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Abbreviations used in this issue:

- ANZDATA = Australia and NZ Dialysis and Transplant Registry
- CKD = chronic kidney disease
- ESKD = end-stage kidney disease
- HR = hazard ratio
- NSAID = nonsteroidal anti-inflammatory drug
- OR = odds ratio

Welcome to the latest issue of Nephrology Research Review.

In this issue, we report the development of a risk prediction model for long-term kidney allograft failure, an ANZDATA analysis demonstrates that acute rejection is associated with an increased risk of longer-term graft failure and death (particularly from cardiovascular disease and cancer), and a US study finds that patients with ESKD who receive dialysis at a for-profit facility are less likely to access kidney transplantation than those receiving care at a nonprofit facility. An analysis of CKD management in Canadian primary care raises questions about our ability to improve outcomes in these patients, a pilot study suggests that hypertonic mannitol may reduce the risk of intradialytic hypotension, and UK researchers remind us of the serious risk of nephrotic syndrome in patients taking NSAIDs.

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
vlado.perkovic@researchreview.com.au

Prediction system for risk of allograft loss in patients receiving kidney transplants

Authors: Loupy A et al.

Summary: This study reported the development and validation of a model for predicting long-term kidney allograft failure. The derivation cohort comprised 4000 consecutive kidney recipients in 4 French centres, and the two validation cohorts comprised 2129 kidney recipients in 3 centres in Europe and 1428 from 3 centres in North America. Among 7557 kidney transplant recipients, 14.1% of allografts failed at a median 7.12 years post-transplant. In the derivation cohort, 8 functional, histological, and immunological factors were found to be independently associated with allograft failure and were combined into a risk prediction score (iBox). The performance of the iBox was confirmed in the two validation cohorts.

Comment: This study highlights the success of transplant immunosuppression development approaches, with a 14.1% failure rate at a median of 7.12 years. Further improvements will need to focus on individuals at high risk, as will more intensive follow-up and management strategies. This study developed a risk prediction model for transplant failure and then validated it across several datasets. It would appear to have potential utility at both an individual level, and when thinking about potential strategies to further improve outcomes.

Reference: BMJ 2019;366:l4923
Abstract

Long-term outcomes after acute rejection in kidney transplant recipients

Authors: Clayton P et al.

Summary: This ANZDATA analysis investigated the long-term effect of acute rejection on outcomes in kidney transplant recipients. 13,614 recipients of a primary kidney-only transplant in 1997–2017 with at least 6 months of graft function were included. The associations between acute rejection within 6 months post-transplant and subsequent graft loss and death were determined using Cox models adjusted for baseline donor, recipient, and transplant characteristics. Acute rejection occurred in 21.4% of recipients and was associated with graft loss and death from rejection-related conditions in this study.

Comment: ANZDATA has made huge contributions to our understanding of the treatment of kidney disease over many decades now. In this study, acute rejection was unsurprisingly found to be associated with graft loss from rejection-related conditions, but also with death, cardiovascular death and cancer. Whether this is related to rejection or its treatments remains to be seen, but highlights the importance of further studies to identify better treatments for people with rejection.

Abstract
Association between dialysis facility ownership and access to kidney transplantation
Authors: Gander J et al.
Summary: This retrospective US study evaluated the association between dialysis facility ownership and access to kidney transplantation. 1,478,564 patients with ESKD treated at 6511 dialysis facilities in the US in 2000–2016 were included. Dialysis facility ownership was categorised as nonprofit small chains, nonprofit independent facilities, for-profit large chains (>1000 facilities), for-profit small chains, and for-profit independent facilities. Three main outcomes were compared between the facilities: placement on the deceased donor kidney transplantation waiting list, receipt of a living donor kidney transplant, or receipt of a deceased donor kidney transplant. Adjusted Cox analyses showed lower relative rates for each outcome in patients treated at for-profit versus nonprofit dialysis facilities: deceased donor waiting list (HR, 0.36), receipt of a living donor kidney transplant (HR, 0.52), and receipt of a deceased donor kidney transplant (HR, 0.44).

Comment: This US study suggests that a predominantly for-profit based dialysis system such as that present in the US leads to perverse incentives that may reduce the likelihood of transplantation, possibly due to either conscious or unconscious biases. It is an important message for service provision in Australia, and suggests that for-profit services must have funding linked to successful outcomes such as transplantation, or at least listing on waiting lists.

Reference: JAMA 2019;322(10):957-73
Abstract

Quality of chronic kidney disease management in Canadian primary care
Authors: Bello A et al.
Summary: This study assessed the quality of care received by CKD patients in Canadian primary care. Data were extracted from the Canadian Primary Care Sentinel Surveillance Network for 46,162 patients with CKD managed in primary care settings in 2010–2015. Twelve quality indicators in 6 domains were assessed: 1) detection and recognition of CKD; 2) testing and monitoring of kidney function; 3) use of recommended medications; 4) monitoring after initiation of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers; 5) management of blood pressure (BP); and 6) monitoring for glycaemic control in those with comorbid diabetes. Only 4 of 12 quality indicators were met by ≥75% of the study cohort (outpatient serum creatinine test within 18 months after confirmation of CKD, BP measurement during follow-up, target BP ≤140/90 mm Hg achieved, and a haemoglobin A1c test for monitoring diabetes during follow-up).

Comment: This analysis of CKD management in primary care raises many worrying questions about our ability to improve outcomes in this population. It reports the low frequency of implementation of simple measures such as albuminuria measurement. The results also suggest that younger individuals who have perhaps the most to gain are least likely to be appropriately managed. Despite the complaints from many clinicians, these results suggest that optimal CKD care will require dramatically different care models to those in use today.

Reference: JAMA Netw Open 2019;2(9):e1910704
Abstract

Hypertonic mannitol for the prevention of intradialytic hypotension
Authors: McCausland F et al.
Summary: This pilot study evaluated the use of hypertonic mannitol for the prevention of intradialytic hypotension (IDH) upon initiation of haemodialysis. 52 patients requiring initiation of haemodialysis for acute or chronic kidney disease were randomised to receive mannitol 0.25 g/kg/h, or a similar volume of 0.9% saline solution during the first 3 haemodialysis sessions. There were no significant between-group differences in mean systolic blood pressure decline upon initiation of haemodialysis. However, the proportion of total sessions complicated by IDH was lower in the mannitol group than in the placebo group (25% vs 43%), as was the risk of an IDH episode (odds ratio, 0.38; p=0.05).

Comment: Few randomised trials have robustly assessed the impact of an intervention on IDH. This pilot study assessed the use of mannitol for the prevention of IDH, and reported mixed findings. While there was no difference in systolic blood pressure change, a lower rate of IDH events was observed. The findings are inconclusive and require confirmation in a larger trial, but offer promise for this difficult clinical problem.

Abstract

A phase 3b, randomized, double-blind, placebo-controlled study of sodium zirconium cyclosilicate for reducing the incidence of predialysis hyperkalemia
Authors: Fishbane S et al.
Summary: The phase 3 DIALIZE study evaluated the use of sodium zirconium cyclosilicate (SZC) for the management of hyperkalemia in haemodialysis patients. 196 adults with ESKD who were managed by 3-times weekly haemodialysis and had predialysis hyperkalemia were randomised to receive SZC 5g or placebo once daily on non-dialysis days. The SZC dosage was titrated to a maximum 15g over 4 weeks to maintain normokalaemia. The primary end-point was the proportion of patients who maintained predialysis serum potassium levels 4.0–5.0 mmol/L during at least 3 of 4 haemodialysis treatments after the long interdialytic interval during the 4-week stable-dose evaluation. 41.2% of SZC recipients compared with 1.0% of placebo recipients met the primary end-point (p<0.001), and 2.1% and 5.1% of patients in the respective groups required rescue therapy to reduce serum potassium levels.

Comment: Refractory hyperkalemia remains a significant problem in a proportion of people with kidney failure requiring dialysis, and is associated with adverse outcomes. This trial demonstrates that oral zirconium can successfully treat hyperkalaemia in a substantial proportion of affected individuals, without any significant harm. It also raises the question of whether use of potassium binders may reduce potassium excursions in people receiving dialysis, and whether this may improve outcomes. An important area for future study.

Abstract

Trends and racial disparities of palliative care use among hospitalized patients with ESKD on dialysis
Authors: Wen Y et al.
Summary: This retrospective US cohort study investigated trends and racial disparities of palliative care in hospitalised patients with ESKD. Analysis of the National Inpatient Sample from 2006 to 2014 identified 5,230,865 hospitalisations of patients with ESKD; 76,659 (1.5%) of them required palliative care. The palliative care referral rate increased significantly over time, from 0.24% in 2006 to 2.70% in 2014 (p<0.01). Black and Hispanic patients were less likely to receive palliative care services than white patients (adjusted odds ratios, 0.72 and 0.46, respectively). These disparities were seen across all hospital subtypes, including those with higher proportions of minorities. Minority patients with lower socioeconomic status were also less likely to receive palliative care.

Comment: Palliative care is an important treatment option that is chosen by a proportion of people with kidney failure. Successful conservative care, and decisions about treatment options, often benefit from the involvement of palliative care teams, but this study shows that such teams are only involved in a small minority of cases in the US. It also suggests racial background and/or socioeconomic status may be an important driver of variations. The results argue for a systematic approach to palliative care discussions, perhaps based around treatment choice workshops.

Abstract
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Minimum Product Information. RENAGEL® (Sevelamer Hydrochloride). Indications: Renagel is indicated for the management of hyperphosphataemia in adult patients with stage 4 and 5 chronic kidney disease. Contraindications: Hypophosphataemia or bowel obstruction and known hypersensitivity to sevelamer hydrochloride or any of the other components of the tablet. Precautions: Safety and efficacy in patients with dysphagia, swallowing disorders, severe gastrointestinal (GI) motility disorders, severe constipation, major GI tract surgery or in pre-dialysis patients have not been established. Patients with renal insufficiency may develop hypocalcaemia or hypercalcaemia. Patients with chronic kidney disease are predisposed to metabolic acidosis. Pregnancy Category B3. Treatment should be re-evaluated in patients who develop severe gastrointestinal symptoms (including serious complications such as bleeding, perforation, ulceration, necrosis and colitis). Interactions: Renagel should not be taken simultaneously with ciprofloxacin. Monitoring of blood concentrations of cyclosporin, mycophenolate mofetil and tacrolimus recommended when used in combination with sevelamer. Very rare cases of increased TSH levels have been reported in patients co-administered Renagel and levothyroxine. Special precautions should be taken when prescribing Renagel to patients also taking anti-arrhythmic and anti-seizure medications. Adverse effects: Diarrhoea, dyspepsia, vomiting, nausea, constipation, pruritus, flatulence, rash and abdominal pain. In very rare cases, intestinal obstruction and ileus/subileus. Dosage and administration: The recommended starting dose for patients not taking a phosphate binder is 800 to 1600 mg, which can be administered as one to two Renagel tablets with each meal based on serum phosphorus level. When patients are converting from a calcium based phosphate binder, Renagel should be given in equivalent doses on a (mg to mg) weight basis compared to the patient’s previous calcium based phosphate binder. The dosage should be gradually adjusted based on the serum phosphorus concentration with a goal of lowering serum phosphorus. The dose may be increased or decreased by one tablet per meal at two week intervals as necessary. The contents of Renagel expand in water therefore tablets should be swallowed intact and should not be crushed, chewed or broken into pieces prior to administration. Patients should be advised not to chew the tablets as sevelamer hydrochloride swells on contact with moisture. Patients should swallow the tablets whole with water. 

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Date of preparation: August 2019. SM_SAN1176.
Risk of nephrotic syndrome for non-steroidal anti-inflammatory drug users

Authors: Bakhrian Syah M et al.

Summary: This UK case-control study evaluated the risk of nephrotic syndrome associated with NSAID use. 2620 primary-care patients with a first diagnosis of nephrotic syndrome were compared with 10,454 patients without nephrotic syndrome. NSAID exposure was classified as current (at the time of nephrotic syndrome diagnosis), recent (discontinuation 1–2 months before diagnosis), or past (discontinuation 2–24 months before diagnosis). Compared with non-use, current use of 15–28 days and >28 days of conventional NSAIDs was associated with a higher relative risk of nephrotic syndrome (adjusted ORs, 1.34 and 1.42, respectively). Recent use (OR, 1.55) and past use (OR, 1.24) were also associated with a higher risk of nephrotic syndrome. Neither current use for <15 days nor distant past use (discontinued >2 years previously) increased the risk of nephrotic syndrome. Past use of selective cyclooxygenase-2 inhibitors was not associated with nephrotic syndrome. The higher risk of nephrotic syndrome seen with NSAIDs was mainly attributable to acetic acid and propionic acid derivatives.

Comment: Has a nephrologist ever prescribed a NSAID? I don’t think I could bring myself to do it. Among the many reasons we viliﬁe these drugs, this study suggests that an association with nephrotic syndrome is a real concern. The increased risk may persist for up to 2 years, and there may be important differences between agents.


Serum magnesium, mortality, and cardiovascular disease in chronic kidney disease and end-stage renal disease patients

Authors: Xiong J et al.

Summary: This meta-analysis investigated the impact of magnesium deﬁciency on vascular calcifications, atherosclerosis and cardiovascular disease in patients with CKD and ESRD. A search of PubMed, EMBASE, Web of Science and the Cochrane Central Register of Controlled Trials identiﬁed 20 studies (n=200,934) that investigated the association between serum magnesium levels and mortality risk in CKD and ESRD patients. Meta-analysis of the data showed that hypomagnesaemia increased the risk of all-cause mortality compared with normal magnesium or hypermagnesaemia (HR, 1.32; p<0.00001). In contrast, hypomagnesaemia was inversely associated with all-cause mortality (HR, 0.86; p<0.001) and cardiovascular mortality (HR, 0.71; p<0.03).

Comment: The literature abounds with data describing the U-shaped relationship between potassium levels and mortality in people with CKD including those on dialysis, but less well studied is the relationship between magnesium and outcomes. This systematic review suggests that low magnesium levels are associated with an increased risk of total and cardiovascular mortality. It argues for randomised trials of magnesium supplementation in CKD and dialysis patients.


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