Welcome to the latest issue of Nephrology Research Review.

In this issue, a US study describes an all-or-nothing approach to caring for patients with advanced CKD, and a comparative trial suggests that sertraline is slightly better than CBT for the treatment of depression in dialysis patients. A large Austrian cohort study highlights the potential role of non-HLA matching as an important driver of kidney allograft survival, a US study reports high rates of lower extremity amputation in ESRD patients, and two studies examine the safety and efficacy of spironolactone in dialysis patients.

We hope you find these and the other selected studies interesting and look forward to any feedback you may have.

Kind Regards,
Professor Vlado Perkovic
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Care practices for patients with advanced kidney disease who forgo maintenance dialysis

Authors: Wong S et al.

Summary: This qualitative study examined care practices for patients with advanced CKD who forgo maintenance dialysis. Electronic medical records of 851 adults receiving care from the US Veterans Health Administration in 2000–2011 who chose not to start dialysis were reviewed. Analysis of the data revealed 3 major dynamics relevant to care practices in these patients. The first dynamic was that dialysis was considered to be the ‘norm’, and it was unusual for clinicians to accept the patients’ decision to not receive dialysis. Clinicians tended to repeatedly question the preference and the patients’ decision-making competency, and used various strategies to encourage patients to start dialysis. The second dynamic arose when patients were considered to be unsuitable candidates for dialysis, with clinicians showing little room for uncertainty in their decision. The third dynamic was when clinicians believed they had little to offer patients beyond dialysis; they often had few alternative recommendations other than referral to hospice care.

Comment: Conservative care is increasingly recognised as an important option but much less is known about how choices are made and supported. This analysis from the US suggests that there is much to do to facilitate and support patients’ choices regarding dialysis. The need to recognise and support uncertainty is a particularly striking finding. I hope we might do better in Australia, but am not sure whether that is true?


Abstract:

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Routine laboratory testing every 4 versus every 6 weeks for patients on maintenance hemodialysis
Authors: Silver S et al.
Summary: This study evaluated the impact of changing the blood testing frequency from every 4 weeks to every 6 weeks on the achievement of haemoglobin and phosphate targets in dialysis patients. A tertiary hospital in Ontario, Canada that provides maintenance haemodialysis therapy to 350–400 adult patients switched the interval for routine blood work from 4 to 6 weeks in March 2014. The proportion of patients who achieved haemoglobin and phosphate targets remained stable after the interval switch, and the haemodialysis unit mortality rate also remained stable. Reducing blood work frequency to every 6 weeks was associated with a cost saving of $85 per patient-year.

Comment: Vast sums of money are spent on routine pathology tests in people on dialysis – some units in the US are reported to run these weekly. This “before and after” study assessed the impact of reducing testing frequency, and found no effect on the likelihood of achieving various target blood levels, or on mortality (although the power for the latter was very weak). It does raise the question of what the most appropriate testing frequency should be.


Abstract

Comparative efficacy of therapies for treatment of depression for patients undergoing maintenance hemodialysis
Authors: Mehrotra R et al.
Summary: This open-label US study determined the effect of an engagement interview on treatment acceptance (phase 1), and the comparative efficacy of sertraline and CBT (phase 2) for treating depression in dialysis patients. 184 patients who had been receiving haemodialysis for at least 3 months and had a Beck Depression Inventory-II score ≥15 were enrolled in phase 1 at 41 dialysis facilities; 120 of them subsequently participated in phase 2. The primary endpoint for phase 1 was the proportion of participants who started treatment within 28 days. For phase 2, the primary outcome was depressive symptoms measured by the Quick Inventory of Depressive Symptoms–Clinician-Rated (QIDS-C) at 12 weeks. The proportion of patients who initiated treatment after the engagement interview in phase 1 did not differ from that in controls (66% vs 64%). In phase 2, treatment with sertraline was associated with lower QIDS-C depression scores at 12 weeks than CBT (effect estimate, −1.64; p=0.035). Adverse events were more common in sertraline than CBT recipients.

Comment: Depression is an important comorbidity for people receiving dialysis, and this double barrel randomised trial suggested that CBT is less effective but better tolerated than sertraline. This sort of evidence is extremely important for helping us fully inform patients about their choices.


Abstract

Contribution of non-HLA incompatibility between donor and recipient to kidney allograft survival
Authors: Reindl-Schwaighofer R et al.
Summary: This genome-wide analysis of an Austrian kidney transplant cohort evaluated the contribution of non-HLA incompatibility between donor and recipient to kidney allograft survival. 477 pairs of deceased donors and first kidney transplant recipients with stable graft function at 3 months were genotyped, and genome-wide genetic mismatches in non-synonymous single nucleotide polymorphisms (nsSNPs) were evaluated. 59,268 nsSNPs affecting a transmembrane or secreted protein were analysed. The median number of nsSNP mismatches in immune-accessible transmembrane and secreted proteins between donors and recipients was 1892. A multivariable model adjusted for HLA eplet mismatch showed that the degree of nsSNP mismatch was independently associated with graft loss.

Comment: While HLA typing has been the mainstay of transplant matching for decades, this large study highlights the potential role of non-HLA matching as an important driver of prognosis. Will this become the future of tissue typing for transplantation? Much more work will be required to achieve this.

Reference: Lancet 2019;393(10174):910-17

Abstract

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PBS 1ST JAN 2019
Vitality measured as self-reported energy level and clinical outcomes in hemodialysis patients: the Japanese Dialysis Outcomes and Practice Pattern Study (J-DOPPS)

Authors: Kurita N et al.

Summary: The J-DOPPS study assessed the association between self-reported “vitality” and clinical outcomes in haemodialysis patients. The responses of 3667 patients to the question “How much time during the past 4 weeks did you have a lot of energy?” were recorded using a 5-level Likert scale. Lower self-reported energy level was associated with tachycardia and use of antidepressants, benzodiazepines, and hypnotics. Higher energy was associated with higher single-pool Kt/V, serum albumin concentration, and body mass index. Compared to the lowest energy level, the second-highest and middle levels were associated with lower all-cause mortality (adjusted hazard ratios [HRs], 0.66 and 0.75, respectively). Each 1-level improvement in vitality was associated with lower mortality (adjusted HR, 0.86).

Comment: Energy levels are important to patients and, in this study, clearly predict outcomes. They are also associated with many drugs, raising questions about the value of these treatments. Can energy levels be changed in a clinically meaningful way by interventions? Sounds like an important area for future research.

Abstract

An organizational-level program of intervention for AKI

Authors: Selby N et al.

Summary: This pragmatic stepped wedge cluster RCT evaluated the impact of a multifaceted intervention on delivery of care and patient outcomes at an organisational level. The trial was performed in 5 UK hospitals, involving adults with AKI. The intervention (AKI e-alerts, an AKI care bundle, and an education programme) was introduced sequentially across fixed 3-month periods according to a randomly determined schedule until all hospitals were exposed. A total of 24,059 episodes of AKI were included in the analysis. Overall, 30-day mortality (24.5%) did not differ between control and intervention periods, but the intervention reduced the hospital length of stay and improved several measures of quality of care (AKI recognition, medication optimisation, and fluid assessment).

Comment: Early recognition of AKI sounds like an important way to improve outcomes. This cluster RCT aimed to assess this and was able to demonstrate that AKI recognition was improved, medications and fluids were adjusted, and hospitalisations were shortened. It was unable to show mortality was improved but this may not have been a terribly realistic goal for the study.

Abstract

Lower extremity amputation and health care utilization in the last year of life among Medicare beneficiaries with ESRD

Authors: Butler C et al.

Summary: This study evaluated health care utilisation in patients with ESRD who underwent lower extremity amputation in their last year of life. 754,777 Medicare beneficiaries with ESRD who died in 2002−2014 were compared with a parallel cohort of 958,412 beneficiaries without ESRD. Overall, 8% of patients with ESRD underwent at least one lower extremity amputation in their last year of life compared with 1% of patients without ESRD. Patients with ESRD who had undergone lower extremity amputation were more likely to have prolonged stays in acute and subacute care settings in their final year. They were also more likely to die in hospital, discontinue dialysis before death, and were less likely to use hospice services.

Comment: This startling study from the US describes very high rates of amputation in the last year of life for people with ESRD, and that this was associated with prolonged hospitalisation. While the focus on increasing access to palliation is appropriate, the study also highlights the need to find new limb-protective strategies in people with ESRD.

Reference: J Am Soc Nephrol 2019; published online Feb 19
Abstract

Safety and cardiovascular efficacy of spironolactone in dialysis-dependent ESRD (SPin-D)

Authors: Charytan D et al., on behalf of the Hemodialysis Novel Therapies Consortium

Summary: The double-blind Spin-D trial investigated the safety and efficacy of spironolactone in ESRD patients. 129 patients undergoing maintenance haemodialysis were randomised to receive placebo or spironolactone 12.5mg, 25mg, or 50mg once daily for 36 weeks. The overall frequency of hyperkalaemia did not differ significantly between spironolactone and placebo recipients (0.49 vs 0.50 events per patient-year), but demonstrated a significant linear trend due to an increased event rate with spironolactone 50mg (0.89 events per patient-year). Hypotension requiring emergency department visit or hospitalisation was infrequent in both groups. Change in diastolic function (assessed by Doppler echocardiography) was similar with spironolactone and placebo, and gynaecomastia was rare.

Abstract

A randomized controlled trial of the effect of spironolactone on left ventricular mass in hemodialysis patients

Authors: Hammer F et al., on behalf of the MiRENDa Study Group

Summary: This German study evaluated the effect of spironolactone on left ventricular mass (LVM), an independent predictor of all-cause and cardiovascular mortality, in haemodialysis patients. 97 patients were randomised 1:1 to receive spironolactone 50mg or placebo once daily for 40 days. The primary efficacy end-point (change in LVM index from baseline to 40 weeks) did not differ significantly between groups. There was also no difference in secondary outcomes of mean 24-hour systolic or diastolic ambulatory blood pressure, left ventricular ejection fraction, 6-minute walk test distance, or New York Heart Association functional class. Moderate hyperkalaemia was more frequent in spironolactone recipients (155 vs 80 events), but severe hyperkalaemia was not (14 vs 24 events).

Reference: Kidney Int 2019;95(4):983-91
Abstract

Comment: These 2 studies looked at spironolactone in dialysis patients. Neither found an increase in severe hyperkalaemia (>6.5 mmol/L), but the German study did find an increased risk of moderate hyperkalaemia, and there does appear to be a dose-dependent relationship. A range of intermediate outcomes were assessed and were generally not very informative, so the results of large scale outcome studies currently underway are awaited with great interest.
**Abstract**

This multicentre pilot trial in Canada determined the feasibility of buttonhole versus stepladder cannulation for home haemodialysis. 50 patients with ESRD who were receiving training for home haemodialysis at 7 Canadian hospitals were eligible for randomisation to a buttonhole or stepladder cannulation technique. Of the 50 eligible patients, only 14 patients (28%) consented to participate in the study. The most common reason for declining to participate was a strong preference for a particular cannulation technique. Patients randomised to buttonhole cannulation required a shorter time to complete home haemodialysis training than those randomised to stepladder cannulation. The buttonhole method was not associated with a reduction in cannulation pain or complications.

**Comment:** Formal feasibility studies are rare prior to larger RCTs in nephrology, but should probably be done a lot more. This study showed that a larger trial comparing buttonhole to stepladder cannulation for home HD was not feasible as designed in Canada. It highlights the need for pragmatic trial designs with inclusive entry criteria, and a better understanding of barriers to trial participation for dialysis patients, so that these can be addressed as much as is possible.


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**PBS eligibility criteria**

1. ≥18 years of age and
2. CKD stage 2 or 3 (eGFR 89 to 30 mL/min/1.73m²) at initiation of treatment and
3. Evidence of rapid progression determined by:
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