

# ABSTRACTS OF SOCIETIES - RENAL ASSOCIATION

## Treatment of Hyperammonaemic Coma in a Patient with a Ureterosigmoidostomy by Haemodialysis

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### Case

A 58 year old female was admitted to the medical unit with coma. Past medical history included reimplantation of both ureters into the sigmoid colon following a childhood road traffic accident. In 1993 she was admitted with unexplained confusion, which responded to rehydration. Over the next 12 years, she was admitted on a further 4 occasions with reduced consciousness, twice requiring ventilation. During each admission her condition improved spontaneously, and no conclusive diagnosis was made. Brain imaging and CSF analysis were consistently normal. EEG during illness was compatible with a metabolic encephalopathy. On this admission biochemical profile and CT of brain were normal. Infection screen was negative. Serum ammonia was markedly elevated at 327  $\mu\text{mol/l}$  (normal range 10-35). A diagnosis of hyperammonaemic encephalopathy was made. She was treated with 4 haemodialysis sessions and colonic irrigation was performed. Serum ammonia returned to normal and was associated with a dramatic improvement in her conscious level. She was discharged on oral lactulose and a low protein diet, with revision to an ileal conduit planned. **Discussion** In patients with a ureterosigmoidostomy, hyperammonaemic encephalopathy, resembling hepatic encephalopathy can result due to increased colonic ammonia production from bacterial ureolysis and subsequent rapid colonic ammonia absorption. Treatment has been advocated with haemodialysis but definitive management requires urinary revision. Increased awareness of this rare cause for metabolic encephalopathy is required to permit prompt intervention aimed at correcting serum ammonia levels.

## Incidence and Treatment of Tunnelled Line Sepsis in a Haemodialysis Population

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### Background and Aims

Tunnelled central venous catheters are frequently used for haemodialysis (HD), but infective complications are a major problem. Recent studies quote infection rates of 3.4-5.5/1000 catheter days with an average of 25% developing metastatic complications. We conducted a prospective audit of our dialysis population, examining the rate of Permeath sepsis, organisms involved, adequacy of treatment, and adherence to local protocols. **Method** We included all patients on dialysis in the RIE and its three satellite dialysis units between 1/4/05 and 31/7/05. Each line sepsis episode was defined as a systemic illness/pyrexia requiring antibiotic therapy, in the absence of another source of infection. The causative organism (where cultured) and antibiotic therapy were recorded. Data was collected with respect to diabetes, nutritional status, line site and concurrent immunosuppression. **Results** 94 patients (7499 catheter days) received HD via a tunnelled line during the audit period. There were 37 episodes of sepsis in 32 patients (4.9/1000 catheter days). 77% of infections were Staphylococcal (including 22% MRSA). Only 19% of patients received protocol first line treatment, while 38% received Vancomycin first line. Of the Staphylococcal infections 88% were sensitive to the antibiotics used first line, and 86% to protocol treatment. Line sepsis rates tended to be higher in diabetics than non-diabetics (6.01 vs 4.36/1000 days), and femoral compared with internal jugular lines (4.52 vs 7.92/1000 days). There was no correlation with immunosuppression or nutritional status. **Conclusions** Infection rates in our unit are comparable to those previously quoted. The majority of infections were sensitive to protocol first line therapy. However, the majority of cases were not treated with protocol antibiotics, partly reflecting those previously known to have MRSA. Failure to adhere to protocol may contribute to high rates of VRE in this population. There is a trend towards higher rates of infection in the diabetic population and those with femoral lines, although study numbers are small. **Actions** This audit will be continued to monitor compliance to treatment protocols. Further study of infection rates in diabetic and non-diabetic populations is necessary. This may suggest the need for more aggressive treatment of exit site infections in this population. Many suggestions have been made for decreasing rates of line sepsis including the use of antimicrobial agents such as Taurolock™

## The Targeted Use of Taurolock® in Reduction of Episodes of Line Sepsis in the Haemodialysis Population.

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Taurolock® is an anti-microbial agent (taurolidine) with anticoagulant properties (citrate). It is being increasingly utilised intraluminally in central venous catheters in the haemodialysis population, to prevent catheter-related infection. This retrospective audit compared the incidence of catheter-related infections per 1000 catheter-days both prior & subsequent to Taurolock® use in 13 patients prescribed Taurolock on the basis of recurrent infections & problematic access. Reduction in catheter-related infections was demonstrated in all patients. The line-infection rate in this group pre-Taurolock® was 15 per 1000 catheter days and post-Taurolock® 3.5 per 1000 catheter days. Undertaking a cost-analysis assuming a 2-night hospital admission per catheter-related infection as an average, we demonstrated a reduction in overall expenditure of £1200. In the view of the multiplicity of benefits gained - both in terms of reduced morbidity and in financial gain - we propose the use of Taurolock® throughout the haemodialysis population with semi-permanent vascular access. This clearly requires ongoing audit with increased patient-numbers, but initial results are extremely encouraging.

## Endophthalmitis Complicating Tunnelled Line Staph Aureus Septicaemia

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A 68 year old patient with chronic renal failure who was dialysing with a right internal jugular tunnelled line presented with fever and was given IV vancomycin and gentamicin. Her blood culture grew methicillin sensitive Staph aureus. Twenty four hours later she complained of blurred vision in her right eye. Urgent ophthalmological review showed vision 6/60 in that eye with marked anterior uveitis, dense vitreous veils and debris centrally. Vitreous tap yielded pus cells but no organisms on gram stain or culture. We instilled 1 mg vancomycin and 2 mg ceftazidime into the vitreous, replaced her tunnelled line and followed this with a 6 week course of IV vancomycin with oral flucloxacillin. Her course was complicated by a dense cataract caused when the vitreous aspiration needle inadvertently touched the lens, but otherwise she recovered well. This unusual complication of tunnelled line septicemia prompted a review of the literature and of current practices relating to line infection.

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## Expression of Gremlin in Diabetic Nephropathy *in vivo* and Epithelial-Mesenchymal Transdifferentiation *in vitro*.

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The Conway Institute of Biomolecular and Biomedical Research, University College Dublin, Ireland 1, Medizinische Poliklinik, Ludwig-Maximilians-University of Munich, Germany 2 and Department of Nephrology, Universidad Austral, Valdivia, Chile 3. Gremlin, a bone morphogenetic protein antagonist, is known to be upregulated in cultured human mesangial cells exposed to high glucose and TGF- $\beta$  *in vitro* and in kidneys from diabetic rats *in vivo*. Here gremlin expression was assessed in human diabetic nephropathy by *in situ* hybridisation, immunohistochemistry and real time PCR and correlated with clinical and pathological indices of disease. Gremlin was not expressed in normal human adult kidneys. In contrast, abundant gremlin expression was observed in

human diabetic nephropathy. While some gremlin expression was observed in occasional glomeruli, gremlin expression was most prominent in areas of tubulointerstitial fibrosis where it co-localised with TGF- $\beta$  expression. Gremlin mRNA levels correlated directly with renal dysfunction, as determined by serum creatinine, but not with the level of proteinuria. There was a strong correlation between gremlin expression and tubulointerstitial fibrosis score. In complementary *in vitro* studies, induction of gremlin expression was observed in cultured tubule epithelial cells undergoing epithelial-mesenchymal transdifferentiation, a proposed mechanism of renal fibrosis, in response to the addition of exogenous TGF- $\beta$ 1. In aggregate, these results indicate that the developmental gene gremlin re-emerges in the context of tubulointerstitial fibrosis in diabetic nephropathy and suggests a role for TGF- $\beta$  as an inducer of gremlin expression in this context.

### Gremlin, a Bone Morphogenetic Protein Antagonist Essential for Pronephric Development, is Expressed in Normal Human Renal Development and Multicystic Renal Dysplasia.

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The inhibition of bone morphogenetic proteins (BMPs) is important in many developing systems such as limb bud and lung. Gremlin, a member of the cysteine knot superfamily, is an antagonist of BMP 2,4 and 7 in the developing chick limb and murine lung, and is expressed in the developing *Xenopus* pronephros, the earliest kidney form. Gremlin is essential for development of the *Xenopus* pronephros as inhibition blocks tubule and duct development and overexpression results in enlarged, and on occasion, ectopic pronephric structures. In view of the expression of gremlin in the developing pronephros, we studied the expression of gremlin in normal and abnormal mammalian kidney development. Gremlin is expressed in developing mammalian metanephros as determined by RTPCR, *in situ* hybridisation and immunohistochemistry. Gremlin expression occurs in the basolateral component of branching ureteric bud in human and mouse and co-localises with Pax-2 expression. Gremlin RNA and protein is expressed in dysplastic renal tubules in children with multicystic renal dysplasia where it co-localises with Pax-2 and TGF- $\beta$ . Gremlin is also expressed in peritubular fibrous tissue in human renal dysplasia similar to its location in diabetic nephropathy. In relatively normal post-natal kidney expression is seen in proximal tubules and the parietal epithelium of Bowman's capsule. Although very preliminary, our results suggest that gremlin may have important roles in both normal and abnormal mammalian metanephric development, perhaps paralleling previously described functions in the *Xenopus* pronephros.

### Factors Affecting 5 Year Paediatric Renal Transplant Survival in the United Kingdom

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Outcome for all UK paediatric renal transplants are reported to UK Transplant for analysis. 596 first paediatric kidney only transplants from cadaveric heartbeating donors in the UK, 1995-2001, were analysed to investigate the influence of donor and recipient variables, year of graft, cold ischaemia time, HLA match and local/exchanged kidneys on five-year transplant survival (death with function treated as transplant failure). Patients were defined as under 18 years old at time of transplant. Cox regression models were fitted to analyse the combined effect of factors on outcome. Investigation showed year of graft, donor age and recipient primary renal disease to have a significant influence on five-year transplant survival of paediatric patients. HLA match was not found to influence outcome significantly. Five-year transplant survival has improved year-on-year for paediatric patients transplanted in the period analysed (RR 0.89, 95% CI 0.80-0.98,  $p < 0.05$ ). Very young donors confer an increased risk of failure compared with donors aged 18-29 years, while donors aged over 40 years are associated with the greatest risk of transplant failure for paediatric patients. Investigation of primary renal disease found that glomerulonephritis was associated with poorer outcome than other renal diseases. In order to compare risk-adjusted outcome of paediatric and adult patients, a combined model for five-year transplant survival was investigated. Relative to recipients aged 24-39 years, outcome was worse for 14-17 year olds (RR 1.9, 1.4-2.5,  $p < 0.0001$ ) and for those aged 18-23 (RR 1.3, 1.01-1.7,  $p = 0.04$ ), but was comparable for those aged 5-10 (RR 1.09, 0.7-1.7,  $p = 0.72$ ) and those aged 11-13 (RR 1.3, 0.8-1.9,  $p = 0.27$ ). Outcome for 14-17 year olds was comparable with that for patients aged 60 years and over.

Transplant survival is improving in paediatric recipients, however adolescents have a worse outcome compared to other paediatric and adult recipients. No funding, no conflict of interest.

### Post Transplant Lymphoproliferative Disease in Paediatric Renal Transplant Recipients

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Paediatric renal transplant survival has improved over the last few years, in part due to the use of newer and more potent immunosuppressive agents. One of the consequences of this is an increase in infective complications post transplant, and in particular, an increase in the risk of post transplant lymphoproliferative disorder (PTLD). We reviewed all of the children transplanted at Yorkhill between January 2001 and December 2004. 30 children (18 males) received grafts at a mean age of 10.1 years. All were first grafts and 30% were living related transplants. Initial immunosuppression consisted of tacrolimus or ciclosporin, azathioprine and prednisolone. One child died 6 months post transplant from an unrelated condition. All other patients are well with functioning grafts. Seventeen (57%) patients were seronegative for EBV prior to transplantation. Thirteen (76%) seroconverted to become EBV positive at a median of 18 weeks (range 8 to 32 weeks). Of the other 4 patients, 1 result is awaited, and 3 have not seroconverted. These three were among the youngest patients, two being 4.3 years and the other 5.6 years at the time of transplant. Four patients (13% of the cohort) developed PTLD at a median time of 29 (range 18 to 77 weeks). All of these patients were seronegative at the time of transplantation. In two patients, the site involved was the bowel, in one it was the liver and the other patient developed a solitary lymph node in the neck. The presentation, diagnosis, monitoring, management and course of these patients will be discussed. All eventually recovered from PTLD and have acceptable graft function. No funding, no conflict of interest.

### Combination Treatment with Pegylated Interferon A and Ribavirin in Potential Renal Transplant Recipients with Chronic Hepatitis C Infection.

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Kidney transplantation improves the survival of patients with end stage renal disease and chronic HCV infection. Chronic HCV infection is however associated with significant morbidity and mortality in HCV-positive renal transplant recipients. This may be helped by appropriate antiviral treatment. The most effective treatment regimen for chronic HCV infection in the general population is the combination of pegylated interferon  $\alpha$  and ribavirin. This is associated with the highest sustained viral response rates (SVR defined as HCV PCR -ve 6 months following treatment). There is little data on the use of combined interferon and ribavirin in patients with advanced CKD. Interferon has been shown to be effective in dialysis patients but can lead to acute renal dysfunction if used in the post-transplant period. Ribavirin has been problematic in patients with CKD because of the risk of severe haemolysis and experience in the transplant period is limited. Antiviral treatment is therefore best undertaken in potential transplant recipients prior to kidney transplantation. We describe three potential kidney transplant recipients with chronic HCV infection treated with combination pegylated interferon and ribavirin. The two patients with genotype 3 achieved a SVR while the third patient with genotype 1 failed to respond. With close monitoring and appropriate dose adjustments of each of the interferon and or ribavirin all three patients tolerated the treatment well with no serious complications. Liver biopsies have been performed in all the patients after the antiviral treatment. One of the patients who achieved an SVR and whose liver biopsy revealed only mild fibrosis and no active inflammation, has now undergone a successful kidney transplantation. The liver biopsies of the two other patients revealed cirrhosis and both are currently being considered for kidney  $\pm$  liver transplantation. The optimal antiviral treatment for chronic HCV infection in patients with CKD who are potential transplant recipients is not known. Also it is yet to be determined whether these treatments impact on the natural history and outcome of chronic HCV infection following kidney transplantation.

## Case Report: An Elusive Diagnosis Of Renal Sarcoidosis

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A 68 year-old female ex-smoker (24 pack-years) under investigation for rapidly deteriorating pulmonary function was transferred from the Scottish Pulmonary Hypertension Unit for management of a precipitous decline in renal function. Having initially presented to her optician with uveitis, a history of multisystem symptomatology was elicited with domiciliary O<sub>2</sub>-dependent breathlessness and dysphagia ensuing over 18 months. Her breathlessness was thought to be due to the combination of mild-moderate airways obstruction and mild pulmonary hypertension. Her baseline renal function was normal and the rapid development of anuric dialysis-dependent acute renal failure was thought to be secondary to urosepsis-induced acute tubular necrosis. An acute renal screen and renal ultrasound was normal. She exhibited severe disseminated intravascular coagulation (DIC) which complicated her management and precluded a renal biopsy being performed. Interestingly, despite an initial normal serum ACE, repeated ACE measurements became elevated and prompted empirical treatment with prednisolone (1 mg/kg). The DIC improved and she underwent a transbronchial biopsy, bone marrow trephine and renal biopsy. The former investigations were normal whilst the renal biopsy revealed a granulomatous interstitial nephritis and necrotising angiitis consistent with aggressive sarcoidosis. Treatment with prednisolone was continued and induced a gradual renal recovery enabling her to become dialysis independent. This case highlights the value in repeating serial ACE measurements in cases where there is strong clinical suspicion of renal sarcoidosis despite initial negative results.

## The Use of a Physical Training Programme to Improve Quality of Life, Nutritional and Functional Parameters in Long Term Haemodialysis Patients

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**Background** It is well recognised that long term haemodialysis patients are at risk of protein energy malnutrition (PEM) and that this in turn may influence morbidity (in particular quality of life (QOL) and functional ability) and mortality in this group. Whilst exercise has been used as an intervention strategy in this population previously the majority of studies have focused primarily on cardiovascular and functional improvement in isolation or have been short term with limited outcome measures. **Aims** The overall aims of this study were to provide qualitative and quantitative data on whether a training programme is a feasible clinical option that could improve QOL, nutritional and functional parameters in haemodialysis patients (HD) **Methods and Outcome measures** This study was exploratory and clinical in nature and as such the methods and outcome measures reflect this. Patients were recruited for a total of 13 months (1 month run in with 12 months of cycling) outcomes were measured at run in (-1 month), baseline (0 months), 3, 6, 9, 12 months. Outcome measures included: Sit to stand, sit & go, handgrip, post dialysis weight, BMI, MAC, TSF, AMC, Calf circumference, Calf Muscle Circumference, Dual Frequency BIA, Appetite VAS, interdialytic food diaries, PCR, Quality Life: (SF36v2), BP: Pre & post U&E's, Po<sub>4</sub>, Alb, Hb, CRP, Leptin, URR, UKM; ESA, antihypertensives. **Results** Six month results based on data analysis to date (n=20) demonstrate significant functional Improvements (Handgrip, Sit to Stand, Timed 3 m up and go), improvement in the physical component of QOL (SF36v2) along with improvements in BP, Hb, pre-dialysis biochemical parameters (potassium, bicarbonate, phosphate) and dialysis adequacy (URR) **Conclusion** From results to date it appears that intradialytic exercise improves functional status, functional aspect of QOL, and improves dialysis, HB, BP and biochemical control. However the study was an exploratory non randomised study based on a small population of stable patients from a single centre and results require to be confirmed in a wider multicentred study using refined outcome measures.

## Screening of Advanced Chronic Kidney Disease - a Five Year Experience

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The late referral of patients with advanced chronic renal failure to a nephrologist is multifactorial but also compromises their preparations for dialysis and is prejudicial to their survival on dialysis. The median creatinine at the time of referral to a nephrologist for patients who started dialysis in 1999 was 390  $\mu\text{mol/L}$  (MDRD GFR = 14 ml/min/1.73m<sup>2</sup>). Measures that hasten referral, will allow preparation for dialysis, control of complications and treatment of comorbid conditions. In June 2000, a programme was designed to screen serum creatinines over 300  $\mu\text{mol/L}$  on all lab requests from GPs and hospital doctors in Ayrshire & Arran. Patients already known to the nephrologists were excluded. In a sample month, there were 354 separate results (over 300  $\mu\text{mol/L}$ ) from 90

individual patients. Results were regularly reviewed and further excluded if creatinine fell or the patient died. For the remainder a standard letter was sent to the requesting clinician suggesting renal referral if appropriate. In the first 5 years (June 2000 - June 2005) letters were sent regarding 246 patients (median age 76). Fifty three still had reversible ARF or died within three months of the letter; seven were already referred. The requesting clinician felt that referral was not appropriate in 56; 23 were being reviewed elsewhere. The programme has led to the referral of 50 patients to the renal service; three were referred to other specialties. In 54 cases no reply was received and the letter was ignored. If all 50 referred patients reached dialysis, this would potentially increase the annual take on rate by 26.6 patients per million. The exercise may also have increased "renal-awareness" among clinicians. The median presenting creatinine for patients starting in 2004 was 251  $\mu\text{mol/L}$  (MDRD GFR = 21 ml/min/1.73m<sup>2</sup>). The review of elevated creatinines in detected chronic kidney disease is labour intensive but may improve renal referral and take on rates.

Funding - none

Conflict of interest - none

## A Cross-sectional Study of Radiological Prevalence and Morbidity Associated with b<sub>2</sub>-microglobulin Amyloidosis in a Chronic Haemodialysis Population

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**Background** Dialysis related amyloidosis (DRA) caused by deposition of b<sub>2</sub> microglobulin contributes to the morbidity associated with chronic haemodialysis. There are characteristic x-ray changes, and it has been suggested that there may be diagnostic appearances present on joint ultrasonography. Our study sought to assess the health burden associated with DRA in contemporary haemodialysis (HD) practice and evaluate the prevalence of radiological changes of DRA in a HD population. **Methods** 49 haemodialysis patients were recruited. Questionnaires were used to measure joint and carpal tunnel compression symptoms and quality of life assessment. Plain film and musculoskeletal ultrasonography of joints was performed. Nerve conduction studies (NCS) assessed median and ulnar nerve conduction. **Results** Increasing time spent on HD was associated with increasing joint and CTS symptoms, and likelihood of having required carpal tunnel decompression. NCS showed a high prevalence of both CTS (28/49), and general neuropathy (22/49) in HD patients. High Flux dialysis membranes demonstrated increased b<sub>2</sub> microglobulin (b<sub>2</sub>m) removal, but similar pre-dialysis [b<sub>2</sub>m] and symptomatology. Time on renal replacement was associated with increasing thickness at the supraspinatus tendon and the hip capsule. Bone cysts were seen in only 5/43 patients, all with greater than 20 years on dialysis. **Conclusions** Joint and carpal tunnel symptoms represent a progressive burden on HD patients. Neuropathic changes may be as important as CTS as a cause of hand symptoms. Ultrasound can offer supportive evidence for DRA, but is not diagnostic. Our prevalence of bone cysts was less than in historical prevalence studies.