline in cognitive function over a HD session.

Conclusion: Cognitive function declines significantly over a single haemodialysis session which has significant clinical implications for health literacy, self-management and tasks requiring cognition such as driving home after dialysis. More research is needed to find the underlying cause of cognitive decline during haemodialysis.

Disclosure of Interest: None Declared

Keywords: Cognitive function, ESRD, Haemodialysis

Rare Renal Disorders

OR14-005

Renal and Obstetric Outcomes of Pregnant Women with CKD 3-5

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Preferred Presentation Method: Oral or Poster

Introduction: Chronic Kidney Disease (CKD) affects up to 6% of women of childbearing age & women with more advanced CKD are now rarely advised to avoid pregnancy. There are variable data on the effect of pregnancy on CKD, and further study is required to support effective pre-pregnancy counselling, and to help minimise morbidity and mortality to mother and baby.

Objectives: This observational study is the largest to our knowledge to look at both renal & obstetric outcomes in women with CKD 3-5 who became pregnant.

Methods: Women with an MDRD eGFR below 60ml/min/1.73m^2, either prior to pregnancy or by 12 weeks of gestation, from 2 tertiary centres were included. Women already on dialysis or with early fetal loss were excluded. Outcomes analysed included a 25% increase in serum creatinine (SCr), requirement for renal replacement therapy (RRT), gestation at delivery, mode of delivery, estimated blood loss and neonatal requirement for intensive care.

Results: Renal outcomes: 88 women (2003-2012) were identified & followed up for a median 1408 days. 12 had a renal transplant, 3 of whom had pancreas transplants. Median age: 32.2yrs (IQR 29.3, 35.8). Median baseline SCr: 128µmol/l (IQR 113, 149). A 25% increase in SCr was seen in 21% (18/88) & this was in the 3rd trimester in 15 of the 18. Baseline eGFR did not predict those with a 25% rise in SCr during pregnancy. During follow up, 16% (14/88) went on to require RRT (1 during pregnancy) & this was more likely in those with a baseline eGFR <30 ml/min/1.73m^2 (46% *vs* 12%, p=0.013).

Obstetric outcomes: There were live births in 100% of cases. Preterm delivery (<37 weeks) was common (58% (51/87)) & median gestation was lower in women with CKD 3b (35 weeks; IQR 32, 37; n=36; p=0.011) or CKD 4/5 (34 weeks; IQR 33, 37; n=11; p=0.013) than those with CKD 3a (37 weeks; IQR 35, 39; n=41). Mode of delivery (28.8% (23/80) emergency caesarean section, 33.8% (27/80) elective caesarean section, 37.5% (30/80) vaginal delivery) and estimated blood loss at delivery were not affected by baseline renal function. Although neonatal requirement for intensive care was high (49.4% (39/79)), this was also unaffected by baseline eGFR.

Conclusion: Women with CKD 3-5 are at risk of adverse renal and obstetric outcomes, with renal decline most commonly occurring in the 3rd trimester. The worse the renal function at conception the greater the risk of requiring RRT and preterm delivery. Our findings further assist with pre-pregnancy counselling of women with chronic kidney disease and their partners.

Disclosure of Interest: None Declared

Keywords: CKD Progression, Pregnancy

Paediatric Nephrology

OR15-001

Rituximab and plasma exchange does not prevent disease recurrence in high risk FSGS following living donor transplantation

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Preferred Presentation Method: Oral or Poster

Introduction: For patients with end stage renal failure (ESRF) secondary to focal segmental glomerulosclerosis (FSGS), disease recurrence (DR) following renal transplantation (RT) is a significant concern. Patients with rapidly progressive primary disease, negative genetic screening and those with previous graft loss secondary to DR are most at risk. There is no consensus regarding the prevention and management of DR.

Objectives: Does plasma exchange (PE) and rituximab prevent DR in high risk FSGS in living donor RT?

Methods: Four consecutive children (age 6-16years, 2 female) with high risk FSGS, including 2 with previous graft loss due to DR, underwent living donor RT between May 2014 and September 2016. All were managed with a uniform protocol of a single dose of rituximab (375mg/m^2) 4 weeks prior to RT and 4 sessions of plasma exchange (PE) in the week prior to RT. DR was defined as urine protein:creatinine ratio >200mg/mmol on 2 consecutive days.

Results: All children had DR; 3 within the first 4 days and 1 at 30 days following RT. One child with previous graft loss (Pt 1) had immediate DR and received PE for 5 months post-transplant. Another had immediate DR as well as impaired graft function and has had a partial response to PE. Despite intensive PE, the child developed graft failure 6 months following RT. The third child, who had previous graft loss (Pt 3) had DR at day 4 which responded to 5 sessions of PE. The fourth child had DR at 30 days following RT which promptly responded to PE. Apart from the child with graft loss, the remaining 3 patients remain well with good graft function 4-24 months following RT.

Conclusion: In this small cohort of patients with high risk FSGS, rituximab and PE pre-RT, did not prevent DR. However, in 3 of the 4 children with DR, including 2 patients with previous graft loss, the disease responded to PE and all 3 have good graft function. We are encouraged by our data to continue advocating the use of living donors for this difficult group of patients.

Disclosure of Interest: None Declared

Keywords: FSGS, Plasma exchange, Renal transplant

Paediatric Nephrology

OR15-002

A Retrospective Case Series 1996-2014 of Simple Renal Cysts in Children in a tertiary paediatric centre

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Preferred Presentation Method: Oral or Poster

Introduction: Simple renal cysts are uncommon in children, however they are increasingly identified on imaging. They are relatively benign in nature but can progress to develop further cysts or renal complications. There is little data on their natural history leading to inconsistent practice in surveillance and follow up.

Objectives: To describe the natural history of simple renal cysts in children. Secondary objective to describe our follow up frequency and rationalise our service.

Methods: We performed a retrospective case series review of children who have had one or two simple renal cysts identified on ultrasound scan (USS) from 1996-2014 and who had at least one subsequent USS. Exclusion criteria included; Multicystic dysplastic kidneys, history of autosomal dominant polycystic kidney disease (ADPKD), cystic dysplastic kidneys, more than two cysts, hydronephrosis, tuberous sclerosis, kidney transplant. Cases were identified through electronic records. USS reports were manually read. Data extracted included demographics, number and location of cysts and morphology. Local ethical approval was granted.

Results: 88 patients had two or more USS. Male: Female 35:53 (39.8%:60.2%). Median age at first USS 8 years (range 10 days-21 years). 16 patients (18%) had only 2 USS. 79 patients (89.8%) presented with 1 cyst, 9 patients (10.2%) with 2 cysts. Overall follow up (time between first and last USS) median 2.6 years (36 days-11.8 years).

Cysts resolved (definition; not seen on 2 sequential USS) in 10 patients (11.4%). A further 10 patients (11.4%) had no cyst on 1 follow up USS, but had no subsequent scans to confirm resolution.

10 patients (11.4%) developed further cysts, median time 3.2 years (range 35-days-5years). Two patients (0.2%) were subsequently diagnosed to have ADPKD. 1 patient developed liver cysts.

9 patients (10%) developed new morphological changes; 7 septations, 1 haemorrhage, 1 complex. Median time 1.5 years (range 50 days to 4.8 years). 3 patients developed calcification, median time 1.3 years (range 1-1.3 years).

2 patients (2%) developed hypertension, follow up 2.6-5.6 years. 23 patients (26.1%) had albumin creatinine ratio (ACR) performed. Median ACR 3.25mg/mmol (range 0.3-118.5). 4 patients (4%) had ACR >30mg/mmol, median time 4.6 years (range 9 months-7.5 years). No patients had an elevated serum creatinine.

Conclusion: Simple renal cysts in children spontaneously resolve in 10 – 20% of cases. However a significant proportion of patients develop further cysts, morphological changes, hypertension and proteinuria. In total 25 patients (28.4%) developed one or more complications. The majority of these complications were detected by 5 years of follow up. Children with simple renal cysts should have at least 3 ultrasound scans and be followed for 5 years.

Disclosure of Interest: None Declared

Keywords: Children, Cystic kidney disease

Patient Education, Involvement and Experience

OR15-003

Improvement of patient and parent / carer experience through high quality information: Results of the infoKID evaluation

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Preferred Presentation Method: Oral

Introduction: In March 2014, the infoKID website was launched providing quality-assured, evidence-based information for parents and carers of children with kidney conditions. Two years on, we undertook an evaluation of the resource to understand the potential for improving patient and family experience and opportunities for further development.

Objectives: Our objectives for the evaluation were to:

1. Review current website trends
2. Develop and promote surveys for patients, parents / carers (PPC) and health care professionals (HCP) to understand how the resource is signposted by HCP and used by both HCP and PPC

Methods: We used Google Analytics to assess sessions on the infoKID website in the UK and worldwide. We held focus groups and clinic chats with 53 families and gathered feedback from HCP to pilot and develop two questionnaires, which were made available online in October 2016.

Results: Between March 2014 and October 2016 there were 178,469 infoKID website visits, with a month-by-month increase worldwide (March 2014: 1771 visits; October 2016: 8764 visits). During October 2016 online surveys made available on the site were undertaken by 79 PPC and 80 HCP. Only 40% of PPC reported being familiar with the infoKID site, compared with 98% of HCP. The majority (86%) of PPC familiar with the site reported preferred times of accessing information at diagnosis and with changes in the condition. PPC familiar with the site reported that the information was easy to understand (93%), trustworthy (100%), increased their knowledge of kidney conditions (90%) and reduced concerns (55%). The majority (90%) of HCP reported signposting families to infoKID, either verbally in clinic (89%), through real-time demonstration of site (40%) and / or by including a link to the site on clinic letters (50%). Interestingly only 5% of PPC reported being made aware of the resource by clinic letters. 54% of HCPs reported that infoKID is a recommended resource for teaching and training within their Trust. Areas for development reported by both PPC and HCP included expanding the library of conditions and including patient stories and social forum.

Conclusion: Improved knowledge and reduced concerns reported by PPC indicate that infoKID has the potential to improve patient experience. HCP should be aware that optimal timing to signpost families to high quality information appears to be at the time of diagnosis or change in the condition.

Disclosure of Interest: None Declared

Keywords: Clinical quality improvement

CKD: Fibrosis and Extracellular Matrix CKD

OR2-001

Urinary endotrophin is associated with CKD progression at 12 months: a prospective observational study

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Preferred Presentation Method: Oral or Poster

Introduction: Progressive fibrosis is the major pathophysiological process in chronic kidney disease (CKD). However, there is little direct information on the relationship between active fibrosis and CKD progression in humans. Collagen type VI (Col6) is a major component of renal fibrosis; endotrophin, which is cleaved during the maturation of Col6, is a dynamic marker of Col6 expression.
Objectives: We tested the hypothesis that urinary endotrophin is associated with clinically relevant progression of CKD.
Methods: We utilised a recently-developed ELISA to measure urinary endotrophin levels in 416 patients enrolled into a prospective observational study of patients with high-risk CKD. Patients were followed up for 12 months, and progression was defined as either commencement of renal replacement therapy or a decline of eGFR ≥ 30%. Urine endotrophin:creatinine ratio (ECR) was calculated and analysed by quartiles. The association between urine ECR and progression was examined by logistic regression, including multivariable analyses controlling for confounding factors. Estimates of association are expressed as odds ratios with 95% confidence intervals.
Results: The cohort was 62% male, with a median age of 64 years, and a median baseline eGFR of 27 mL/min/1.73 m^2 (IQR 19-35). By 12 months, 46 (11%) of 416 patients had progressed. Compared to the lowest quartile, the third and fourth quartiles of urine ECR were significantly associated with an increased risk of CKD progression (Q3: 6.36 [1.88, 21.44], *P*=0.003; Q4: 20.94 [6.66, 65.90], *P*<0.0001), and remained significant in a model adjusted for eGFR, ACR, and mean arterial blood pressure (Q3: 3.62 [1.03, 12.74], *P*=0.044; Q4: 8.96 [2.51, 31.96], *P*=0.0007).
Conclusion: Urinary ECR was independently associated with risk of CKD progression at one year, and may provide a dynamic marker of renal fibrosis that can identify patients at highest risk from CKD. This study provides the basis for further work, which may include validation in an independent CKD cohort, and utilising early changes in ECR to indicate the potential efficacy of anti-fibrotic therapies in CKD.

Disclosure of Interest: None Declared

Keywords: CKD, CKD Progression, Fibrosis

CKD: Fibrosis and Extracellular Matrix CKD

OR2-002

Multiparametric Magnetic Resonance Imaging Assessment of Chronic Kidney Disease

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Preferred Presentation Method: Oral or Poster

Introduction: Progression of Chronic Kidney Disease (CKD) occurs as a result of a common pathway of mechanisms of inflammation and fibrosis that may be independent of the underlying aetiology.

In current clinical practice, assessment of renal parenchymal damage is confined to renal biopsy, which is limited by sampling error and is associated with patient risk. Recent advances in Magnetic Resonance Imaging (MRI) allow assessment of structural and functional changes relevant to kidney disease.

Objectives: We performed a multiparametric MRI study to assess its utility and reproducibility in patients with CKD.

Methods: 21 people were studied, 14 patients with CKD Stage 3-4 who had renal biopsies performed as part of routine clinical care, seven healthy volunteers (HVs) as a comparator group. Patients and HVs had two multiparametric renal MRI scans performed 7-14 days apart. Biochemical and clinical parameters were collected at the first scan.

MRI scans were performed on a 3T Philips Ingenia scanner. Structural assessment included kidney volume, longitudinal relaxation time (T_1) mapping and diffusion weight imaging (DWI) to compute apparent diffusion coefficient (ADC) as markers of fibrosis and/or inflammation. Functional assessments were Arterial Spin Labelling (ASL) to measure renal perfusion, phase contrast to measure blood flow in the renal artery and Blood Oxygenation Level Dependent (BOLD) Imaging as a measure of renal oxygenation. Coefficient of variance (CV) was calculated for each MRI measure between the two scans.

Results: CKD patients had a mean age of 57±18yrs, ten were male, mean baseline estimated Glomerular Filtration Rate (eGFR) was 39±13mls/minute/1.73m^3 and mean urine Protein Creatinine Ratio (PCR) was 59±64mg/mmol. Biopsy results showed six patients had ischaemic nephropathy, four had tubulointerstial disease and four had IgA nephropathy. HVs had a mean age 35±15yrs, six were male and all subjects had an eGFR>60mls/minute/1.73m^3 and urine PCR <15mg/mmol.

CKD patients had higher T_1 and lower ADC values than HVs indicating the presence of more fibrosis/inflammation. CKD cortical and medullary T_1 values were 1587±79ms and 1765±70ms respectively compared to HVs of 1410±85 and 1677±78 ($p<0.001$) respectively. ADC values were lower in CKD patients at 2.05±0.34(μm^2/ms) versus 2.29±0.09(μm^2/ms) in HVs ($p=0.01$). Renal perfusion (ASL) was lower in CKD patients, 146±36ml/100g/min versus 222±79ml/100g/min ($p=0.003$). There were no differences in renal volumes and T_2* (BOLD) between groups. No single MR measure correlated with CKD patient eGFR.

Reproducibility was excellent for cortical and medullary T_1 (CV=2.65% and 1.98% respectively), T_2*(CV=2.58%), ADC (CV=8.16%) and renal volume (CV=2.98%).

Conclusion: This study demonstrates that mutiparameteric MRI differentiates between HVs and CKD patients, and is reproducible. The MR results reflect the known pathophysiological changes expected in CKD; reduced perfusion and the presence of fibrosis and/or inflammation, but interestingly did not demonstrate a difference in T_2* a potential marker of renal hypoxia. In future work, we plan to correlate histology findings on renal biopsy with MR measures and investigate methods of differentiating between fibrosis and inflammation using MRI.

Further studies are required to build on this initial work to determine how best multiparametric MRI can be used to assess whole kidney pathology and prognosis.

Disclosure of Interest: None Declared

Keywords: None

CKD: Fibrosis and Extracellular Matrix CKD

OR3-001

Gdf11 is induced in the murine and human kidney in response to injury, with experimental administration worsening fibrosis after unilateral ureteric obstruction.

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Preferred Presentation Method: Oral

Introduction: Gdf11 supplementation has been reported to improve organ function and repair in the brains, hearts, muscle and acutely injured kidneys of aged mice, but the effects of its longer term supplementation on aged and fibrotic kidneys remains unknown.

Objectives: We tested the hypothesis that gdf11 supplementation would increase proliferation and oppose fibrosis in aged mice following unilateral ureteric obstruction (UUO)

Methods: UUO surgery was performed in Boston, USA and Edinburgh, UK. RNA extracted from UUO kidneys were analysed by RNA sequencing (Genewiz UK, 2x100bp, paired end reads, n=4/gp). Human recombinant gdf11(Peprotech, Boston) supplementation on epithelial phenotype was tested in human proximal tubular epithelial cells (cell name) *in vitro*. The effect of human gdf11 on aged kidneys was assessed by dosing 20-24 month old male mice 0.25mg/kg gdf11 or vehicle alone daily for 28 days. The effect of human gdf11 on renal fibrosis was assessed by dosing with 0.25mg/kg or 0.5mg/kg daily for 4 days pre-UUO and 7 days post UUO. Experimental readout included staining and western blotting for alpha-SMA (myofibroblasts), collagen I, CD31 (endothelial cells) and p16ink4a (senescence). Publically available microarray datasets were interrogated for data of renal gdf11 transcript levels in human aging and chronic kidney disease using www.nephroseq.org.

Results: Published human renal biopsy microarray datasets demonstrated no alteration in renal gdf11 transcript levels in the human kidney with age ($p=0.96$ for trend with age), but showed that gdf11 increases significantly in human kidneys with CKD ($p<0.0001$ vs control kidney). RNAseq studies of murine UUO (with validation by qPCR) showed that gdf11 was markedly upregulated after UUO (>2 fold increase; $p<0.0001$ UUO vs control).

In vitro studies demonstrated that gdf11 treatment both *in vitro* and *in vivo* resulted in upregulation of the TGF signalling pathway mediator pSMAD3 compared to vehicle treatment (both >10x fold induction, $p<0.05$). Treatment with gdf11 in vitro also induced markers of mesenchymal transdifferentiation in RPTECs, with significantly reduced E-cadherin, aquaporin-1 and increased N-cadherin (all $p<0.05$ vs control).

Sustained 28d treatment with gdf11 to aged mice had no impact on levels of myofibroblasts or vascularity compared to vehicle treatment (both p=ns), although levels of p16ink4a were significantly reduced ($p<0.05$ vs control).

In experimental UUO, treatment with 0.25mg/kg and 0.5mg/kg gdf11 resulted in significantly more alpha-SMA expression (74% increase vs vehicle, $p=0.01$) and Collagen I deposition at d7 post UUO (31% increase, $p=0.008$), with the high dose also resulting in 75% mortality in gdf11 treated animals. Gdf11 treated animals had less cell cycle activity, less p16ink4a+ve senescent cells and less apoptotic cells visible on staining (all $p<0.05$ vs vehicle).

Conclusion: Contrary to the beneficial effects observed in other organs, and the single report of beneficial short term gdf11 treatment in AKI, we observed no evidence of gdf11 supplementation protecting the aged kidney at baseline or in reducing fibrosis after UUO. Our results show that gdf11 promotes the G0 cell cycle state and supplementation appears to be profibrotic after injury, suggesting that increases in gdf11 transcript seen in human and murine kidneys with CKD may be of pathogenic significance. Gdf11 may not be beneficial, indeed antagonism of gdf11 merits study as an anti-fibrotic therapy. in renal disease.

Disclosure of Interest: None Declared

Keywords: Fibroblast, Fibrosis

Acute Kidney Injury

OR3-002

URINARY TRACE ELEMENTS AS NOVEL BIOMARKERS OF ISCHAEMIC ACUTE KIDNEY INJURY: DATA FROM A PORCINE MODEL

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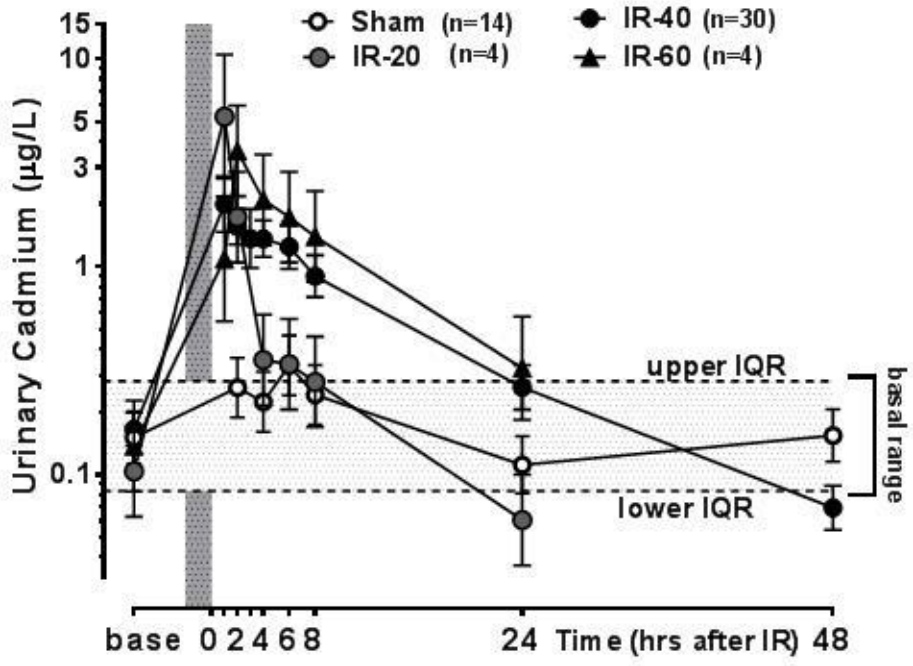
Preferred Presentation Method: Oral

Introduction: Introduction: Acute Kidney Injury (AKI) is a rapid deterioration in kidney function over hours or days. AKI is often preventable or treatable with simple measures if patients at risk are identified early. Current, commercially available, serum or urinary biomarkers for AKI may identify those at-risk earlier than serum creatinine (i.e. 6h rather than 24-48h) but an 'ideal' should be even earlier detection. Here, we present evidence from a porcine model to suggest urinary trace elements as excellent histopathological biomarkers of AKI.

Objectives: Objectives: To determine urinary trace elements before and after induction of ischaemic AKI in a porcine model.

Methods: Methods: Female pigs (n=30; 50-70 kg) were randomized to an ischemic AKI protocol (20 to 60 mins bilateral renal artery clamping) or sham-control group (n=14) and blood and urine sampled at intervals (from as early as 30mins to 48h, post-injury).

Image:



Results: Results: Three minerals (total elemental cadmium, copper, iron) consistently and reproducibly increased in urine (x2-10 fold increase above baseline, stratifying with duration of ischaemia) within an hour of ischaemic kidney damage (e.g. cadmium from a baseline of 0.14 [0.07-0.28] to 5.18 [2.33-7.17] µg/L at 30mins; median [IQR]). Area-

under-the-Receiver-Operator-Curve (AUROC) suggest cadmium and copper to be very good early biomarkers (AUROC, >0.80, all cases). Diagnostic criteria for urinary cadmium at 24h post-injury and at a cut-off of 0.26 µg/L are: sensitivity, 95%; specificity, 72%; positive predictive value, 90%; negative predictive value, 84%.
Conclusion: Conclusion: We report for the first time a new paradigm for early diagnosis of AKI – measurement of specific minerals in urine. Cadmium and copper have many advantages as potential biomarkers of AKI: they are sensitive, specific and stable at room temperature – qualities beneficial to biomarker development. Validation in multiple clinical settings is in progress and preliminary evidence is positive.

Disclosure of Interest: None Declared

Keywords: AKI, Animal model

Epidemiology & Public Health

OR4-001

Stroke in Haemodialysis (HD): Using National Datasets to determine incidence, Risk factors & Outcomes

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Preferred Presentation Method: Oral or Poster

Introduction: Stroke is up to 10 times more common in those on HD for end-stage renal failure (ESRF) compared to general population. It is unclear whether risk factors for stroke are the same or whether there are ESRF specific risk factors.

Objectives:

Using data from the Scottish Renal Registry (SRR) & Scottish Stroke Care Audit (SSCA) we assessed for variation between those with and without ESRF.

Using data from the Scottish Renal Registry (SRR), the Scottish Stroke Care Audit (SSCA), the Scottish deaths registrar and the Scottish discharge diagnosis dataset (SMR01) we sought to determine risk factors significantly associated with stroke in ESRF.

Methods: Patients were included in the study if they were receiving HD for ESRF at 01/01/05 or began HD during the follow-up window (01/01/05–31/12/13). We identified all first occurrences of fatal or non-fatal stroke during follow-up. Details on dialysis treatments were taken from the SRR. Follow-up was censored at stroke, death, cessation of HD or end of study. We used multi-variable survival analysis to identify independent risk factors for stroke, first for occurrence of any stroke, second for ischaemic stroke and third for first ever stroke. We adjusted for age, sex, duration of RRT, prior history of atrial fibrillation (AF), stroke, diabetes, cardiovascular disease, pre-dialysis SBP, pre-dialysis weight, haemoglobin and serum phosphate.

Results: 5531 patients were included with 13,645 cumulative patient-years of follow-up. 363 (6.6%) suffered at least one stroke during this period and stroke incidence rate was 26.6/1000 patient-years. There were 200 ischaemic, 45 haemorrhagic & 118 where the stroke subtype was not specified. Fatality at 7, 28 & 365 days after stroke was 22.6, 34.7 & 61.7%, respectively. In comparison to patients with no stroke, those with stroke were older (69.9 vs 64.7 years, $p<0.0001$), had more diabetic nephropathy (27 vs 21%, $p=0.0081$), AF (12.4% vs 7.4%, $p=0.0015$), prior stroke (9.9 vs 3.8%, $p<0.0001$), hypercholesterolemia (18.2% vs 13.2%, $p=0.0087$), higher median systolic BP (142 vs 138mmHg, $p=0.0011$), lower weight (70.3 vs 72.7kg, $p=0.0048$) & higher serum phosphate (1.61 vs 1.51, $p=0.0002$). In all survival models age (HR 1.002, 95% CI 1.001, 1.003), prior AF [HR 2.51, 95% CI 1.66, 3.80], median phosphate [HR 1.87, 95% CI 1.4, 2.5] and body weight [HR 0.98, 95% CI 0.97, 0.99] ($p<0.0001$) were associated with occurrence of stroke.

Conclusion: In those with ESRF on haemodialysis stroke rate is high with high case fatality. Traditional stroke risk factors were associated with stroke in this population in addition to higher serum phosphate & lower body weight. Studies examining effects of modifying these risk factors are urgently required.

Disclosure of Interest: None Declared

Keywords: Cardiovascular Disease, Epidemiology

Cardiovascular Disease

OR4-002

In-center nocturnal haemodialysis is associated with favourable cardiac remodeling and reduced levels of myocardial fibrosis: Results from the MIDNIGHT study, a non-randomised controlled trial

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Preferred Presentation Method: Oral

Introduction: There is increasing evidence that extended hours haemodialysis (HD) is associated with improved cardiovascular outcomes. In-center nocturnal haemodialysis (INHD) is an established, though often unavailable, way of offering extended hours HD to patients.

Objectives: To assess the effects of a 6 month program of INHD on cardiac structure and function in prevalent HD patients compared to matched controls on conventional hemodialysis (CD).

Methods: This prospective, non-randomized controlled trial recruited 13 prevalent HD patients who switched to INHD (up to 8 hours HD overnight thrice weekly) and 12 matched control subjects who remained on CD (4 hours thrice weekly). Changes in cardiac structure and function were assessed using multi-parametric cardiac magnetic resonance imaging (CMR) at baseline and after 6 months. CMR outcome measures included left ventricular (LV) mass and volumes, myocardial fibrosis assessed by native T1 mapping, global longitudinal strain (GLS), global circumferential strain (GCS) and aortic stiffness assessed by aortic pulse-wave velocity (aPWV).

Results: Mean age of patients (n=25) was 56 years, 84% male. Nine CD patients and eight INHD patients completed baseline and follow-up CMR scans. There was a significant reduction in LV mass in the INHD group compared to the CD group over six months (mean difference; INHD= -14.75g [CI: -29.62–0.12], CHD= 6.54 g [CI: -7.48–20.57], P=0.02), with a significant improvement in LV mass/LV end-diastolic volume in the INHD group compared to CD group (mean difference; INHD= -0.07g/ml [CI: -0.15–0], CHD= 0.06g/ml [CI: -0.01–0.13], P=0.01), and no change in LV end-diastolic volume. There was a significant reduction in global native T1 in the INHD group compared to the CD group (mean difference; INHD= -30.62ms [95% CI: -56.49, 4.75], CHD=0.4ms [95% CI: -25.47, 26.27], P=0.05) and non-septal native T1 values (mean difference; INHD= -30.93ms [95% CI: -58.44, -3.41], CHD=8.96ms [95% CI: -18.56, 36.47], P=0.02). There were non-significant improvements in ejection fraction, GLS, GCS and aPWV in the INHD group compared to the CD gourp. Reduction in LV Mass correlated significantly with reduction in native T1 ((r=0.526, P=0.03).

Conclusion: A six-month program of extended hours INHD is associated with a reduction in LV mass, favourable LV remodelling and reductions in myocardial fibrosis measured with native T1 mapping compared to control patients on thrice weekly, 4-hour HD. These data merit testing in future larger trials of INHD.

Disclosure of Interest: None Declared

Keywords: Cardiovascular Disease, Clinical trial, Haemodialysis

Haemodialysis

OR4-003

Associations between haemodialysis facility practices related to fluid volume management and intra-dialytic hypotension and adverse outcomes in the DOPPS

I. Dasgupta [1,*], G. N. Thomas [2], J. Clarke [2], A. Sitch [2], A. Karaboyas [3], B. Bieber [3], M. Hecking [4], R. Pisoni [3], F. Port [3], B. Robinson [3], H. Rayner [1]

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Preferred Presentation Method: Oral or Poster

Introduction: Fluid overload is associated with morbidity and mortality in haemodialysis (HD) patients. Intra-dialytic hypotension (IDH) is also associated with cardiovascular (CV) mortality and events.

Objectives: To investigate associations between HD facility practices related to the management of fluid volume and hypotension and adverse events.

Methods: Data on 10250 patients, from 269 facilities across 12 countries from DOPPS phase 4 (2009-12) were analysed. Cox proportional hazards models were used to estimate associations between facility practices reported by Medical Directors and patient outcomes (all-cause mortality, CV mortality, CV events, time to first inpatient hospitalisation) adjusting for country**,** age, gender, dialysis vintage, pre-dialysis systolic BP, CV comorbidities, diabetes, BMI, smoking, residual renal function, Kt/V, and vascular access. We tested 10 practices in separate models for each practice and outcome (n=40): (1) protocol for fluid volume management, (2) routine clinical assessment of fluid status, (3) blood volume monitor (BVM), (4) bio-impedance device (BID), (5) BVM and BID, (6) limit to fluid removal, (7) isolated ultrafiltration and use of (8) a protocol, (9) routine sodium profiling and (10) low dialysate temperature for managing IDH. Multiple imputation was used for missing data. Due to multiple variable testing, 99% confidence interval (CI) was used to determine significance.

Results: Having a specific protocol for fluid management in the dialysis facility was associated with lower all-cause deaths (HR: 0.79, 99%CI 0.65-0.96) and CV deaths (HR: 0.73, 99%CI 0.56-0.95). Routine clinical assessment of fluid status was associated with lower time to first inpatient hospitalisation (HR: 0.86, 99%CI 0.76-0.97) and CV events (HR: 0.85, 99%CI 0.73-0.98). The use of low temperature dialysate to limit or prevent IDH was associated with lower CV deaths (HR: 0.76, 99% CI 0.59-0.98). On the other hand, the use of sodium profiling for IDH was associated with higher CV events (HR: 1.22, 99%CI 1.03-1.44), CV deaths (HR: 1.37, 99%CI 1.06-1.75) and all-cause deaths (HR: 1.35, 99%CI 1.14-1.61).

Conclusion: The HD facility practices relating to fluid volume management and IDH are significantly associated with patient outcomes. These merit further investigations in randomised trials.

Disclosure of Interest: None Declared

Keywords: Cardiovascular Disease, Haemodialysis

Rehabilitation & Exercise

OR5-001

The effects a of 12-week supervised aerobic or combined exercise programme on muscle size, strength, and physical performance in non-dialysis CKD patients.

D. W. Gould [1,*], E. L. Watson [1], S. Xenophontos [1], T. J. Wilkinson [1], J. L. Viana [2], A. C. Smith [1]

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Preferred Presentation Method: Oral or Poster

Introduction: Skeletal muscle wasting is common amongst patients with CKD and associates with reduced physical performance and mortality. Resistance training can increase muscle size, strength, and physical performance. On the other hand, aerobic exercise has proven cardiovascular benefits, but its effect on muscle mass are equivocal. Current exercise recommendations suggest performing both exercise modes concurrently in the same session; however supporting data is scarce and it is unknown if the contrasting modes will compromise the individual benefits when combined.

Objectives: This randomised trial investigated the effects of 12-weeks aerobic (AE) or combined exercise (CE) on muscle size, strength, and physical performance in non-dialysis CKD patients.

Methods: Following a 6-week control period of normal activity, 36 patients (eGFR 25.7 ml/min/1.73m^2 [range 9-41]; age 59.6yrs [range 27-80]) were randomised to AE (3x/week at 70-80% VO_{2peak}; n=16) or CE (3x/week as AE + lower limb resistance exercise at 70% 1 repetition maximum; n=16). Measurement of rectus femoris cross-sectional area (RF-CSA), knee extensor muscle strength (1-RM), and exercise capacity by incremental shuttle walking test (ISWT) were performed before and after the 6-week control period, and again following 12-weeks exercise. Control data was analysed separately as this was prior to randomisation. Exercise data was analysed using paired samples t-tests to determine the separate effects of each intervention. The magnitude of change was calculated for each variable and linear regression used to determine differences between groups.

Results: No changes were seen for any variable following the control period. Following 12-weeks of exercise, both groups showed improvements in muscle strength (AE 9kg p=.001 & CE 22kg p=<.001) and physical performance (AE 27m p=.016 & CE 32m p=.010). The increase in muscle strength following CE was greater than following AE (p=.002), but there was no difference between groups for improvement in ISWT. RF-CSA increased by ~10% (p<.001) following CE compared to ~5% (p=.126) following AE. The magnitude of change was not different between groups (p=.213).

Conclusion: Both exercise programmes led to improvements in physical performance and muscle strength. The improvement in strength and muscle size was greater in those performing CE compared to the AE group. This study suggests that exercise modes can be combined in the same session without interference, and that CE should be recommended over AE alone for improving muscle size and strength.

Disclosure of Interest: None Declared

Keywords: CKD, Exercise, Physical function

Epidemiology & Public Health

OR5-002

Coding for Chronic Kidney Disease: risk factors, audit-related improvement, and patient management. Results from the National Chronic Kidney Disease Audit

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Preferred Presentation Method: Oral or Poster

Introduction: Using data from the UK National Chronic Kidney Disease Audit, we set out to explore risk factors for coding and coding improvement, and the relationship between coding and patient management.

Objectives: Study objectives were to investigate (i) risk factors for coding chronic kidney disease (CKD) in patients with biochemical evidence of CKD stage 3-5 in primary care, (ii) factors associated with coding improvement following initial audit and provision of quality improvement tools, and (iii) the relationship between coding status and receipt of four key indicators of primary care CKD management.

Methods: We used logistic generalised estimating equation modelling with practice-level clustering to investigate factors associated with coding and coding improvement. Proportions of patients (i) achieving blood pressure targets in the past year, (ii) being offered statins, (iii) receiving proteinuria testing in the past year, (iv) receiving flu vaccination in the past year, and (v) pneumococcus vaccination in the past five years are reported for those with a CKD stage 3-5 read code, those with a renal disorder code but no CKD stage 3-5 read code, and those without a renal disorder code or a CKD stage 3-5 read code.

Table:

	Coded CKD	**Uncoded CKD with renal disorder code**	**Uncoded CKD without renal disorder code**
Met blood pressure target in past year*	51.5%	41.7%	45.6%
ACR/PCR test in past year	49.4%	31.5%	14.3%
Flu vaccination in past year	78.9%	70.6%	64.8%
Pneumococcus vaccination in past 5 years	13.7%	13.0%	11.8%

Results: Amongst 277,922 patients with eGFR evidence of CKD stage 3-5 in the NCKDA, 34% were not coded with a CKD stage 3-5 read code. Following the initial audit and access to practice quality improvement tools, 8% of those with uncoded CKD were subsequently allocated CKD codes at follow-up. We found that older patients, those with more severe CKD stage, males, those in England (versus Wales), those offered statins, with diabetes and with hypertension all had higher odds of having a code for CKD. There was no evidence that social deprivation was associated with coding. Furthermore, these same characteristics were also associated with coding improvement following audit.

We found marked reductions in the proportion of patients with these management indicators in those with uncoded versus coded stage 3-5 CKD, and further reductions amongst those with uncoded CKD who had no renal disorder code (see Table).

Conclusion: Coding of CKD is associated with patient characteristics, including age and major CKD risk factors. In turn, coding is positively associated with clinical management of CKD; higher proportions of patients with coded CKD or a renal disorder code achieve recommended interventions. More work is needed to further characterise those with uncoded CKD and to explore outcomes for these patients.

Disclosure of Interest: None Declared

Keywords: CKD

Glomerular Pathobiology

OR6-001

PLA2R positive Membranous Nephropathy associated with viral infection

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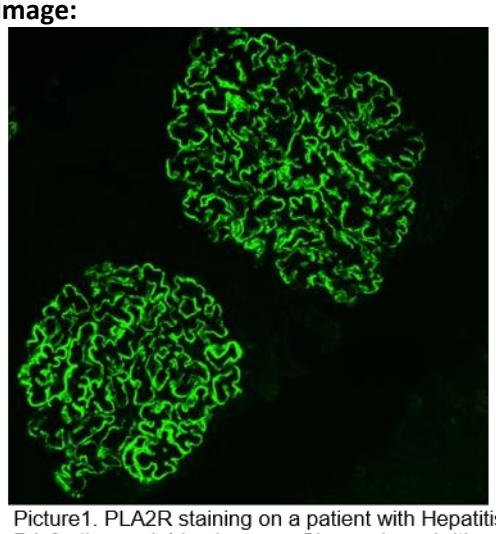
Preferred Presentation Method: Oral or Poster

Introduction: Membranous Nephropathy (MN) can be associated with hepatitis infection and less commonly with HIV infection. The significance of anti-phospholipase A2 receptor (PLA2R) antibodies in this setting is not known.

Objectives: The objective of this study was to investigate the role of anti-PLA2R antibodies in patients with hepatitis B, C or HIV infection and correlate findings to viral activity and clinical outcomes.

Methods: A retrospective study of biopsy proven MN from January 2006 to January 2015 was undertaken. A total of 11 patients with MN and Hepatitis B (HBV), C (HCV) or HIV infection were identified. Biopsies were stained for PLA2R and clinical information was reviewed.

Image:



Picture1. PLA2R staining on a patient with Hepatitis B infection and Membranous Glomerulonephritis

Results: The cohort consisted of 11 patients, 4 women and 7 men with a median age of 41 years (range 23 to 68).

HIV was detected in 5 patients, HBV in 4 and HCV in 3 (one patient HIV/HBV coinfection).

PLA2R staining was positive in 6 biopsies: 1 HIV, 2 HBV, 3 HCV (picture 1). Circulating anti-PLA2R antibodies were detected in 3 of these patients at the time of biopsy. Viral load was undetectable at the time of biopsy in all but one patient with HBV.

In the PLA2R negative group 3 patients had HIV, 1 HBV and one HIV/HBV coinfection. Viral load was detectable in one patient with HBV and one with HIV.

Mean proteinuria was higher in the PLA2R positive compared to the PLA2R negative group (uPCR= 801.6 vs 374.4mg/mmol) although this was not statistically significant.

Electron microscopy in both groups showed subepithelial, subendothelial and mesangial electron dense deposits (EDD). EDDs of all stages were present but stage II were the more frequent.

Tubuloreticular inclusion bodies (TRI) were seen in 2 patients with interferon treated HCV in the PLA2R positive group; no TRIS were seen in the PLA2R negative group.

Follow up was available for 10 patients. At 24 months 9 had preserved renal function. One PLA2R and HCV positive progressed to ESRD. One patient with PLA2R positive MN and HIV went into spontaneous partial remission, others received tacrolimus (n=7), rituximab (n=2) or cyclophosphamide with high dose steroids (n=1).

Conclusion: PLA2R positivity can be found in MN associated with hepatitis infection and we describe a rare case of PLA2R positive MN and HIV. It is possible that the viral infection triggers the immunological activity leading to the anti-PLA2R antibody response. MN can present even when infection is controlled and viral load undetectable.

Disclosure of Interest: None Declared

Keywords: Glomerulonephritis, Hep B, Membranous

Glomerular Pathobiology

OR6-002

The RituxiRescue regimen (Rituximab, Mycophenolate Mofetil & no increase in oral steroids) for lupus nephritis leads to sustained disease remission over years and steroid minimisation in patients on maintenance steroids at the time of renal flare.

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Preferred Presentation Method: Oral or Poster

Introduction: Due to their side effect profile minimising the dose and duration of steroid exposure is a goal in the treatment of lupus nephritis (LN). We have shown that the RituxiRescue regimen (2 x 1g of rituximab ± 125-500mg methylprednisolone on days 1 & 15, maintenance mycophenolate mofetil but **no increase** in baseline steroids) led to good remission rates and steroid reduction at 1 year in 18 patients with active LN (Pepper et al. NDT, 2009). We report outcomes for a larger patient cohort followed to 5 years.

Objectives: To demonstrate that the RituxiRescue regimen leads to sustained renal remission and steroid sparing over 5 years in patients on maintenance oral steroids with active LN.

Methods: Retrospective analysis of 38 patients with active class III, IV or V LN, on steroids for ≥ 4 weeks & treated with the RituxiRescue regimen since Dec 2005 with 5 years of f/up by Mar 2016. **Remission:** Complete (CR): uPCR ≤ 50, eGFR ≥ 60 or ↓ ≤ 20% if < 60 at baseline. Partial (PR): ↓ in uPCR < 50% + eGFR ≤ 20% from baseline (if not nephrotic) + uPCR < 300 (if nephrotic). **Relapse (from CR/PR):** uPCR > 100 + ≥ 50% from CR/PR ± eGFR ↓ ≤ 20% from baseline.

Table:

Table 1	**Baseline n=38**	**1 yr n=37 (%)**	**5 yrs n=33 (%)**	**Median time to event** (months)
CR/PR		23 (62.2)	30 (90.9)	CR: 8.3 (4.4-22.9) PR: 8.0 (1.1-14.6)
1st relapse from CR/PR		3 (8.1)	5 (15.2)	18.5 (10.4-28.0)
Mean steroid dose (mg)	14.9	7.4	3.1	
No. off oral steroids		7/37 (18.9)	15/33 (45.5)	18.2 (10.7-43.0)

Results: 5 patients lost to f/up by 5 years. High proportions achieved CR/PR at 1 & 5 years with low rates of renal relapse (Table 1). 1 death occurred (28 y/o male, non-adherent) at 21.9 months. 2 non responders (eGFR ≥ 50% at 1 year) progressed to ESRD. **Relapses** were treated with repeat doses of rituximab in 5/8 episodes with **no** increase in steroid dose. **Mean steroid dose** was ↓ by 10.1mg (95% CI 6.7-13.6, p=0.000) between 0 & 5 years. **Adverse events/steroid toxicity:** Hospital admissions for infection in 19, 23.8% of these in the 1st year. Steroid toxicity was evident in 42% (16/38) of patients, 62.5% (10/16) was bone-related.

Conclusion: The RituxiRescue regime led to sustained disease remission, steroid dose reduction & cessation by 5 years. Poor renal outcomes were rare. As steroid related toxicity was still seen with low dose steroids (probably reflecting cumulative burden prior to RituxiRescue) our data supports using the RituxiRescue regimen to avoid increasing steroid dose at relapse.

Disclosure of Interest: None Declared

Keywords: Corticosteroids, Lupus , Rituximab

Medicines Management

OR6-003

Rituximab is Highly Effective Treatment for Small Vessel Vasculitis in Absence of Circulating ANCA

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Preferred Presentation Method: Oral or Poster

Introduction: The use of Rituximab has been shown to be effective in ANCA associated vasculitis as shown in RAVE and RITUXIVAS studies. Rituximab depletes antibody producing B cells, the basis for its treatment in ANCA associated vasculitis. Literature suggests that ANCAs are absent in up to 10% of cases. The outcomes in ANCA negative vasculitis treated with rituximab is a rarely studied group of patients.

Objectives: To assess the efficacy of rituximab treatment in ANCA negative vasculitis.

Methods: This retrospective, single centre study reviewed the case notes of 10 patients with vasculitis who were treated with rituximab and were ANCA negative at the time of treatment treated over a 3 year period (2012-2015).

Table:

Gender M:F (%)	40:60
Ethnicity	Caucasian (100%)
ANCA Status (%) at presentation	Anti-PR3 (50%) Anti-MPO (10%) Negative (40%)
Organ Involvement (%)	Renal (60%) Multisystem (70%)
Dialysis required (% of those with renal involvement)	50%

Results: Indications for rituximab were cyclophosphamide resistance in 9(90%). 1(10%) patient had suspected urothelial malignancy. Mean age at presentation was 60 years (range 35-77 years).

1g of Rituximab was given fortnightly, a mean dose of 4.5g of rituximab was given in total. All patients were ANCA negative at the time of Rituximab treatment.

7 (70%) patients achieved remission following rituximab treatment, defined clinically and by low inflammatory markers.

2 (20%) patients achieved partial remission. 1 of these patients had destructive ENT granulomatous disease and the other developed AA amyloid secondary to vasculitis. 1 (10%) died whilst receiving rituximab treatment as the result of a perforated bowel.

Mean eGFR at treatment commencement for those with renal involvement (dialysis independent) (mls/min/1.73m2) was 28. Mean eGFR at follow up for those with renal involvement (dialysis independent) (mls/min/1.73m2) was 32.

Conclusion: In this retrospective study, use of rituximab in the absence of circulating autoantibodies has shown:

- 70% complete remission
- 20% partial remission
- 10% mortality
- Of those with renal involvement 1(16%) has remained dialysis dependent
- The treatment was tolerated well with no infections requiring hospital admission

Rituximab, as well as leading to B cell depletion, facilitates B cell/T cell interaction. B cells are also known to be present in tissue infiltrate without being detected peripherally. These findings support the use of rituximab in vasculitis in the absence of circulating autoantibodies.

To the best of our knowledge this is the largest published series in use of rituximab in ANCA negative patients.

Disclosure of Interest: None Declared

Keywords: ANCA, Glomerulonephritis, Rituximab

Acute Kidney Injury

OR7-001

Urinary trace elements as biomarkers of acute kidney injury after intensive care unit admission

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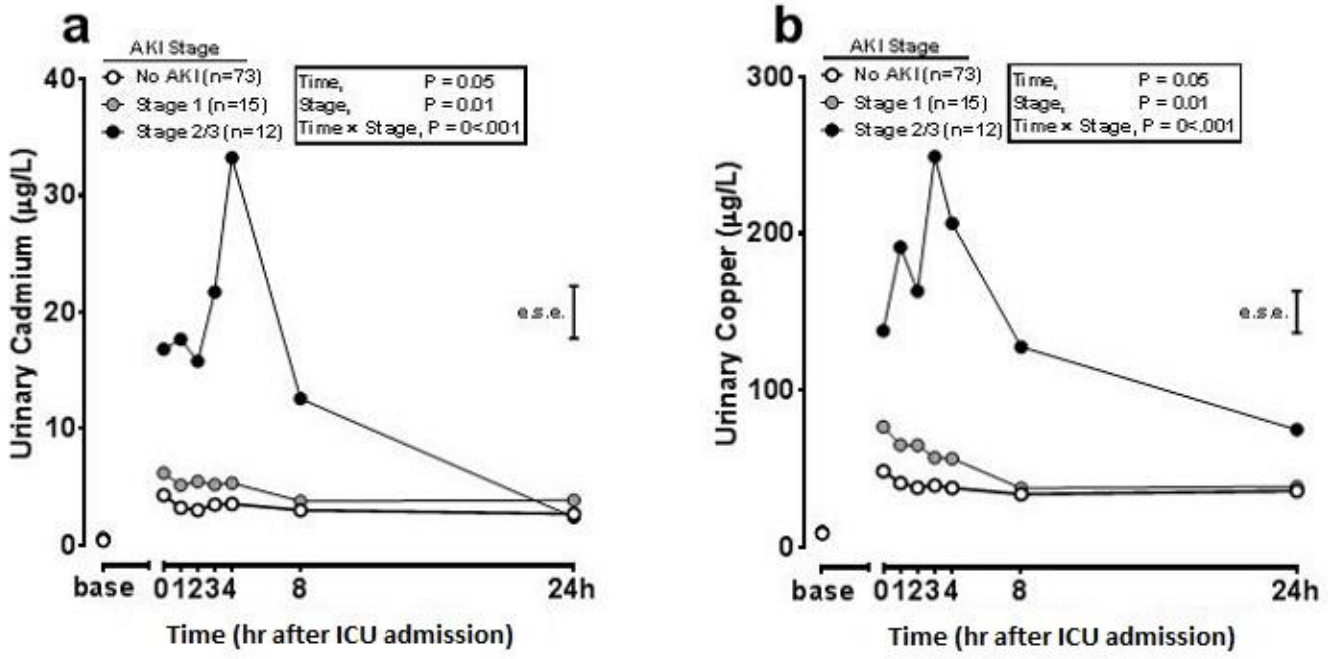
Preferred Presentation Method: Oral or Poster

Introduction: Acute kidney injury (AKI) is common and serious, complicating up to 50% of intensive care unit (ICU) admissions. Development of AKI can lead to increased mortality, prolonged length of stay, chronic kidney disease and huge cost (>£1 billion per year in the NHS). AKI is detected using serum creatinine (SCr) which is recognised to be a late and poor marker, taking 24-48 hours to rise after renal damage. A need exists for an early marker of AKI. From a porcine model of AKI (Gardner et al AJP-Renal 2014) we have identified that urinary cadmium (Cd) and copper (Cu) are promising biomarkers of AKI which may be used to detect AKI in the ICU.

Objectives: As part of a programme of research investigating urinary Cd and Cu as early biomarkers of renal tubular injury in different clinical settings, we conducted a single centre prospective observational study of patients admitted to ICU to determine whether urinary Cd and Cu predict development and stage of AKI.

Methods: We recruited patients admitted to ICU for any cause. Urine was sampled at 0, 1, 2, 3, 4, 8 and 24 hours following admission. Urinary elements were measured using ICP-MS and analysed with correction for urinary Cr by Restricted Maximum Likelihood estimating equations (Genstat v18, VSNi, UK). SCr was measured as part of standard care and recorded daily for 5 days, on ICU and hospital discharge. AKI was detected and staged using KDIGO SCr criteria or renal replacement therapy (RRT) during ICU admission. Data are presented as means (SD or SEM as appropriate). Outcome measures were development of AKI and KDIGO stage.

Image:



Results: We enrolled 104 patients and 100 were included in the analyses; median age was 58yr; 62% male. Admissions were 78% emergency (31% surgical; 16% trauma; 31% medical) and 22% elective (surgical). Sepsis complicated 27% admissions. Based on KDIGO SCr alone 27% developed AKI (15% stage 1, 3% stage 2, 9% stage 3); 1% required RRT. 17% had AKI at or before ICU admission. Mortality at 30 days was 20%. Urinary Cd and Cu were already elevated at ICU admission in patients that developed stage 2/3 AKI (Fig 1a,b). Levels peaked at 4h and 3h after admission respectively. Urinary Cd and Cu levels in patients with no-AKI and stage 1 AKI increased, but to a lesser extent vs Stage 2/3 AKI (Fig 1a,b).
Conclusion: Urinary Cd and Cu are elevated on ICU admission in those patients who develop stage 2-3 AKI, peaking at 3-4 hours, making them excellent putative biomarkers for AKI.

Disclosure of Interest: None Declared

Keywords: AKI, Creatinine

Acute Kidney Injury

OR7-002

ACUTE KIDNEY INJURY IN ELECTIVE SURGERY: REDUCING THE INCIDENCE WITH PRE-OPERATIVE RISK ASSESSMENT AND POST-OPERATIVE MONITORING

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Preferred Presentation Method: Oral or Poster

Introduction: Acute Kidney Injury (AKI) remains a significant and life-threatening complication that can occur peri-operatively. It is an important complication to recognise and its incidence and deaths can be reduced if high risk patients are identified and managed appropriately.

Objectives: To assess the efficacy of implementation of pre-operative AKI risk assessment based on NICE AKI Clinical Guideline 169 for patients undergoing hip and knee arthroplasty in Aintree University Hospital.

Methods: A retrospective study was conducted for patients who underwent elective hip or knee arthroplasty at Aintree University Hospital over a 12 month period from September 2014 in comparison to a cohort of patients who underwent similar surgery prior to the implementation of NICE AKI Clinical Guideline 169. Pre-operative risk factors such as demographics, comorbidities and blood pressure were collected according to NICE AKI Clinical Guideline CG169. Peri-operative blood pressure, haemoglobin loss and creatinine were recorded for analysis. Cox Regression analysis to identify the risk factors for AKI and Kaplan Meier Survival analysis perform to compare the survival of the 2 cohorts.

Table:

Hb loss > 10g/l	> 20g/l	> 30g/l	>40g/l	>50 g/l
Patient numbers 18	86	188	172	75
Blood Pressure < 110/60	Pre-op	Intra-op	Post - op	
Patient numbers	1	330	192	

Results: There were 565 patients that underwent hip and knee arthroplasty. The male to female ratio was 239:326. The patients age band were > 75 (n=130), 50-75 (n=400) and <50 (n=35). The average age was 67 (26-96). There were 51.7% with hypertension, 11.9% with Diabetes, 77.1% had Chronic Kidney Disease (CKD G3A n=84, 14.9%, CKD G3B n= 19, 3.4% and CKD G4 n=1, 0.1%). There were 193 patients on ACEI/A2RB, 101 on NSAID, 46 on Metformin and 15 on Furosemide. Eleven patients acquired an AKI post-operatively. All incidences of AKI resolved and no deaths ensued. Those CKD G4 not known to the nephrology team were referred to nephrology pre-operatively.

The year before implementation of NICE AKI Clinical Guideline 169 there were higher incidences of AKI (n=18 and deaths (n=7) with 2 deaths as a result of acute kidney injury. There were similar number of arthroplasty operations done in the year (n=569). Similar comorbidities in the patients with hypertension 56.4%, Diabetes 13.7% and CKD G3 and G4 were 21.2%. There were 214 patients on ACEI/A2RB, 124 on NSAID, 46 on Metformin and 66 on Furosemide.

Conclusion: Our study is the first to demonstrate the efficacy of implementation of NICE AKI Clinical Guideline 169 in elective orthopaedic surgery in the reduction of incidences of AKI and the all cause mortality. Therefore AKI risk stratification pre-operatively and peri-operative prevention measures of AKI are essential in all patients undergoing elective arthroplasty. We hope to develop an AKI risk stratification tool with the findings above.

References: NICE AKI Clinical Guideline 169

Disclosure of Interest: None Declared

Keywords: None

Diabetic Nephropathy

OR8-001

Evaluation of a cannabinoid receptor (CNR1) antagonist/ CNR2 agonist on podocyte markers in a mouse model of experimental diabetes

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Preferred Presentation Method: Oral or Poster

Introduction: Obesity is an independent risk factor for the development of diabetic nephropathy (DN). Treatment of DN currently focuses on blood pressure control (renin/angiotensin), glycaemic control measures, as well as lifestyle alterations. The potential for earlier intervention strategies within disease progression following clinical assessment remains to be addressed. Increased activity of CNR1 and decrease in CNR2 in mice is associated with progressive loss of renal function including structural changes in the glomerular filtration barrier. Of these the earliest cellular features of diabetic nephropathy is the irreversible loss of podocytes, which can also predict disease progression.

Objectives: The extent of the role played by the endocannabinoid system in diabetes has not yet been elucidated, although considerable evidence indicates the involvement of cannabinoid receptors (CNRs) in DN progression. The aim of the current study was to elucidate whether treatment with a ligand characterised as both a CNR1 neutral-antagonist* and CNR2 partial agonist could protect against strucutural changes in the glomerular filtration barrier such as podocyte loss in a model of experimental diabetes. *a ligand that is not expected to produce inverse cannabimimetic effects in absence of endogenous cannabinoids (endocannabinoids)

Methods: Conditionally immortalised mouse podocytes were cultured for *in vitro* assessment of CNR1 signalling on insulin sensitivity. Male DBA/2J mice were fed high carbohydrate diet, injected with either 150 mg/kg STZ to induce hyperglycaemia or vehicle (v/kg) as control, and monitored for onset of albuminuria.

Results: Mouse podocyte cultures treated with synthetic endocannabinoid, CNR1 agonist (ACEA, 100 nM for 30 min) showed marked reduction in insulin sensitivity ($pAkt^{S473}$) as expected. Treatment of podocytes with our CNR1 neutral antagonist/ CNR2 partial agonist resulted in recovered insulin sensitivity at 10 nM treatment (30 min) and this effect was more pronounced when combined with Rimonabant (1 nM), a CNR1 inverse agonist. Furthermore, pre-treatment of podocytes with the CNR1 neutral antagonist/ CNR2 partial agonist (1- 10 nM) reduced the effect of CNR1 activation on insulin signalling in podocytes. To confirm our findings *in vivo*, we administered our compound to mice fed high carbohydrate diet and injected with STZ (150 mg/kg), following onset of hyperglycaemia (fasting blood glucose (FBG), >450 mg/dl). Treatment with CNR1 neutral antagonist/ CNR2 partial agonist or vehicle was administered according to either an acute or chronic regime; conditions of hyperglycaemia and albuminuria were monitored routinely.

Conclusion: Our results so far support the hypothesis that targeting overactive CNR1 is a viable therapeutic strategy to augment early pathological changes in the diabetic kidney.

References: Welsh et al. 2010. Cell Metab., 12(4): 329-40

Barutta et al. 2011. Diabetes, 60(9):2386-96

Jourdan et al. 2014. PNAS, 111(50):E5420-E5428

Disclosure of Interest: None Declared

Keywords: Diabetic nephropathy, Growth factors, Podocyte

CKD: Fibrosis and Extracellular Matrix CKD

OR8-002

Development of a refined subtotal nephrectomy mouse model to study progressive renal disease.

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Preferred Presentation Method: Oral or Poster

Introduction: Chronic kidney disease (CKD) is a growing public health problem. Effective pre-clinical modelling of progressive CKD would be advantageous to examine pathophysiology and test novel interventions. The rat subtotal nephrectomy (5/6th) model is a commonly used model of progressive renal disease and replicates many aspects of human progressive CKD [1]. However, a robust mouse model would be desirable and the two-step surgery model has shown to mimic several features of progressive CKD in CD1 and SV129 strains whereas the C57/blk strain is relatively resistant [2].

Objectives: Develop a refined subtotal nephrectomy (STNx) model in mice, modelling progressive renal failure.

Methods: SV129S2 Mice (Envigo), 8-10 weeks of age, were randomised to sham or a single-step STNx surgery where the right kidney and the poles of the left kidney were removed. Urine and blood was collected (analysed by SURF, University of Edinburgh) and blood pressure measured by tail cuff plethysmography at baseline and every two weeks post-surgery. Animals were culled at 6 weeks (n=5 STNx; n=3 sham) or 10 weeks post-surgery (n=5 STNx, n=4 sham). Kidney and heart tissue was collected and fixed in zinc solution, snap frozen for RNA extraction, or underwent fluroscence-activated cell sorting (FACS).

RNA was extracted from kidney tissue or FACS sorted cells using the miRNeasy kit (Qiagen). Gene or miRNA expression was determined via qRT-PCR using specific primers and normalised to U6 for miRNA or 18S for gene expression.

3µM sections of zinc fixed, paraffin embedded kidney and heart slices were stained with picrosirus red for total collagen. Quantification of collagen present was carried out in ImageJ.

FACS: Kidneys were processed by MACS tubes using an enzyme digestion solution. Single cell suspensions were blocked then incubated with CD45-APC, Lotus Lectin – Fluorescein, F4/80-Pe-Cy7, CD31-BV605, PDGFBRβ-PE and passed through BD Aria II using DAPI as a live/dead indicator.

Results: The one surgery STNx model was run for 10 weeks post-surgery and the mortality rate was 5%.

Blood pressure significantly rose in the STNx mice compared to sham mice over 10 weeks (121+/-10 vs 102+/-7 mmHg at 4 weeks; 152+/-7 vs 115+/-8 mmHg at 10 weeks, $p<0.05$; STNx vs sham). The STNx mice also developed pronounced proteinuria with a significantly increased ($p<0.01$) albumin:creatinine ratio (ACR) over the 10 weeks (97 vs 1368; sham vs STNx).

The STNx animals had pronounced left ventricular hypertrophy with heart weights double of those observed in sham mice (0.34g sham vs 0.69g STNx) and histological analysis revealed perivascular and interstitial fibrosis was evident.

STNx kidneys had significant levels of fibrosis with widespread glomerulosclerosis and tubulointerstitial fibrosis evident compared to shams. A significant 8 fold increase in collagen gene expression (Col1a and 3a) was also observed in STNx kidneys ($p<0.001$ vs sham). Pro-fibrotic miRNA expression of miR-21 (6 fold), 214 (3 fold) and 199a (2.5 fold) was also significantly increased ($p<0.05$) in STNX vs sham kidneys and showed selective renal cell population expression.

Conclusion: Our refined one surgery model of subtotal nephrectomy in SV129 mice is a robust model of progressive renal disease which develops significant renal fibrosis, left ventricular hypertrophy, cardiac fibrosis, proteinuria and hypertension.

References: 1. Mullins LJ. Dis Model Mech. 2016. 9:1419-1433.

2. Leelahavanichkul A, Kidney Int. 2010. 78:1136-1153.

Disclosure of Interest: J. O'Sullivan Conflict with: Recipient of a Medical Research Scotland PhD part funded by Regulus Therapeutics, S. Finnie: None Declared, L. Denby Conflict with: Holder of a Medical Research Scotland PhD Studentship part funded by Regulus Therapeutics.

Keywords: Animal model, CKD Progression, Fibrosis

Diabetic Nephropathy

OR8-003

Insect nephrocytes as a model for human podocyte ageing

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Preferred Presentation Method: Oral or Poster

Introduction: Mammalian podocytes exhibit age-dependent functional decline that may be associated with reduced renal function. In addition, disruption of metabolism may hasten cellular ageing and impact podocyte function in conditions such as diabetic nephropathy. Studying ageing using mammalian models is ethically, technically and temporally challenging. Alternative models are therefore attractive. *Drosophila* nephrocytes are large pericardial cells with slit diaphragms that are functionally and genetically analogous to human podocytes.

Objectives: In this work we examined whether *Drosophila* nephrocytes may be used to model podocyte ageing.

Methods: Nephrocyte ageing was analysed in *Drosophila* aged for 1 to 5 weeks (about late 'middle age' for a fly). Nephrocyte ageing in insulin signalling mutants was also analysed, as was the impact on ageing of silencing insulin signalling genes specifically in nephrocytes using the *dKlf15-Gal4* driver. Antisera were raised to dumbfounded (duf; ortholog of the human NEPH1 protein) and used to stain nephrocytes. Endocytic function of nephrocytes was monitored using fluorescently tagged 10kDa dextran. Intracellular calcium was monitored in nephrocytes expressing the *GCamp6* calcium reporter under the control of the *Dorothy-Gal4* driver

Results: Pericardial nephrocytes underwent age-dependent hypertrophy, developed abnormal calcium handling, reduced endocytic function and death. Nephrocytes were smaller and exhibited extended health-span in flies heterozygous for loss-of-function mutations in *Chico (IRS1)*, *PI3K* and *Thor2* (*4E-BP*). In contrast, silencing insulin signalling genes (*InR* and *Akt*) specifically in nephrocytes, led to a premature ageing phenotype

Conclusion: These data confirm nephrocyte ageing within *Drosophila* and highlight the possibility conserved ageing mechanisms relevant to mammalian podocytes. The data also indicate that disruption of insulin signalling may have both a protective and deleterious impact on cellular ageing which depend on the genetic context for loss of function. It is concluded that the *Drosophila* nephrocyte is an instructive and tractable model of podocyte ageing in humans

Disclosure of Interest: None Declared

Keywords: Animal model, Diabetes, Podocyte

Glomerular Pathobiology

OR8-004

Identification of novel NUP93 mutations in SRNS and evidence for a functional role for this protein in the regulation of podocyte biology.

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[1]Bristol Renal, University of Bristol, Bristol, [2]Bournemouth University, Bournemouth, [3]University of Oxford, Oxford, [4]North Bristol National Health Service Trust, [5]University of Bristol, Bristol, [6]Evelina London Children's Hospital, [7]King's College London, London, United Kingdom

Preferred Presentation Method: Oral or Poster

Introduction: Nuclear pore complexes (NPCs) are aqueous channels composed of proteins called nucleoporins (NUPs). NPCs penetrate the nuclear envelope and tightly regulate the transport of proteins and RNA between the nucleoplasm and cytoplasm. Interestingly, *NUP107*, *NUP205* and *NUP93* have recently been implicated in paediatric Nephrotic Syndrome (NS).

Knockdown of *NUP93* in human podocytes impairs nuclear pore assembly cell migration, proliferation rate as well as Nup205 expression. *NUP93* mutations cause disrupted assembly of NPC and in HEK293T cells abolish interaction of the protein with SMAD4 andimportin 7. No *in vivo* knockdown of *NUP93* has ever been reported.

Objectives: *Drosophila* express two orthologs of human NUP93 (Nup93-1 and Nup93-2). It remains unclear whether either of the two *Nup93* paralogs (*Nup93-1* or *Nup93-2*) in *Drosophila* has a role in pericardial nephrocyte development or function.

Methods: Paedatric SRNS patients, collected via the national UK Renal Registry (RaDaR) were exome sequenced. *Drosophila Nup93* knockdown was achieved by RNA interference using the nephrocyte-restricted drivers *Dot-Gal4* and *dKlf15-Gal4*. Micrographs of the adult *Drosophila* pericardial nephrocytes stained with wheat germ agglutinin and phalloidin (to visualise the heart) were obtained. Electron microscopy of *Nup93* mutants and wild type *Drosophila* nephrocytes was also performed.

Results: 3 novel mutations in the *NUP93* gene were found in a sporadic and two familial SRNS patients who had FSGS on biopsy and progressed to ESRF within 2-12 months from diagnosis. The sporadic patient had p.(Leu695Ser) and p.(Leu756Ser) mutations whereas the two siblings, whose parents are consanguineous, shared a homozygous p.(Ala475Thr) variant. The sporadic patient was diagnosed at 6 years of age while both siblings were 1 year old at diagnosis suggesting that the p.(Ala475Thr) mutation may cause a more severe phenotype.

Silencing *Nup93-1* or *Nup93-2* in *Drosophila* using nephrocyte-restricted drivers led to a significant reduction (up to 82%) in adult pericardial nephrocyte numbers. Antibody staining against the NPC proteins was severely disrupted in nephrocytes. In addition, in the nephrocytes surviving to adulthood, morphology was highly abnormal in *Nup93-1* and *Nup93-2* silenced flies with a collapsed cellular profile with indented margins and large vacuoles abundant in the cytoplasm.

Conclusion: We have identified three novel *NUP93* mutations responsible for SRNS.

Silencing of either *Nup93* paralog in Drosophila caused a severe nephrocyte phenotype, signalling an important role for this protein in podocyte biology.

Disclosure of Interest: None Declared

Keywords: Animal model, FSGS, Nephrotic syndrome

Service Delivery, Quality & Innovation

OR9-001

Outcome data for Nephrology day case procedure undertaken by Advanced Nurse Practitioner to reduce cost and length of stay

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Preferred Presentation Method: Poster

Introduction: Advanced level practice encompasses aspects of education, research and management but is also firmly grounded in direct care provision or clinical work with patients, families and populations (1). The role of the ANP in Nephrology is no different to other areas of nursing, in that it can be very challenging but also extremely rewarding as patients with renal disease can frequently present as a complex case. The Day case area and service is currently overseen by single full time ANP with support of nephrology consultants (as mentors) and Registered nurse.

Objectives: The short stay day care unit area is nurse led and is designed to provide nephrological care for elective patients on a Monday to Friday basis. The procedures that take place include renal biopsy, dialysis line insertion/removal and peritoneal dialysis cannula insertion/removal and fistuloplasty. The Short stay unit protects the need for Inpatient bed admission.

Methods: During the last 5 years, ANP has received training and can independently perform native renal biopsy, tunnelled neck line insertion and PD cannula insertion/removal (please see table 1 below). Retrospective review of case note for 403 patients who underwent procedure.

Results: The day case area has significantly improved the renal service leading to less occupancy of hospital bed and reduced cost (see table 1). The success rate for native renal biopsy and PD cannula insertion is 97% and 94 % respectively. It has also improved patient experience, as it is well structured and run by dedicated team with same day discharge.

Renal biopsy, Line insertion/removal data 2015 to 2016

PD Cannula insertion data from 2012 to 2016

129 native renal biopsy 97% discharged same day (3 patients had haematuria requiring overnight stay.

118 PD Cannula insertion 94% success rate of placement

9 PD Cannula removal 100% success rate

9 PD Cannula manipulation 50% success rate

50 Tunnelled line insertion 96% success rate

84 Tunnelled dialysis line removal 100% success rate

Conclusion: The ANP led day case procedure service can significantly improve patient experience, length of stay and cost whilst at the same time maintaining safety. It also allows a training environment and support for junior doctors who wish to gain experience in procedures. Having this expertise has enabled the department to have extra staff competent in undertaking procedure and also enabling patients to start acute peritoneal dialysis. The unit audits practice yearly and the safety of procedures are discussed at monthly Governance meetings.

References: 1. Department of Health (2010). Advanced Level Nursing: A Position Statement

Disclosure of Interest: None Declared

Keywords: Patient experience, Patient outcome measures, Patient safety

Service Delivery, Quality & Innovation

OR9-002

Evaluation of a secondary care CKD email advice service for GPs in North West London

S. Zaman [1,*], H. Beckwith [2], C. F. Brewer [1], H. Watts [1], E. Salisbury [1], S. Singh [1], J. Tomlinson [1], E. Brown [1], J. Levy [1], L. Lightstone [1], A. Frankel [1]

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Preferred Presentation Method: Oral or Poster

Introduction: In September 2015, a CKD email advice service was introduced to facilitate communication between nephrologists at Imperial College Healthcare NHS Trust and General Practitioners (GPs) in North West London.

Objectives: To analyse the use of this E-advice service, measure satisfaction of users and identify areas of improvement relevant to this and similar E-advice services.

Methods:

Part 1: Emails received between January 2016 and November 2016 were reviewed. Questions and responses were categorised by subject and response times were measured.

Part 2: An online survey was sent to all users of the E-advice service to assess satisfaction. Thematic analysis[1] was used to code 'free-text' responses from GPs.

Image:

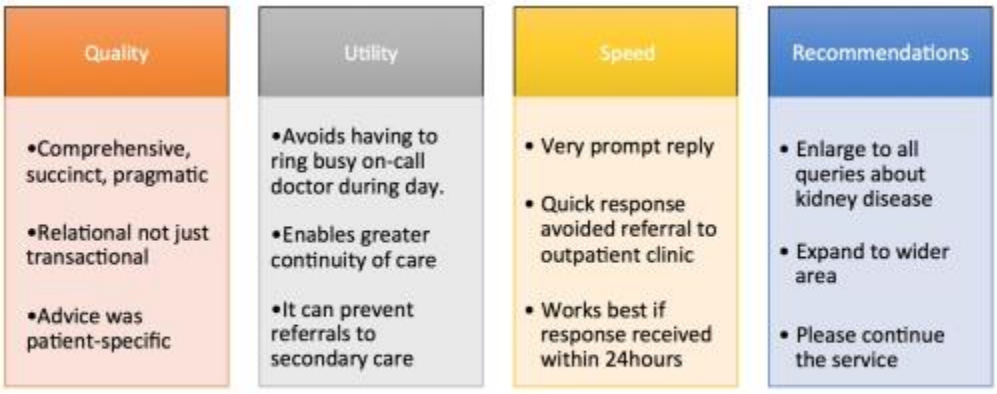

Figure 1: Themes and codes identified by thematic analysis of free-text responses to a survey of users of the CKD E-advice service between January and November 2016.

Table: Table 1: Summary of referral advice given via the E-advice service

Number of GPs requesting referral to Nephrology outpatient clinic	21 (19.6%)
Advised to refer to Nephrology clinic at that point	2 (9.5%)
Advised that referral currently not required	17 (81.0%)
Triggers for future referral identified	9 (42.9%)
Advised to refer to another speciality clinic	2 (9.5%)

Results:

Part 1: 107 emails were received, an average of 0.5 emails/working day (increased from 0.2/working day between Sep 2015 & Jan 2016). Mean response time was 23 hours. Discussions regarding blood pressure control (26%), prescribing in CKD (25%) and management of declining renal function (21%) were most common. 21 GPs (20%) requested referral to the nephrology clinic, of which 17 (81%) were managed without immediate referral to outpatient secondary care services. Table 1 summarises referral advice resulting from these enquiries.

Part 2: 43 GPs (40%) responded to the survey. 100% stated that their question was answered by the nephrologist via the e-advice service. 68% stated that they would have referred the patient to the nephrology outpatient clinic if their question had not been answered. 100% claimed they would recommend it to a colleague. Figure 1 shows key themes and codes identified.

Conclusion: The CKD E-advice service receives a growing volume of queries from GPs in North West London with an average response time of under one day. This model is an effective method of promoting the principles of the NICE CKD guidelines[2], preventing avoidable admissions or referrals to secondary care by supporting the treatment of CKD patients in primary care and meeting the objectives of the GP Forward View[3] by improving the interface between GPs and nephrologists.

References: 1. Braun V, Clarke V. (2006). Using thematic analysis in psychology. *Qualitative Research in Psychology*, 3(2). pp. 77-101. ISSN 1478-0887. Availalbe from: http://eprints.uwe.ac.uk/117335

2. National Institute for Health and Clinical Excellence (2014). Chronic kidney disease in adults: assessment and management. NICE Guidline (CG182).

3. National Health Service England (2016). General Practice Forward View. Gateway publication (Ref 05116).

Disclosure of Interest: None Declared

Keywords: CKD, Clinical quality improvement, Renal service planning

Patient Education, Involvement and Experience
OR9-003
Patient Led Research Hub for Renal Research: a Progress Report

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[1]Cambridge Clinical Trials Unit, Cambridge University Hospitals NHS Foundation Trust, [2]Experimental Medicine and Immunotherapeutics, University of Cambridge, Cambridge, United Kingdom

Preferred Presentation Method: Oral or Poster
Introduction: Patients bring crucial insight into research priorities for disease and lifestyle needs. Recognising this, the Department of Health and NIHR have pushed Patient and Public Involvement (PPI) to the forefront of research funding. Many initiatives have proved successful, and interested members of the public are now able to seek a breadth of involvement opportunities. However, involvement is generally consultation based with limited ability to effect change. Further, a mismatch between patients' wishes and researched interventions exists, with most studies prioritising drug trials. A new initiative launched in May 2015 by the Cambridge Clinical Trials Unit (CCTU) addresses this disparity.
Objectives: The Patient Led Research Hub (PLRH) aims to provide the resources, expertise and infrastructure to turn patients' own research ideas into high-quality clinical projects. Activities are supported by medical experts, trialists, statisticians, a health economist, and administrative staff.
Methods: PLRH strategy and governance are reviewed by the Cambridge Biomedical Research Centre (BRC) and Cambridge University Health Partners PPI Research Oversight Group. Seed funding was provided by the BRC.

To develop a research idea:

1. Patients/support organisations contact PLRH
2. A preliminary assessment ensures the project is technically feasible
3. Proposers are invited to a round-table discussion to explore the project
4. Proposers join the management team and collaborate on a formal proposal, study design and funding applications
5. With external funding, the project is conducted by the CCTU
6. Proposers maintain a management role throughout the study and dissemination

Results: PLRH has received 15 formal queries from 12 different patient organisations. Preliminary assessment found 13 technically feasible: 2 are currently active, 7 in development.

Case Study
Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most common inherited renal disease. PKD Charity proposed a fluid intake study to investigate early evidence that drinking large amounts of water can slow cyst growth. Directed by lived experience, several features are included to ensure practical trial participation, and technology can be repurposed for general patient use. DRINK is now recruiting with funding from the British Renal Society.
Conclusion: Patients can provide an unconflicted vested interest in research. PLRH has attracted multiple high quality research proposals, confirming the need for more collaborative research. However, developing research proposals is time consuming and labour intensive: further investment is now required to support emerging projects.

Disclosure of Interest: None Declared

Keywords: Patient empowerment

Patient Education, Involvement and Experience

OR9-004

Measuring Patient Activation and Quality of Life Outcomes - the experience of 10 renal units

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Preferred Presentation Method: Oral or Poster

Introduction: The Transforming Participation in CKD programme is a partnership between NHS England and the UK Renal Registry to support people with a Long Term Condition (LTC) to build their knowledge, skills and confidence to help them self-manage their condition. Self-management has the potential to foster and enable a genuinely equal partnership between those with a LTC and clinician, improving experience and quality of life outcomes.

Objectives: The aim of this study was to explore the feasibility and initial results of routinely collecting data on the Quality of Life (QOL) of people in secondary care with kidney disease in England.

Methods: The survey tool consisted of (1) 5 questions on overall health (EQ-5D-5L), (2) 17 questions on symptoms (iPOS-S renal) and (3) 13 questions on the ability of the patient to manage their health (patient activation level measure PAM) A paper copy of the survey was given to outpatients with pre-dialysis chronic kidney disease or a kidney transplant and those on maintenance haemodialysis/peritoneal dialysis. Completed surveys were returned to the Registry and scanned into the database. The EQ-5D-5L use scales from '0' representing no problems/concerns to '5'representing the highest level of severity/concern. The iPOS-S renal questions use scales from 0 to 4 representing increasing severity of symptoms. These were collapsed and recoded to absent or mild (0, 1), and moderate/severe/overwhelming (2, 3, 4).

Results: 10 out of 52 renal units in England submitted data as part of phase 1 of the TP-CKD programme with 1,053 patients completing and returning the survey between March and August 2016.

The majority of patients completed the survey on their own (58.8%) with 15.2% receiving help from staff and 20.8% completing the survey with help from a friend or relative. The majority of surveys were completed at the renal unit (61.1%), although a large proportion of surveys were completed at home (24.2%) and 10.2% of surveys were completed in a clinic setting. Almost 70% of patients completing the survey were older than 55 years of age with only 2.6% completing the survey in the 18-24 age group.

The presence of at least moderate symptoms ranged greatly from 9.2% for vomiting and 13.3% for diarrhoea with 27.2% feeling depressed and 37.2% reported as feeling anxious and worried. In all patient groups the five most prevalent symptoms were weakness and lack of energy (58%), poor mobility (49%) pain (39%) difficulty sleeping (38%) and shortness of breath (36%).

At least moderate impairments in mobility, self-care, usual activities, pain/ discomfort, anxiety/depression were reported in 49%, 48%, 39%, 27% and 24% respectively. Amongst respondents, 32% and 15% had patient activation levels 3 and 4 respectively, showing moderate to high activation in managing their own health.

Conclusion: The routine national collection of patient reported outcome measures (QOL) and PAM poses practical and logistic challenges, but the high burden of reported symptoms and the low activation levels of the majority of patients makes it important to capture them alongside traditional markers of quality of care.

Disclosure of Interest: None Declared

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