Expert Forum
Nephrology Meeting
Making Education Easy
October 2009

In this review:

Welcome

to this review of the recent Annual Nephrology Meeting held in Rotorua chaired by John Collins, Ian Dittmer, Maggie Fisher and Jenny Walker. We have summarised the important points of the presentations made at the meeting for your information.

Renal disease and ethnicity in NZ

Kidney disease in Māori and Pacific people in NZ

Presented by: Dr John Collins, Renal Physician, Auckland City Hospital and Greenlane Clinical Centre

End-stage renal disease in NZ

Australian and New Zealand Dialysis and Transplant Registry (ANZDATA) show that during 2003–2007, the proportion of Māori and Pacific people starting dialysis has consistently been 3- to 4-fold greater than for Europeans, with diabetes being the primary cause of new end-stage renal disease (ESRD) cases in 63% and 65% of Māori and Pacific people, respectively, compared with 17% of Europeans. The prevalence of diabetes among Māori is about 2.5-fold greater than for Europeans,[1] while the incidence rate of ESRD secondary to diabetes is 13.6 and 14.7 in Māori and Pacific people respectively, and the respective incidence rates for ESRD secondary to glomerular nephritis are 1.9 and 2.3. Interestingly, in terms of patient survival, Pacific people appear to fare better (see Figure 1).

There was also reduced access to renal transplantation for Māori and Pacific dialysis patients aged <60 years without diabetes between 2005 and 2007 compared with nonindigenous dialysis patients (17% and 18, respectively, vs. 35%); similar disparities for indigenous minorities in other English speaking developed countries have also been reported.

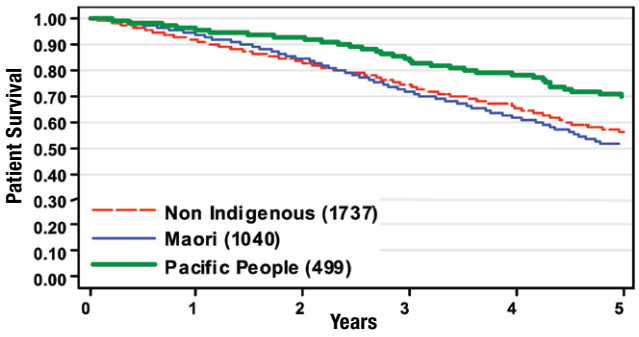

Figure 1: Patient survival following renal transplant 2001–2007 (ANZDATA), adjusted for age, diabetes, gender and comorbidities.

Kidney transplant outcomes among Maori and Pacific people in NZ

NZ data between 1991 and 2007 reveal that Māori accounted for 14% of first kidney-only transplants and 29% of those starting renal replacement therapy. Of more concern are transplant outcomes, with Māori and Pacific people experiencing substantially worse graft survival than nonindigenous people (adjusted hazard ratios 2.19 [95% CI 1.66, 2.88] and 2.12 [1.48, 3.00], respectively). In addition, Māori had a greater likelihood of post-transplant death (adjusted hazard ratio 1.74 [1.21, 2.50]) with increased proportions of cardiac disease and infections being the cause. We also know that in 2000, Māori men in NZ had a higher mortality rate and a shorter life expectancy than non-Māori men, even after adjusting for social deprivation.

Differences in health outcomes in Māori

Unfortunately, no comprehensive study on the early stages of kidney disease in NZ has ever been conducted. However, several sources have indicated that albuminuria, hypertension and some forms of glomerular disease are more common among Māori and Pacific people.[2–6] Some novel risk factors for kidney disease that may be particularly important for these populations include periodontitis, low birthweight and hyperuricaemia.

In summary, there is currently insufficient evidence to allow conclusions about the presence or extent of these healthcare disparities for Maori and Pacific people to be drawn.

Take home points

- Compared with NZ Europeans, Māori/Pacific people have:
  - a higher incidence of diabetes, hypertension, albuminuria and glomerulonephritis, which are associated with a higher incidence of ESRD.
  - a preponderance of identifiable risk factors that partly explain the increased incidence and poorer outcomes
  - worrying mortality trends (for Māori).
- There is currently insufficient evidence to draw conclusions about the presence or extent of these healthcare disparities

Renal disease and ethnicity in NZ (continued)

Proteinuria and ethnicity

Presented by: Dr Drew Henderson, Nephrologist, Hawkes Bay Hospital

NZ patient records have shown that Māori and Pacific people are disproportionately represented in renal clinic presentations. Moreover, while Pacific people experience similar survival rates to nonindigenous people, survival rates among Māori patients are worse. The rate of diabetes is higher among Māori/Polynesians, which corresponds to a higher rate of ESRD, and this population also has higher rates of proteinuria and microalbuminuria at diabetes presentation. These patients are also prescribed similar treatments and are not referred to renal services later than other patients. Together, these data support the observation that renal disease appears to be more malignant among Māori/Polynesians, and challenge the widely held beliefs that the differences are mainly attributable to less access to healthcare and poorer compliance with treatment in these patients.

Ethnic differences in renal disease at time of presentation to Hawkes Bay Renal Clinic

Dr Henderson presented the findings of a retrospective study based on the following hypotheses:

- Māori have worse proteinuria at time of presentation independent of diabetic status and eGFR
- Māori patients are not referred later than other patients
- Māori patients present with CKD at a younger age
- Māori have already received an appropriate prescription at presentation.

All referrals to a Hawkes Bay renal clinical over a 2.5-year period were analysed. Māori (self declared) accounted for 31% of all referrals and their mean age was around 5 years younger than NZ Europeans, while the proportion of Pacific people referred was comparable to that in the general population (~2%).

Mean eGFR at referral was significantly greater among Māori compared with NZ Europeans (46 vs. 39 mL/min; p=0.03). Diabetes was more common among Māori than NZ Europeans (55% vs. 28%; p<0.01), and mean eGFR in these patients was also greater among Māori. The proportion of patients presenting with an eGFR <15 mL/min did not differ between Māori and NZ European (10% for each ethnicity). Mean Pr/Cr ratio was also greater among Māori than NZ Europeans (280 vs. 88 mg/mmol; p<0.01), and this difference was also evident in both diabetic and nondiabetic subgroups, and for each CKD stage. The number of patients not receiving an ACE inhibitor did not differ significantly between Māori and NZ Europeans, but Māori did have higher mean arterial pressure at referral (105.6 vs. 97.8mm Hg; p=0.06), due primarily to a significantly greater diastolic BP (86.7 vs. 74.5mm Hg; p<0.01). A larger study with a multivariate analysis is needed to determine what drives these differences.

Take home points

- Renal clinic referral is more frequent in the Māori population
- Māori patients are likely to be younger at time of referral
- Māori patients are more likely to have diabetes
- Māori patients have better preserved eGFR at presentation, but significantly worse proteinuria
- Māori patients are no more likely to present to clinic with an eGFR <15mL/min than NZ Europeans
- ACE inhibitors use in both NZ Europeans and Māori with diabetes is high prior to first renal clinic visit
- Māori are more likely to have diastolic hypertension at their first clinic visit

Māori diabetic disease in the Waikato

Presented by: Dr Maggie Fisher, Clinical Director, Renal Service, Waikato DHB

Māori accounted for 62.5% of 891 patients treated at the Waikato Dialysis Unit between 1991 and 2005, and 67.5% of them were treated for end-stage kidney failure caused by diabetes. Other comorbidities (coronary artery disease, stroke and peripheral vascular disease) did not differ much between Māori and non-Māori. Māori also presented late more than non-Māori (43.7% vs. 27%), although this has improved over recent years. There was also a greater incidence of proteinuria in Māori, right from initial presentation through to end-stage disease.

Incidence of ESRD among diabetes patients in the Waikato

Based on known data, there is an assumption that Māori with diabetes are more likely to develop renal failure. The study set out to determine the incidence of renal failure among Māori with diabetes in the Waikato region, and also to investigate the natural progression of kidney disease in patients with diabetes. Participants included adults diagnosed with diabetes prior to 2003 without a history of renal complications from the Waikato Regional Diabetes Service database and retrospectively followed from 2003–2006.

Baseline characteristics revealed that Māori patients were younger than NZ Europeans (55 vs. 62 years) and nearly all the Māori participants had type 2 diabetes (95% vs. 84% for NZ Europeans). In the subgroup of participants who developed ESRD, 10 and 38 had type 1 and type 2 diabetes, respectively. Moreover, 28 Māori with type 2 diabetes (1.8%) started dialysis within the 3-year follow-up period, compared with just 2 NZ Europeans (0.04%). A further 12 Māori with type 2 diabetes from the Waikato region, but who were not included in the study, also started dialysis during the study's follow-up period. Hazard ratios for ESRD were 6.7 (95% CI 3.0, 15.0) for type 1 vs. type 2 diabetes and 25.2 (10.7, 59.7) for Māori vs. NZ European diabetics, which increased to 46.4 (10.7, 201) when only those with type 2 diabetes were included in the analysis. The age-adjusted incidence rates of ESRD among Māori with diabetes were higher than among NZ Europeans (19.3 vs. 1.27 per 100 person-years for type 1 diabetes and 4.39 vs. 0.11 per 100 person-years for type 2 diabetes). Survival curves were also considerably worse for Māori than for NZ Europeans (see Figures 2–3).

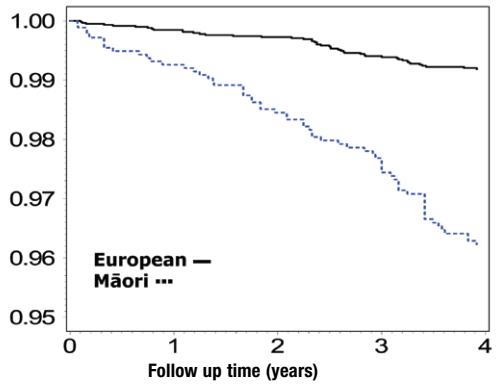

Figure 2: Survival curves for European and Māori patients from Cox's proportional model, after accounting for age and gender, for time to renal admission

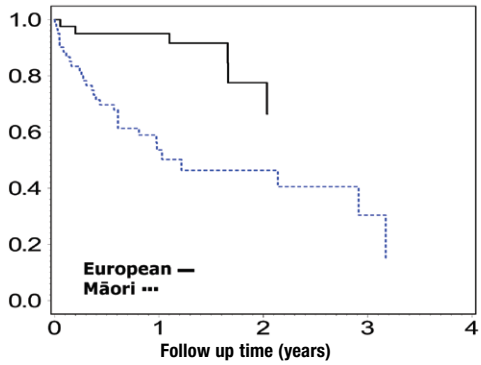

Figure 3: Survival curves for European and Māori patients from Cox's proportional model, after accounting for age and gender, for time to dialysis/transplant from first renal admission.

Take home points

- Ethnic disparities exist in ESRD incidence among patients with diabetes
- There is a need for early identification and intensive management of at-risk patients
- There is an urgent need for further research into the aetiology of renal disease in the Māori population

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Nephrocalcinosis

Presented by: Terry Feest, Professor of Clinical Nephrology, Bristol and Renal Physician, Auckland

This presentation by Prof. Feest is drawn from 300–400 cases of nephrocalcinosis over around 35 years followed by Prof. O.M. Wrong and Prof. Feest. Nephrocalcinosis is a generalised increase in calcium in the kidney, seen as diffuse calcification on x-rays, and is a sign or symptom of a wide variety of disorders. In most (~90%) of patients nephrocalcinosis is due to calcium oxalate, in most other patients calcium phosphate. It is not clear whether nephrocalcinosis begins in the tubule lumen or renal tissue. A few biopsies in renal tubular acidosis have indicated interstitial calcification erupting into the tubule, but it may be the reverse in other conditions.

Cortical nephrocalcinosis occurs in only around 3–4% of cases, often after haemolytic uraemic syndrome, or in ischaemic or dystrophic kidneys. It is usually a sign of infarction: most cases are children with glomerulonephritis.

Medullary nephrocalcinosis is the most common type and can be divided into three broad categories (see figure 4).

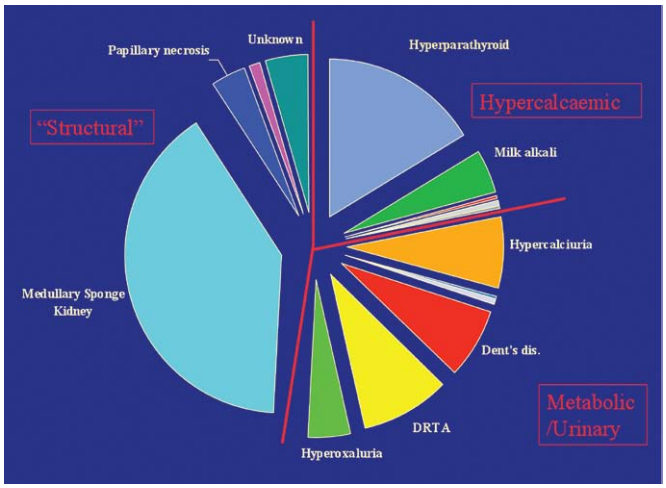

Figure 4: The Jobbing Nephrologist's Guide to Medullary Nephrocalcinosis

Hypercalcaemic nephrocalcinosis

Hypercalcaemic nephrocalcinosis only occurs with prolonged hypercalcaemia, and is not uncommon in patients who have had low-grade hyperparathyroidism for many years. These patients may present with stones and may have had serum calcium and parathyroid hormone (PTH) levels in the upper limits of normal for a number of years. This may also be seen in milk alkali syndrome when patients take large amounts of calcium carbonate, almost always in the form of 'Rennies': these patients are also very hypercalciuric.

Hypercalciuric nephrocalcinosis

Hypercalciuria can be due to absorptive processes (increased gut absorption, serum calcium not efficiently suppressing conversion to 1,25-dihydroxyvitamin D, high normal calcium/low PTH), resorptive processes (tubular leak, low normal calcium/high PTH) or other. In clinical practice, 'other' seems most common. It is important not to restrict dietary calcium in these patients, as this increases oxalate absorption and thus urinary oxalate, and increases the tendency to stone formation. Stone growth/formation occurs largely during the night when the urine is most concentrated, so the most useful treatment is to increase water intake during the evening/night to reduce nocturnal urinary concentration. Bendrofluazide can also be useful as it lowers urinary calcium without affecting oxalate.

Dent's disease

Patients with Dent's disease usually have hypercalciuria and profound proximal tubular proteinuria. Other common features include hypophosphataemia, amino-aciduria, hypokalaemia, nephrocalcinosis, ESRF, bone disease and distal renal tubular acidosis. It is an X-linked recessive condition, although tubular proteinuria and other mild disease may occur in women who rarely develop ESRF. It can cause male infertility.

Distal renal tubular acidosis

Distal renal tubular acidosis (RTA) is a collection of syndromes with differing underlying pathologies involving differing molecular mechanisms. Primary distal RTA includes familial types (both dominant, and recessive with neural deafness) and transient infantile (now very rare). Secondary distal RTA is more common and may be associated with autoimmune disorders or stones, obstruction or transplantation. Sporadic distal RTA also occurs. Features include nephrocalcinosis (80%), urine concentration defects (80%), acidosis (70%) hypokalaemia (50%), osteomalacia/rickets (25%), hypertension (11%), urine salt loss and urinary tract infection (particularly women). With appropriate care patients may thrive.

Case: One of two brothers with sensor-neuronal deafness and distal RTA who was originally seen in 1974 and originally lost to follow-up later presented again.[1] He had received long-term sodium bicarbonate, and had thrived, becoming a local weightlifting champion, never experiencing any renal symptoms. X-ray findings in November 2008 were virtually identical to those from 30 years previously.

Hyperoxaluria

Primary hyperoxaluria - case: A man (born in 1965) with congenitally absent right kidney underwent multiple procedures for stones. From 2000, his plasma oxalate level was 17–20 µmol/L. In 2007, he developed peripheral neuropathy and began haemodialysis in December that year. Possible autonomic neuropathy was diagnosed in 2000, and he underwent daily home dialysis in an attempt to lower his oxalate level. He wants a renal transplant, but prognosis is poor in these patients.

Secondary hyperoxaluria: In enteric hyperoxaluria such as patients who have had intestinal bypass there is high oxalate absorption in the colon due to the shorter small gut failing to absorb bile acids which damage the colon and lead to increased oxalate absorption, hyperoxaluria and potentially to renal failure.

Medullary sponge kidney

Medullary sponge kidney is characterised by cystic dilatation (7.5mm) of the collecting tubules lined by flattened cuboidal/columnar cells. Ectatic tubules fill with debris, including calcium. It is unclear if the entire kidney is always affected. Importantly, medullary sponge kidney cannot be diagnosed by ultrasonography. Other conditions associated with medullary sponge kidney include hemihypertrophy and salivary gland stones. 30% of patients become hypertensive. Most patients retain reasonably normal renal function, but ESRF secondary to recurrent stones and infection has been seen.

The underlying mechanisms of medullary sponge kidney are not known, but there is some evidence that glial-derived neurotrophic factor (GDNF) and receptor tyrosine kinase (RET; GDNF's receptor) are important for prompting ureteric budding during embryogenesis, and gene abnormalities are being investigated, even though family history is rare.[2–3]

Cases: In most of the 103 cases in an unpublished case series, the patient presented with symptoms of colic, stone passage and dysuria. Among 10 asymptomatic patients, three had microscopic haematuria and seven were being investigated for hypertension. The peak age presentation was 20–30 years. The features of medullary sponge kidney in these patients were nephrocalcinosis/stone (>70%), loin pain without stones (>30%, particularly women), haematuria (>40%), recurrent UTI (>35%) and nocturia (>25%). There was an equal distribution between genders, and a family history was rare.

A man presented in 1975 with painless haematuria. He had medullary sponge kidney with widespread nephrocalcinosis, macrohaematuria, calculi and profound hypercalciuria. He underwent multiple interventions, and in 1992 underwent left lower pole nephrectomy, but ended up developing an addiction to pethidine (meperidine), which he was receiving for severe pain. In 1998, he underwent a full left nephrectomy privately (despite advice not to do so). Predictably, he developed pain in his right kidney the following year (he died of hepatitis C liver disease in 2005).

Treating nephrocalcinosis

Success depends on the type. Primary causes such as hyperparathyroidism or milk alkali syndrome should be treated. In most other cases, treatment often only slows or halts progression. The main treatment is to drink a lot of water in the evening/night to avoid increased nocturnal urine concentration. Bicarbonate in RTA may be helpful, but other types are very difficult to treat and removing the calcinosis is probably not achievable. Prognosis depends on the primary cause, and in most cases is generally good provided patients are managed well with avoidance of recurrent obstruction and infection. However, the prognoses are worst for nephrocalcinosis secondary to Dent's disease and hyperoxaluria.

Take home points

- Despite often dramatic radiological features, the clinical course of nephrocalcinosis is usually benign if obstruction and infection are prevented/treated promptly
- Nephrocalcinosis can cause (usually) subtle changes in tubular function
- There are clearly several more conditions that cause nephrocalcinosis that have yet to be identified and studied.

References:

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2. Costantini F & Shakya R, GDNF/Ret signaling and the development of the kidney. Bioessays 2006;28(2):117–27
3. Gambaro G et al. An unusual association of contralateral congenital small kidney, reduced renal function and hyperparathyroidism in sponge kidney patients: on the track of the molecular basis. Nephrol Dial Transplant 2005;20(6):1042–7

Catheter-associated bloodstream infections at Auckland Hospital before and after initiation of antibiotic locks

Presented by: Dr Gerald Waters, Renal Trainee, Auckland Hospital

Dr Waters was awarded the Morrison award at the meeting for this presentation.

This audit compared the rate of catheter-associated bloodstream infections (CABSIs) during the 18 months before and after the introduction of gentamicin (10 mg/mL) locks in December 2006 at Auckland Hospital.

All patients aged ≥18 years undergoing dialysis exclusively at the acute unit within the hospital or the Grafton Rd outpatient unit were included. The rate of possible, probably or certain CABSIs (defined as ≥1 positive peripheral or central blood culture) after the introduction of antimicrobial locks was significantly lower than before their introduction (0.84 vs. 1.39 per 1000 catheter-days; p=0.03; relative risk 0.61 [95% CI 0.37, 0.98]). The number of *S. aureus* infections did not differ between the two periods, but the number of infections with Staph epi/CNS, other Gram+ and other Gram- infections decreased after the locks were introduced. The number of infections was also reduced for each line type, but the totals and differences were too small for random variation to be excluded. Data regarding metastatic infection, mortality and time from catheter insertion to infection generally tended to show a positive effect, but the totals and differences were also small, while hospital length of stay data were confounded by outliers and patients staying in hospital for long periods due to other conditions/procedures. There were also decreases in both gentamicin sensitivity and resistance after the locks were introduced, but the significance of these differences is not clear due to the small numbers. A cost analysis indicated that there was a savings of $24,000 after the locks were introduced, with the cost associated with the locks being offset by shorter hospital stays.

The study's limitations included: 1) exclusion of tunnel infections with no positive blood cultures; and 2) inadequate blood cultures were taken in some infections. Possible confounders included: 1) a greater number of IJ lines used prior to the introduction of the locks; 2) possible changes in practice (although the educational programme and protocols did not change); and 3) possible changes in compliance.

Take home points

- Significant reduction in infection rate by about 40% with cost benefit
- Reduction mainly due to organisms other than *S. aureus*
- No evidence of gentamicin resistance

Peritonitis in the Waikato: an audit

Presented by: Dr Kim Wong, Renal & General Physician, Waikato DHB

This audit from the Waikato Midland Peritoneal Dialysis Service showed that during 1997–2008, 863 patients underwent peritoneal dialysis, and 51% of them had diabetes and 60% were Māori. Half were from the Waikato region, with the remainder from the other regions covered by the service. The age distribution was similar to the overall NZ distribution, with the mean starting age 56 years.

The peritonitis rate was 1:19.3, which compares well with NZ's peritonitis rate of 1:18.5 (ISPD-recommended minimum acceptable rate 1:18). The yearly peritonitis rates from 1989 to 2008 showed some fluctuation, some of which appeared to correspond to changes in practice, techniques and equipment (see figure 5). The differences in peritonitis between the use of Fresenius and Baxter products prompted an audit for the period 1999–2002. Factors that were found to contribute to peritonitis were: 1) the change from ultra set to 'Y flush' tubing; 2) nasal screening for *S. Aureus*; 3) awareness of sterile nontouch 'mask' techniques; 4) audit activity in 2003; and 5) Baxter vs. Fresenius. However, it was found that patients on Fresenius had a higher rate of comorbidities, and this is probably the main reason for the poorer outcomes associated with this system. Another finding of this audit was that 17% of patients contributed to 37% of the total peritonitis episodes.

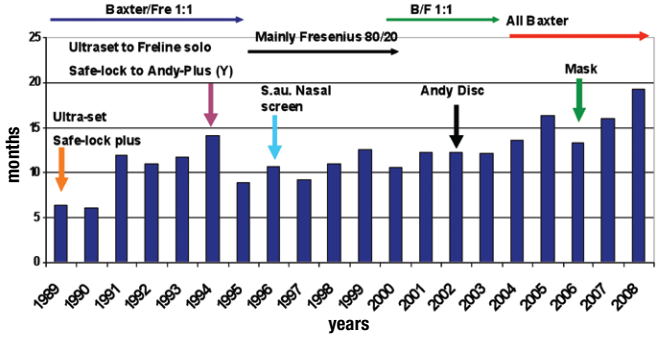

Figure 5: Peritonitis rate: patient-months/episodes

The cultured organism profile in the Waikato audit was similar to the NZPD Registry and Australian profiles, with a high proportion (~30%) of coagulase-negative *Staphylococcus* spp. There were several changes in the empirical treatment protocols over the audit period, although since 2001 the protocol has been gentamicin 0.6 mg/kg (max 60mg) and cephazolin 2g IP (repeated at night if administered before midday). Around 70% of peritonitis cases resolved with antibiotics, 17% required catheter removal, 4% relapsed and were then cured and 3% died (outcome unknown in 7%); these data are comparable with 1996–2000 NZ data. For specific organisms, resolution with antibiotics was lower (60%) for *E. coli* and only 50% for *Serratia* spp. (with 40% requiring catheter removal), while >70% and >80% of coagulase-negative *Staphylococcus* and *Streptococcus* cases, respectively, resolved with antibiotics.

The percentage of patients with >1 episode of peritonitis remained relatively stable at ~50% over the audit period, which is relatively consistent with Australian data. Reasons for stopping peritoneal dialysis as a proportion of total PD patients included death in 34.8% of patients, 22.7% switched to haemodialysis, 6.3% underwent transplant surgery, and 4.3% transferred to another area/service (outcome unknown in 9.1%).

Take home points

- Peritonitis rate comparable with the rest of NZ (19.3 vs. 18.5 patient-months)
- Rigorous attempts to improve peritonitis are needed
- Peritonitis-causing organisms are similar to the rest of NZ
- High representation of diabetes and lower socioeconomic groups
- Need to address how to deliver care to the needy group and how to reduce the proportion of patients developing peritonitis

Audit of cardiovascular risk factors among Whangarei Hospital renal outpatients

Presented by: Dr Kaye Logan, Canterbury DHB

This cardiovascular (CV) risk audit of Whangarei Hospital nondialysis, nontransplant renal outpatients was conducted over a 10-week period during Jul–Sept 2009. There were 131 patients aged 15–86 years, 89% of whom were returning patients, 60% were male and 76% were from Whangarei itself. Most patients had stage 4 or 5 CKD (44% and 7.3%, respectively); 35% were stage 3, 3% were stage 2 and 10.7% were stage 1. CKD was caused by hypertension/vascular disease in 38% of patients, diabetes in only 25% and glomerulonephritis in 12%, while other causes were each <10%. Relevant comorbidities included ischaemic heart disease (29%), cerebrovascular disease (13%) and peripheral vascular disease (12%). Only 13% of patients were current smokers, and 80% had never smoked or had not smoked for ≥5 years. However, 55% of the patients had a BMI >30.

Control of risk factors

Using BP guidelines of <125/75mm Hg if proteinuria >1 g/24h and <130/80 if less proteinuria, 70% of patients had a target BP set, and 55% of those had reached their target. Most patients were receiving >3 agents, with <10% receiving none. An angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB; the main agents recommended for treating CKD patients with proteinuria and those with diabetic nephropathy and are widely used in secondary CV disease prevention) was being received by 97 patients, and all but 6 of those not receiving one had a clear reason (e.g. contraindicated, not indicated, were due to start that day).

Type 2 diabetes was present in 44% of patients, and type 1 was present in 1%. Target glycosylated haemoglobin (Hb_{A1c}) <7% was achieved by 41%. With respect to proteinuria, 70% had proteinuria measured in the previous year, and 80% and 51% of those with significant proteinuria (>30 mg/mmol) were receiving an ACE inhibitor and had achieved BP targets, respectively.

Cholesterol levels had been checked in the previous year in 78% of the patients, but among those not checked, 75% were repeat patients. Cholesterol lowering therapy with a statin was being received by 72% (74% and 80% of CKD stages 3 and 4–5, respectively), but only 27% had achieved the audit's target cholesterol level of <4 mmol/L. Aspirin therapy was being received by 68% of patients, 62% of whom had established vascular disease; 7% of patients were receiving warfarin.

The suggested action plan for the clinic in response to the audit included:

- Set target BP 125/75mm Hg for proteinuria >100 mg/mmol, otherwise 130/80mm Hg, and discuss with patient and communicate to GP
- Prescribe ACE inhibitors or ARBs as first line
- Provide smoking cessation advice
- Provide lifestyle advice (possible in nurse-led clinics)
- For diabetics: 1) set target Hb_{A1c} fraction <7%; 2) refer to dietician; 3) maximise oral hypoglycaemic agents; 4) consider need for insulin; 5) refer to hospital clinic for management advice; and 6) refer to podiatrist
- Prescribe statin if cholesterol >4 mmol/L and titrate to achieve target
- Consider starting aspirin

Future plans included: 1) implementation of the above action plan in the clinic; 2) re-audit after 12 months with particular emphasis on BP, diabetes and cholesterol control; 3) address whether more emphasis needs to be placed on lifestyle, diet and exercise advice; and 4) obtain more evidence/data from the population.

Renal autoregulation

Presented by: Prof Rob Walker, Head of Dept, Medical and Surgical Sciences, Dunedin School of Medicine

Renal autoregulation is a complex process involving a number of known mechanisms, and others that are still being discovered.

Myogenic response and tubuloglomerular feedback (TGF) mechanisms

The myogenic response prevents changes in systemic BP being transmitted to the glomeruli. The mechanism involved includes stretching of vascular smooth muscles in response to an increased intraluminal pressure. Depolarisation occurs leading to vascular smooth muscle constriction via a calcium-mediated event, and the tension is relieved.[1] It is also now believed that specific epithelial sodium channel (ENaC) on vascular smooth muscle cells and vascular endothelial cells are probably important for sensing the changes in intraluminal pressure. It has been proposed that increased vascular wall tension opens the extracellular matrix attached to the channel, which mechanically opens the ENaC allowing sodium influx.

The TGF mechanism essentially exists to conserve salt (NaCl). When the NaCl level is low, GFR and NaCl reabsorption are increased, and systemic BP is therefore increased. Conversely, a high NaCl decreases GFR. The proposed mechanism involves uptake of NaCl by macula densa cells, adenosine is generated, and a transient increase in Ca^{2+} results in vasoconstriction and decreased renin secretion.

Renin release can also occur very quickly via other mechanisms. For example, very small decreases in perfusion pressure to the afferent arteriole lead to renin release, mostly into the interstitial space of the juxtaglomerular apparatus (JGA), within one second.[2] This shows that pressure-dependent changes in the renin-angiotensin system are a major cause behind hypotensive resetting associated with renal blood flow autoregulation.

Increased angiotensin II induced via pressure-driven renin stimulation is mandatory for the TGF response. In addition, angiotensin II directly constricts the pre- and postglomerular vessels, and thereby affects the NaCl load delivered to the macular densa, and also has important effects in the proximal tubules, including increased NaCl reabsorption. Therefore, marked changes in NaCl delivery to the macular densa can occur at a constant filtered load. This change in NaCl load markedly affects metabolism and decreases tissue oxygen tension in the kidney.

A 'third' mechanism

A third renal autoregulation mechanism is related to renin. There is marked heterogeneity of cortical renin synthesis, with clear evidence that, in addition to the JGA, robust renin synthesis occurs in the principle cells of the connecting tubule and collecting duct; the collecting duct is the main source of prorenin in diabetes.[2] Moreover, while angiotensin II inhibits renin release in the JGA, it stimulates its release in the collecting duct, and therefore this 'third' mechanism mirrors TGF. It is also probably of tubular origin, at the level of the collecting tubule. Increased NaCl delivery to the collecting tubule leads to dilatation of preconstricted afferent arterioles, which is the opposite effect to the macular densa response.

Toma et al have reported new evidence from animal studies that, in diabetic hyperfiltration, increased glucose directly acting on succinate receptors in the JGA afferent arterioles triggers renin release and vasodilation of afferent arterioles within a few minutes, rather than triggering sodium and glucose uptake in the proximal tubule as previously thought.[3] Increased glucose entering the Krebs cycle increases succinate, which activates G-protein coupled receptor GPR91, a very important detector of cell metabolism. Calcium levels are increased, along with NO and PGE2 release, which results in increased renin release from the JGA. The GPR91 protein is located only on the endothelium of the glomeruli and afferent arterioles, and not on JGA cells.

This succinate receptor mechanism is probably very important for closely regulating the oxygen requirements and energy balance in the hypoxic environment of the kidneys, as succinate accumulates when energy requirements and oxygen supply and demand are out of balance, and glucose increases reduce renal oxygen tension and mitochondrial respiration.

Take home points

- Complex interplay between tubular mechanisms, myogenic responses and vascular responses
- Differential cortical synthesis and release of renin
- Intracellular metabolic and oxygen sensing via succinate

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Tuberculosis in renal patients: screening with QuantiFERON®

Presented by: Dr Murray Leikis, Wellington Renal Unit

Chronic renal failure/haemodialysis is a significant risk factor for the development of active tuberculosis (TB; relative risk ~10–25).[1–3] A retrospective review identified 7 cases of culture-confirmed TB at the Wellington Renal Unit during the 10 years until December 2008, with an incident rate of 1.2% for patients starting on dialysis during the same time. All except one (a Māori patient) were born overseas, and all had comorbidities with type 2 diabetes being the most common (4 patients). Disease sites included peritoneal (n=4), pulmonary (2), pleural (2), cervical node (1), sacroiliitis (1) and spinal (1). The mean time from start of dialysis to diagnosis was 538 days (11–1351; one case was diagnosed at post-mortem), and of the 6 who died, the mean time to death was 348 days with 4 dying within 1 year of diagnosis.

One study has found that isoniazid therapy for haemodialysis patients with latent TB significantly reduced the development of TB compared with placebo.4 However, identifying patients with latent TB can be problematic. Features of the *in vitro*, cell-mediated immunity-based test 'QuantiFERON®-Gold in-tube test' include: 1) cost of around $54; 2) usually only performed Monday–Thursday; 3) blood samples require a special tube with exact blood volumes, and need to be shaken vigorously; 4) each test requires a positive (mitogen) and negative control, from which the sample's status is calculated; 5) results are reported as positive, negative or indeterminate; and 6) should be performed prior to dialysis.

TB screening at the Wellington Renal Unit

The 2003 MOH guidelines for TB control in NZ recommend that dialysis patients should be tested for TB,[4] which reflects CDC an European guidelines. A decision was made at the Wellington Renal Unit to test all haemodialysis patients for latent TB. QuantiFERON® testing was carried out in 65 haemodialysis patients. Initially, only 6 were positive, 53 were negative and 6 were indeterminate. All 6 positive results were in diabetic patients born overseas. Four of the indeterminate result patients were retested and found to be negative (the other two patients were in the terminal phase of their non-TB illness so were not retested). Chest x-rays for those with negative tests revealed one patient from China who had some midzone scarring, so was retested and found to be positive; the TB antigen level of the original test was only 0.01 U/mL below the threshold for a positive result (≥0.35 U/mL).

All patients with a positive TB test received a 9-month regimen of isoniazid plus pyridoxine and started monthly liver function test monitoring, and those awaiting renal transplantation remained on the waiting list. Moving forward, the unit plans to: 1) offer latent TB screening (QuantiFERON-Gold®) to all new and existing peritoneal and haemodialysis patients; 2) test all patients prior to transplant; 3) follow up all TB-positive cases; and 4) offer staff testing and counselling.

Take home points

- Renal patients are high risk for TB
- TB in renal failure can be hard to diagnose; is often extrapulmonary
- QuantiFERON® is a simple, inexpensive diagnostic test for latent TB
- Latent TB can be treated
- The latent TB rate was lower than expected

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Anti-inflammatory effect of insulin infusion in patients on maintenance haemodialysis: a randomised controlled pilot study

Presented by: Dr Frederiek Vos, Department of Medical and Surgical Sciences, Dunedin School of Medicine, University of Otago

A single-blind randomised controlled pilot trial tested the hypothesis that insulin has an anti-inflammatory effect on biochemical markers in patients undergoing haemodialysis during the first 24 hours. Participants were 11 stable nondiabetic patients with polycystic kidney disease (n=4), atherosclerotic renal vascular disease (2), glomerulonephritis (1) and other (4) who were randomised to receive an infusion of short-acting insulin (Actrapid) 2 U/h plus glucose (adjusted to glucose levels) during 4-hour haemodialysis or conventional haemodialysis in a cross-over design (dialysate 5 mmol/L glucose).

All evaluated markers of inflammation (C-reactive protein [CRP], interleukin (IL)-6, tumour necrosis factor-α, vascular cell adhesion molecule-1 and neopterin) and oxidative stress (protein thiols, peroxides, dityrosine) were comparable between the groups at baseline. Plasma CRP levels were significantly lower in insulin recipients than in those who underwent conventional dialysis during the acute phase of haemodialysis and at 24 hours (see figure 6). None of the other markers measured differed significantly between the two groups. In addition, median insulin levels were maintained within a physiological range in the insulin group, whereas they decreased in the conventional dialysis group (225.5 vs. 38.1 pmol/L at the end of dialysis).

The CRP reduction in this study is consistent with observations in other patient groups (acute MI and coronary artery surgical patients),[1,2] while studies that have failed to show any beneficial effect used fixed-dose insulin/glucose regimens that were associated with hyperglycaemia.[3,4] While it has been shown that CRP production is induced predominantly by IL-6,[5] the reduction in CRP seen in this study without any change in IL-6 suggests that regulation of CRP is multifactorial. Plasma CRP levels are an independent predictor of cardiovascular disease, although it is not clear if reducing CRP levels also reduces long-term cardiovascular risk, nor was it determined how long suppression of CRP production was sustained in this study.

Methodological limitations of the trial included: 1) small number of participants; 2) exclusion of established cardiovascular disease and diabetes; 3) participants fasted during dialysis; and 4) insulin metabolism and elimination were altered.

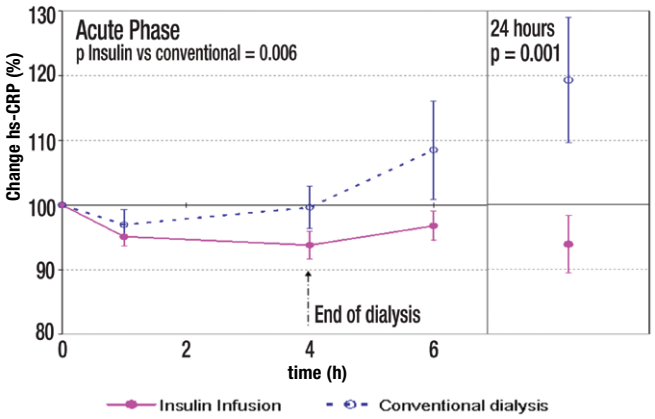

Figure 6: Plasma C-reactive protein levels (mean ± SE) as percentage baseline in the acute phase and at 24 hours in the insulin infusion treatment and the conventional dialysis groups.

Take home points

- Low-dose insulin infusion during haemodialysis has an acute anti-inflammatory effect by reducing plasma CRP levels in the immediate dialysis phase and at 24 hours
- Further studies are needed to clarify the beneficial effect of insulin in the haemodialysis setting in the short term, and on overall outcome in the long term

Stability of antibiotics in peritoneal dialysis solution: a pilot study

Presented by: Dr Gillian Balbir Singh, Peritoneal Dialysis Unit, Middlemore Hospital

Stability of antibiotics in peritoneal dialysis solutions results in a reduction in loading of peritoneal bags by patients and staff, thereby reducing multiple problems associated with this procedure. Gentamicin, cephazolin and vancomycin have been shown to be stable for 2, 8 and 28 days at 20–26°C, respectively, but only in Baxter products. This pilot study tested the stability and compatibility of cephazolin 2g and gentamicin 60mg separately and combined in 2.3% Fresenius CAPD solution after being stored at 18–21°C for 1 hour, 3 days and 7 days and then heated to 35°C over 40 minutes for use. Liquid chromatography-mass spectrometry was used to determine the mass of the analyte as an assessment of stability; three distinct molecular weights are detected by mass spectrometry for gentamicin (450, 464 and 478 m/z), while only one is detected for cephazolin.

Overall, the daily change in the mass of the analytes was not statistically significant, and this was also true for cephazolin on its own and in combination with gentamicin (see table 1). The masses for two of the three molecular weights detected for gentamicin on its own did differ by statistically significant amounts each day; however, these differences were not considered to be clinically significant. A cost analysis revealed that by providing preloaded antibiotic bags to peritoneal dialysis patients, an estimated savings of $13,000 each year could be made for the hospital.

Limitations of the study included: 1) only three bags for each sample; 2) potential sampling errors (minimised by having one person loading the bags); 3) potential interaliquot variations (minimised by using different syringe variations according to the size of the aliquot required); 4) volume over- and underfill of dialysis bags; and 5) intra-assay variance (minimised by performing all assays on the same day).

Analyte	Change Per Day (%)	p Value
All	–0.143	0.759
Cephazolin	0.402	0.404
Cephazolin + gentamicin	–0.429	0.606
Gentamicin 450 m/z	–1.598	0.011*
Gentamicin 450 m/z + cephazolin	–0.975	0.156
Gentamicin 464 m/z	–0.881	0.116
Gentamicin 464 m/z + cephazolin	0.348	0.715
Gentamicin 478 m/z	–1.260	0.039*
Gentamicin 478 m/z + cephazolin	1.0268	0.492

Table 1. Daily change in mass of cephazolin and gentamicin

Take home points

- Fresenius CAPD solutions with preloaded cephazolin and/or gentamicin are stable and compatible for 1–7 days
- Could potentially be safely applied when required to reduce demands on staff and patients, at least until culture results are available
- Would help reduce patient and hospital costs
- Could help improve patient compliance to treatment and help ensure continuity of treatment
- But, still needs to be confirmed in a clinical study

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Health finding and renal services

Presented by: Nick Polaschek,
Senior Project Manager/Team Leader, Ministry of Health

Health funding basics

DHBs are bulk funded, with the goal of providing fair funding to meet relative needs and costs of the DHBs' populations and the intentions of enabling flexibility in meeting health needs at the local level. Funding is set by the population-based funding formula, while inter-district flows (IDFs) allow for funding to be transferred from one DHB for services available at another. Funding is based on the population share and weighted for relative health needs, and health-need proxies include age, sex, ethnicity and deprivation. Adjustments are made for rurality, costs of overseas visitors and unmet needs (e.g. Maori, Pacific, high deprivation). Funding is costed by four service groups (hospital and community, primary care, elderly, mental health), and reviewed every 5 years. Annual funding increases are made in response to the 'forecast funding track' (which allows changes associated with labour and equipment costs, new technology, increased efficiency), demographic changes and new initiatives (DHB and central), minus top slices (e.g. bad debts, national services, etc). DHB capital projects over $10M require central review.

Funding for provider arm services includes net IDF flows, and is agreed with the DHB using price-volume (PV) schedules. Both the PV and IDF schedules are supplied to the MOH in Distract Annual Plans (DAPs). The DHBs are accountable for their funding via the following documents: Statement of Intent (SOI; a high-level plan tabled in parliament), the DAP (effectively an agreement with the MOH, and includes indicators of performance), Crown Funding Agreement and variations (CFAs; contract between DHBs and MOH) and an Operating Policy Framework (OPF; business rules by which DHBs operate).

The annual funding 'ritual' includes: 1) funding model development in October; 2) funding allocation in December; 3) DAPs submitted in March; and 4) Ministerial sign off and parliament approval (Budget) in May. The actual funding is then made available monthly.

The big picture

The government is facing dropping revenues while expenditure continues to rise, and from this year expenditure exceeds revenue for the first time in several years and is forecast to continue to do so for several more years. This means that: 1) health funding increases can not continue; 2) 'clinical leadership' is 'in' (i.e. clinicians will have more say); 3) more regionalisation of health services; and 4) more central leadership.

Key issues for renal services

DHBs determine funding for renal services. They typically agree volumes for the different renal purchase units and provider arms. Any growing service is problematic in the financially constrained DHB situation. Service delivery, staffing and facilities can be complicated in regional renal services that involve significant IDFs. The key issues for renal services going forward include:

- How to manage increasing demand for renal replacement therapy
- Regionalisation of renal services
- Transplantations may be co-ordinated at a national level
- There is currently an opportunity for the National Renal Advisory Board (which is viewed as an exemplar of clinical leadership) to exert some influence
- Current national renal work represents an opportunity to establish renal in central agency
- Renal needs to align with other long-term conditions to maintain a national profile

Summary of renal transplant centres visited by Prof Stephen Munn, Clinical Director, Intra-abdominal organ Transplant Services, Auckland City hospital during his sabbatical

Size	RTx performed/WL*	Graft survival**
UCSF Medical Center, San Francisco, California		
560 beds, 26 ORs	348(232 DDTs)/5059	94.98% (adult) 98.11% (paediatric)
Features: very little trauma or acute operating; joint selection of patients; strong academic focus; strong sense of pride		
University of Colorado Anschutz Medical Center, Aurora, Colorado		
568 beds	117(62 DDTs)/572	94.45 (all adult)
Features: very hierarchal model; strong live-related programme; highly innovative although not particularly academic		
Mayo Medical Center (Rochester Methodist Hospital [RMH] and St Mary's Hospital [SMH]), Rochester, Minnesota		
RMH: 794 beds, 41 ORs SMH: 1265 beds, 55 ORs	174(39 DDTs)/412 11(6 DDTs)/11 - paediatric only	95.78 100%
Features: joint patient selection; very busy services; complete electronic records; very innovative; strong protocols; summer student programme		
University of Minnesota Medical Center, Minneapolis		
1868 beds	184(76 DDTs)/635	95.97% (adult) 95.31% (paediatric)
Features: two sites; historically strong transplant programme; joint patient selection, but surgical driven; research encouraged		
Toronto General Hospital (TGH)/Sick Children's Hospital (SCH), Toronto		
471 beds (TGH) 320 beds (SCH)	~100 adult and ~20 children/300	Unclear; paediatric 5-year graft survival 96%
Features: RTx historically the domain of urologists and paediatric surgeons; very strong transplant programme; very collegial		
Edinburgh Royal Infirmary, Edinburgh		
900 beds; 2 transplant-specific ORs	91(61 DDTs)/n.a	94% (adults) 98% (paediatric)
Features: strong academic emphasis; strong joint approaches		
University of Geneva Hospital, Geneva		
>2000 beds	30–40 per year/"quite small"	n.a
Features: separate elective and acute ORs; strong pyramidal structure with powerful/political professors; many junior staff; RTx dominated by nephrologists		
Ospedale Riuniti, Bergamo		
Features: old, large nonacademic hospital; all renal transplants performed by paediatric surgeons; perform around 30 RTx per year		

*2008 unless otherwise stated; **1-year unless otherwise stated. RTx = renal transplant; DDT = deceased donor transplants; WL = waiting list; OR = operating room; n.a = not available

Take home points

- Kidney transplant programmes around the world have different organisational structures, but achieve excellent results
- Those with strong allegiances between nephrology and surgery tend to be the largest
- Innovation continues to have a strong emphasis
- Regenerative medicine is in a growth phase; 87 stem-cell studies recruiting human subjects are underway

Case series/reports

Spontaneous remission of severe hyperparathyroidism

Presented by: Dr Emad Maher

Secondary hyperparathyroidism is a common complication of ESRD, often resulting in parathyroidectomy. Approximately 4.2% of patients develop recurrent hyperparathyroidism postparathyroidectomy. There have been 52 cases of spontaneous remission in primary hyperparathyroidism reported (the first in 1951), but only 8 in secondary hyperparathyroidism (the first in 1982), most of which involved a single neck gland. None identified the cause of parathyroid infarction, but it has been postulated that excessive growth outstrips the vascular supply. All eight cases occurred in patients on haemodialysis, only three presented with physical symptoms (sore throat, dysphagia, fever) and two presented with hypocalcaemia. A case of a 53-year-old man who experienced spontaneous remission of severe hyperparathyroidism was presented.

The man had started haemodialysis 13 years after being diagnosed with membranous nephropathy. Three years later (1983) he underwent deceased donor renal transplantation, which failed early, and he underwent a second deceased donor transplant in 1988. His clinical course was complicated by recurrent skin squamous cell carcinoma, which required a reduction in his immunosuppressive therapy in addition to surgery and radiotherapy. In 1993, he experienced late rejection and his membranous nephropathy recurred. Five years later, his renal graft failed and 3-hour haemodialysis sessions 5 days/week were restarted with standard heparin 1500U.

The man developed severe hyperparathyroidism over the subsequent years, and despite intensive medical treatment, he required subtotal parathyroidectomy in 2000; all four glands were affected, with a small amount of tissue left in the right lower gland, and pathological findings were consistent with hyperplasia. The procedure was complicated by a right middle cerebral artery stroke followed by near complete recovery.

Over the following 9 years, the man's parathyroid hormone level gradually increased with paricalcitol and cinacalcet treatment. He subsequently presented with flu-like symptoms and was prescribed antibiotic therapy. Nine days later, he presented to an emergency department with a sore throat, neck swelling, dysphagia, earache and cough. He was discharged home so he could undergo haemodialysis, but his neck swelling increased overnight and he presented the next morning with a neck circumference of 49cm (usual 38cm). Physical examination revealed only massive uniform swelling, and his haemoglobin level had fallen to 88 g/L. A CT scan revealed a large retropharyngeal collection displacing his larynx and trachea and extending from the hard palate to the mediastinal carina. His calcium level was 1.67 mmol/L, and he was treated with a calcium infusion and calcitriol. CT angiography confirmed an extensive haematoma with an area of active extravasation related to the right inferior thyroid artery. Catheter angiography confirmed bleeding from his right inferior thyroid artery and his right thyrocervical trunk, both of which were successfully embolised.

Case series/reports (continued)

Two unfortunate deaths from exsanguination in haemodialysis patients prompting root-cause analyses

Presented by: Dr Ian Dittmer, Transplant Nephrologist, Renal Clinical Director, Auckland DHB

Case 1

A middle-aged man with ESRF secondary to glomerular nephritis had presented with very high venous pressures (a fistulogram was ordered). He underwent routine haemodialysis after which he returned home for haemodialysis. The following morning, he was found dead with a large amount of blood in his bed. A post-mortem examination revealed he had exsanguinated from his fistula, despite no particular fistula abnormalities, which raised the following questions: 1) had his elevated venous pressure caused a problem?; 2) had he picked at his scab?; and 3) was adequate advice on bleeding provided? The root-cause analysis concluded that the man had died from exsanguination from his AV fistula, and that he was provided with appropriate information (and that the action to be taken was to disseminate the case details to the NZ group).

Case 2

An elderly 40kg woman with a long history of stage 4–5 CKD and severe cardiovascular disease that had required stenting had started haemodialysis following angioplasty. She was slowly improving when the lines clotted during one dialysis session in hospital. The lines were changed, but she was found unresponsive with large amounts of blood in her bed several minutes after restarting dialysis. During an unsuccessful attempt at resuscitation, it was noticed that her venous line had become disconnected. The questions raised for this case were: 1) had the machine's venous alarm failed; 2) how long after reconnection did the event occur; and 3) were routine procedures followed? The machine's black box indicated that it was alarming correctly, and that the period of time between reconnection and the event was 5–10 minutes. It was also noted that the machine's documentation advises that venous pressure alarms do not detect disconnection with any degree of certainty. The actions to be taken as a result of the root cause analysis were: 1) ensure adequate observation of line connections; and 2) disseminate of the case details to the NZ group. As part of the first action point, it was recommended that blankets or clothing should not cover the line connection to allow for staff observation; however, patients often prefer their chest to remain covered.

Literature review

There is very little information available in the literature on exsanguination during haemodialysis. There was a discussion about venous disconnection and needle dislodgement at an EDTNA/ERA meeting, which revealed widespread variation in practice, and resulted in multiple recommendations with no evidence base. Informal collections of data in the UK and the US have recognised that it is an uncommon but potentially fatal problem, with only one case report being published. Dr Dittmer noted that staff need to be vigilant to identify at-risk patients.

Practices that help reduce the chance of exsanguination during haemodialysis

- Ensure there is a clear, large area around the needle site
- Use a consistent taping method
- Ensure lines are looped loosely
- Set the lower limit of venous pressure close to actual venous pressure
- Use a blood leak detection device

Trastuzumab use in pregnancy: a case of foetal renal toxicity

Presented by: Dr Nicola Hay, Renal Physician, CCDHB

Case report

Twin boys of a 29-year-old woman who had received trastuzumab during pregnancy for metastatic breast cancer developed renal toxicity, and one of the twins subsequently died.

The woman, who was on a methadone programme for a history of IV drug abuse and was a current smoker, was diagnosed with infiltrating ductal breast cancer in 2006. She received neoadjuvant chemotherapy followed by left mastectomy and axillary node dissection 5 months after diagnosis, and HER-2 positive disease with locally metastatic disease was diagnosed. Her treatment plan included chemoradiation therapy (4 cycles of paclitaxel) followed by 17 planned doses of trastuzumab (Herceptin) every 3 weeks plus tamoxifen starting in Nov 2006. However, in May 2007, she presented with an unplanned pregnancy estimated to be 24–26 weeks' gestation.

The woman's trastuzumab therapy was discontinued after 9 doses. A series of scans revealed oligohydramnios affecting one twin (twin 1) more than the other. Premature membrane rupture subsequently occurred and the twins were delivered by Caesarean at 31 weeks; both twins were free of dysmorphic features, with birthweights of 1590 and 1705g; the mother had not experienced pre-eclampsia and placenta histology did not reveal any features of concern.

Both twins had respiratory distress, underwent methadone withdrawal and required supplemental feeding; twin 1 also received erythropoietin for anaemia. Itrasonography revealed increased renal echogenicity in both twins, and they developed severe renal failure with creatinine peaks of 275 µmol/L on day 7 and 174 µmol/L on day 5 for twins 1 and 2, respectively, followed by slow spontaneous improvements to respective values of 100 and 48 µmol/L. Both were discharged with home O_2 and supplemental feeding after a 3-month hospital stay. However, the next day, twin 1 returned with RSV-positive respiratory tract infection. After returning home that day, his respiratory status deteriorated, and he developed respiratory arrest on route to hospital. He was resuscitated, but remained profoundly unwell, and he died 1 week later (no autopsy was performed). Twin 2 continued to make good progress during follow-up, although his GFR remained slightly reduced.

The woman's conception date was estimated to be late Nov to early Dec 2006 (just after trastuzumab and tamoxifen were started). She had received her last dose of paclitaxel early Nov 2006, and had been poorly compliant with tamoxifen therapy. She had continued to abuse morphine and receive methadone throughout her pregnancy, and she had also received a radioactive isotope in Nov 2006 and had undergone mammography in Jan 2007.

Acute renal failure in neonates

Although data on acute renal failure in neonates are sparse, preterm neonates are more susceptible due to immature kidneys, haemodynamic changes and increased risk of hypovolaemia. Creatinine levels take longer to decrease to normal levels from the mother's level at birth in preterm infants than in term infants. When evaluating cases of acute renal failure in newborns, the family, gestational and obstetric/neonatal histories are very important, as there are a number of potential causes. Management of acute renal failure in neonates is similar to adults.

Role of trastuzumab

Trastuzumab binds to HER2 (overexpressed in 20–30% of invasive breast cancers) resulting in inhibition of HER2-dependent tumour proliferation. It was originally classified as FDA pregnancy risk category B due to no apparent foetal harm in extensive animal studies, even though placental transfer does occur. However, there have been 11 cases of foetal effects following *in utero* exposure beyond the first trimester, and the FDA pregnancy risk was revised to category D in 2008/2009. These reports have typically described transient abnormalities with normal postnatal renal function and development in neonates who survived; three cases had a fatal outcome.

While the mechanism of foetal renal toxicity associated with trastuzumab is not known, it has been proposed that it could be related to the presence of epidermal growth factor receptor complexes localised in the apical portion of foetal renal tubule epithelial cells as heterodimers in ErbB2 (HER2). Trastuzumab may therefore block this receptor and adversely affect foetal renal function; note that this receptor is not seen in adult renal tubule epithelial cells, and there have been no trastuzumab-associated renal complications reported in adults.

Cases of granulomatous interstitial nephritis (GIN)

Presented: by Dr Tracey Putt, Nephrology Dept, Dunedin Hospital

GIN is a rare cause of nephritis seen in 0.5–0.9% of all renal biopsies, and is usually associated with sarcoidosis, infections or medication use. It is more common among males, and patients usually present with nonspecific symptoms and advanced renal impairment with minimal proteinuria. Transplant GIN is mainly associated with mycobacteria or fungi. Since 1992, there has been an increasing number of case reports of proton-pump inhibitor (PPI)-induced acute interstitial nephritis, but only two published case reports of GIN associated with omeprazole use, the first of which was published in 1998.[1] However, a few cases appear in case series of GIN that may be due to PPI use.[2–4] One of the largest series included 18 cases over a 15-year period, among which only one was potentially associated with omeprazole.[2] GIN usually presents with advanced renal impairment with initial proteinuria with noncaseating granuloma of macrophages surrounded by T-cells with or without multinucleate giant cells on biopsy. Management included corticosteroid treatment in 16 cases for an average 25 months. One third of patients had subsequent relapse and were commenced on steroid-sparing treatment – usually azathioprine. Improvement was seen in 17 cases over 45 months, with the greatest improvement occurring within the first 3 months, and none required long-term renal replacement therapy. Notably, there was no correlation between biopsy features and cause or outcome. GIN behaves differently than the acute interstitial nephritis usually seen with PPIs, which usually resolves with withdrawal of medication ± short-course corticosteroids.

Two cases of GIN identified from ~70 biopsies performed in Dunedin over a 1-year period were presented.

Case 1

The first patient was a 68-year-old man with a history of active colitis in remission (not consistent with Crohn's disease), a lupus-like syndrome from mesalazine (Pentasa), controlled hypertension and hypothyroidism. Six weeks after starting treatment with omeprazole for 'reflux', he presented with symptoms of unusual taste, nausea and lethargy. He was hypertensive and euvolaemic, with routine blood tests revealing acute renal failure (urea 39 and creatinine 581), and urinalysis showing blood and protein. Renal biopsy findings were of necrotising granulomata consistent with GIN. Omeprazole was discontinued, he was commenced on corticosteroids and discharged the following day. After 15 days of corticosteroid treatment, his symptoms had resolved and his creatinine level had fallen to 245. However, 4 weeks later, his creatinine level had increased to 405 with haemoglobin of 94, and corticosteroid therapy was restarted with erythropoietin added. Corticosteroid therapy was slowly tapered over 9 months. He was asymptomatic at his most recent follow-up, but his creatinine level had increased to 354 and his corticosteroid dosage was increased. At latest follow-up, he was under consideration for a repeat renal biopsy and azathioprine therapy. We propose that this man has omeprazole-induced GIN.

Case 2

The second patient was a 58-year-old man with schizophrenia treated with fluoxetine and olanzapine. A routine annual blood test revealed acute renal impairment with a creatinine level of 506 with mild proteinuria and haematuria. He had mildly elevated inflammatory markers, anaemia, hypocalcaemia and hyperphosphataemia. A chest x-ray was normal apart from bulky hila, but no other features consistent with sarcoidosis. A renal biopsy revealed moderate interstitial fibrosis and a prominent interstitial infiltrate with noncaseating granulomas in varying stages. Treatment with prednisone, ranitidine, calcium (Calcitab), calcitriol and erythropoietin (Recormon) was started. At most recent follow-up, sarcoidosis was being considered as the underlying condition.

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