Nephrology Research Review™

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In this issue:

Abbreviations used in this issue:

AKI = acute kidney injury; **ANCA** = antineutrophil cytoplasmic antibody; **CKD** = chronic kidney disease; **eGFR** = estimated glomerular filtration rate; **ESKD** = end-stage kidney disease; **IgA** = immunoglobulin A; **NSAID** = non-steroidal anti-inflammatory drug; **PICC** = peripherally inserted central catheter; **SGLT2** = sodium-glucose cotransporter 2; **SONG** = Standardized Outcomes in Nephrology.

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Welcome to the latest issue of Nephrology Research Review.

In this issue we report exciting findings for patients with membranous nephropathy that should change current practice, the pivotal IDEAL study demonstrates a clear impact on dialysis timing in Canada, and a useful risk prediction tool has been developed for patients with IgA nephropathy. A Canadian study quantifies the risk of AKI in older patients taking NSAIDs, and US investigators highlight the frequency and implications of fatigue in the early stages of CKD.

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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Rituximab or cyclosporine in the treatment of membranous nephropathy

Authors: Fervenza F et al., for the MENTOR Investigators

Summary: The MENTOR study compared the use of rituximab and cyclosporine in patients with membranous nephropathy. 130 patients with membranous nephropathy, proteinuria ≥5 g/24h, and creatinine clearance ≥40 ml/min/1.73m^2 who had been receiving angiotensin-system blockade for at least 3 months were randomised to receive intravenous rituximab (two 1000mg infusions administered 14 days apart; repeated at 6 months in patients with partial response) or oral cyclosporine (starting dose 3.5 mg/kg/day for 12 months). At 12 months, 60% of patients in the rituximab group and 52% in the cyclosporine group had a complete or partial remission (p=0.004 for noninferiority). At 24 months, 60% and 20% of patients in the respective groups had a complete or partial remission (p<0.001 for both noninferiority and superiority). In patients in remission who tested positive for anti-phospholipase A_2 receptor (PLA2R) antibodies, the decline in anti-PLA2R autoantibodies was faster and greater with rituximab. 17% of patients in the rituximab group and 31% in the cyclosporine group had a serious adverse event (p=0.06).

Comment: This is a breakthrough study showing that rituximab is at least as good as cyclosporine in patients with membranous nephropathy and at least 5g of proteinuria daily, and may actually have some advantages at 2 years and perhaps in terms of serious adverse events. While some argue that cyclophosphamide should have been the comparator, I think this trial should and will change practice.

Reference: N Engl J Med 2019;381:36-46

Abstract

Association between the publication of the Initiating Dialysis Early And Late trial and the timing of dialysis initiation in Canada

Authors: Ferguson T et al.

Summary: The Initiating Dialysis Early And Late (IDEAL) trial demonstrated that early initiation of dialysis (at eGFR 10–14 ml/min/1.73m^2) in patients with ESKD was not associated with improved survival or clinical outcomes compared with late initiation (eGFR 5–7 ml/min/1.73m^2). This study evaluated the impact of publication of the IDEAL trial results in 2010 on the timing of dialysis initiation in Canada. 28,468 patients who commenced dialysis in 2006–2015 were included. Prior to publication of the IDEAL trial, an increasing trend was seen in the monthly proportion of patients starting dialysis early (p=0.004). After the IDEAL trial, there was an immediate decrease in the proportion of early dialysis starts (p<0.001).

Comment: It is great to see the pivotal IDEAL study having an impact in changing clinical practice in Canada – we have too few examples like this in nephrology. The implementation of the results of major clinical trials with clear impactful findings is an area that needs much more attention.

Reference: JAMA Intern Med 2019;179(7):934-41

Abstract

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Evaluating a new international risk-prediction tool in IgA nephropathy

Authors: Barbour S et al.

Summary: This article described the development of a prediction model for disease progression in patients with IgA nephropathy. Overall, 3927 adults with biopsy-proven IgA nephropathy in Europe, North America, China and Japan were included. Three prediction models were developed: a clinical model (using eGFR, blood pressure, and proteinuria at biopsy) and 2 full models (using the same risk factors as the clinical model but also including the MEST histologic score, age, medication use, and either racial/ethnic characteristics or no racial/ethnic characteristics). Compared with the clinical model, the two full models (with and without race/ethnicity) were shown to be more accurate at predicting the risk of a 50% decline in eGFR, and improving patient risk reclassification. External validation confirmed the accuracy of the two full models.

Comment: The increasing understanding that treatment of IgA nephropathy, particularly with immunosuppressive agents, has major risks as well as probable benefits highlights the need to target therapies carefully. This helpful study has developed a risk prediction tool that can assist us to better identify individuals at high risk for whom the risks of treatment might be particularly worthwhile.

Reference: JAMA Intern Med 2019;179(7):942-52
Abstract

Use of peripherally inserted central catheters in patients with advanced chronic kidney disease

Authors: Paje D et al.

Summary: Current guidelines recommend against placement of PICCs in patients with advanced CKD. This prospective cohort study evaluated the use of PICCs in hospitalised patients with at least stage 3b CKD in 52 hospitals in Michigan. 20,545 patients who received a PICC between November 2013 and September 2016 were included. 4743 (23.1%) of patients had eGFR <45 ml/min/1.73m^2 and 699 (3.4%) were receiving haemodialysis. 30.9% of patients who received a PICC in the intensive care unit (ICU) had an eGFR <45 ml/min/1.73m^2 compared with 19.3% of patients who received a PICC in a hospital ward. PICC-related complications in wards occurred in 15.3% of patients with eGFR <45 ml/min/1.73m^2 and in 15.2% of those with eGFR ≥45 ml/min/1.73m^2. Corresponding percentages in ICUs were 22.4% and 23.9%, respectively. PICC placement in patients with eGFR <45 ml/min/1.73m^2 varied widely between hospitals.

Comment: It is very concerning to see that PICC line placement is so common in CKD patients, potentially making vascular access more challenging in those who need haemodialysis in the future. The one silver lining is that complication rates were surprisingly not higher in CKD patients, at least in the short term. Long-term follow-up would be of interest, but better systems and protocols for PICC lines are key.

Reference: Ann Intern Med 2019;171(1):10-18
Abstract

Nonsteroidal anti-inflammatory drug use and risk of acute kidney injury and hyperkalemia in older adults

Authors: Nash D et al.

Summary: This population-based Canadian study determined the 30-day risk of AKI and hyperkalaemia in older adults (≥66 years) after NSAID initiation. 46,107 new users of NSAIDs were matched with 46,107 nonusers with similar baseline health. NSAID use versus nonuse was associated with a significantly higher 30-day risk of AKI (odds ratio [OR], 1.41) and hyperkalaemia (OR, 1.50) but not all-cause mortality. A prediction model was developed that incorporated 6 predictors of AKI or hyperkalaemia: older age, male gender, lower baseline eGFR, higher baseline serum potassium levels, angiotensin receptor blocker or angiotensin-converting enzyme inhibitor use, or diuretic use.

Comment: While it is not surprising (or that interesting) that NSAIDs increase the risk of AKI in older individuals, this study is useful for quantifying that risk and showing that AKI is actually quite uncommon compared to matched non-users (0.82% vs 0.59%), with hyperkalaemia even less common (0.27% vs 0.23%). Perhaps I will be a little more circumspect when lecturing people using NSAIDs about renal risk in the future.

Reference: Nephrol Dial Transplant 2019;34(7):1145-54
Abstract

Fatigue in nondialysis chronic kidney disease: correlates and association with kidney outcomes

Authors: Gregg L et al.

Summary: This longitudinal cohort study evaluated the association between fatigue and kidney outcomes in patients with nondialysis CKD. 266 outpatients with nondialysis CKD stages 2–5 were assessed for self-reported fatigue on 3 scales (Quick Inventory of Depression Symptomatology-Self Report [QIDS-SR16], Beck Depression Inventory-I [BDI-I], and short form 12 health survey) and evaluated for the composite end-point of progression to dialysis initiation, death, or hospitalisation after 12 months. 69.2% of patients reported fatigue on the QIDS-SR16 scale and 77.7% reported fatigue on the BDI-I. Unemployment, comorbidities, use of antidepressants, and lower haemoglobin levels were found to be correlated with fatigue. Patients that reported any versus no fatigue on QIDS-SR16 were more likely to reach the composite end-point (adjusted hazard ratio, 1.63).

Comment: Thanks to initiatives such as SONG, there is growing awareness of the importance of fatigue to patients receiving dialysis. This study highlights the very high frequency of fatigue in earlier stages of CKD, and that it appears to predict adverse outcomes. It suggests that greater attention to fatigue as a potential treatment target in CKD is warranted.

Reference: Am J Nephrol 2019;50:37-47
Abstract

Safety of a restrictive versus liberal approach to red blood cell transfusion on the outcome of AKI in patients undergoing cardiac surgery

Authors: Garg A et al.

Summary: This prespecified substudy of a randomised controlled trial compared the impact of a restrictive versus liberal approach to red blood cell transfusion on AKI in patients undergoing cardiac surgery. 4531 patients undergoing cardiac surgery with cardiopulmonary bypass who had a moderate-to-high risk of perioperative death were randomised to a restrictive threshold for red blood cell transfusion (transfuse if haemoglobin <7.5 g/dl, intraoperatively and postoperatively) or a liberal threshold (transfuse if haemoglobin <9.5 g/dl in the operating room or intensive care unit, or if haemoglobin <8.5 g/dl in the nonintensive care ward). Patients in the restrictive-threshold group received 38% fewer transfusions than patients in the liberal-threshold group (p<0.001). The incidence of AKI was comparable in the 2 groups overall (27.7% and 27.9%, respectively), and in patients with preoperative CKD (33.6% and 32.5%, respectively).

Comment: This secondary analysis of a major randomised trial adds to the growing literature arguing against aggressive treatment of anaemia, this time in the acute context. No difference in kidney function was observed, and fewer transfusions were required, suggesting a conservative approach is a better option.

Reference: J Am Soc Nephrol 2019;30(7):1294-1304
Abstract

Analysis from the EMPA-REG OUTCOME® trial indicates empagliflozin may assist in preventing the progression of chronic kidney disease in patients with type 2 diabetes irrespective of medications that alter intrarenal hemodynamics

Authors: Mayer G et al.

Summary: This analysis of the EMPA-REG OUTCOME trial investigated the effects of empagliflozin on renal function in patients with type 2 diabetes who were also taking other agents that alter intrarenal haemodynamics (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, calcium channel blockers, diuretics and NSAIDs). In the EMPA-REG OUTCOME trial, 7020 patients were randomised to receive empagliflozin 10 or 25mg or placebo in addition to their standard care. Cox proportional hazards models showed that risk reductions in incident or worsening nephropathy with empagliflozin were consistent across medication subgroups.

Comment: The more we learn about the effects of SGLT2 inhibitors in the kidney, the less we seem to know. It might have been expected that SGLT2 inhibitor benefits in EMPA-REG OUTCOME would be modified by some of the co-therapies used that affect glomerular haemodynamics, but no such effect was observed in this secondary analysis. Does this mean that glomerular haemodynamic effects are less important than we thought? I certainly don't know.

Reference: Kidney Int 2019;96(2):489-504
Abstract

Mycophenolate mofetil versus cyclophosphamide for the induction of remission in nonlife-threatening relapses of antineutrophil cytoplasmic antibody-associated vasculitis

Authors: Tuin J et al.

Summary: This study in the Netherlands compared the efficacy and safety of mycophenolate mofetil and cyclophosphamide for the induction treatment of nonlife-threatening relapses of ANCA-associated vasculitis. 84 patients with a first or second relapse of ANCA-associated vasculitis were randomised to induction treatment with cyclophosphamide or mycophenolate mofetil (both in combination with glucocorticoids); maintenance therapy comprised azathioprine in both arms. At 6 months, 66% of mycophenolate mofetil recipients and 81% of cyclophosphamide recipients were in remission (p=NS). Disease-free survival rates at 2 and 4 years were 61% and 39%, respectively, for cyclophosphamide, and 43% and 32%, respectively, for mycophenolate mofetil.

Comment: It is great to see a reasonably sized trial in relapsing ANCA-associated vasculitis, comparing cyclophosphamide to mycophenolate, along with steroids in both arms. While no statistically significant differences in outcomes were seen, this may have been due to the moderate size and the data suggest the possibility that mycophenolate may be less efficacious.

Reference: Clin J Am Soc Nephrol 2019;14(7):1021-28
Abstract

Risk of ESKD in older live kidney donors with hypertension

Authors: Al Ammary F et al.

Summary: This US study determined the 15-year risk of ESKD and mortality in older kidney donors (≥50 years) with hypertension compared with those without hypertension. A cohort of 24,533 older donors (2265 of whom had pre-donation hypertension) from 1999–2016 were linked to Centers for Medicare and Medicaid Services data and the Social Security Death Master File to determine ESKD development and mortality. 24 ESKD and 252 death events occurred during a median follow-up of 7.1 years. The 15-year risk of ESKD was calculated to be 0.8% in donors with hypertension compared with 0.2% in donors without hypertension (adjusted hazard ratio, 3.04; p=0.01). There was no association between donor hypertension and 15-year mortality.

Comment: It is a little confronting to see people over the age of 50 classified as 'older donors' but nonetheless this important study shows that such individuals with hypertension had significantly higher rates of ESKD over 15 years, particularly if they were using blood pressure-lowering therapy. The numbers here are helpful, allowing us to quote the values of 0.8% versus 0.2% over 15 years to potential donors to inform decisions.

Reference: Clin J Am Soc Nephrol 2019;14(7):1048-55
Abstract

Independent commentary by Professor Vlado Perkovic, who is Executive Director of The George Institute, Australia, Professor of Medicine at UNSW Sydney, and a Staff Specialist in Nephrology at the Royal North Shore Hospital. His research focus is in clinical trials and epidemiology, in particular in preventing the progression of kidney disease and its complications. He leads several international clinical trials, and has been involved in developing Australian and global treatment guidelines. He has played a central role in the development of an affordable dialysis system, which was a Eureka Prize finalist in 2017. Vlado is a member of the National Health and Medical Research Council Principal Committee on Research Translation, and is on the Board of the Australian Clinical Trials Alliance and the Association of Australian Medical Research Institutes. He is Chair of the International Society of Nephrology Advancing Clinical Trials (ISN-ACT) group; and is a Fellow of the Royal Australasian College of Physicians, and the Australian Academy of Health and Medical Sciences. He serves on the Editorial Boards of a number of leading specialist and general journals, including the Journal of the American Society of Nephrology, Circulation, and the New England Journal of Medicine.

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