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Making Education Easy

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Abbreviations used in this issue:

ATAGI = Australian Technical Advisory Group on Immunisation; **CKD** = chronic kidney disease; **eGFR** = estimated glomerular filtration rate; **HR** = hazard ratio; **rATG** = rabbit anti-thymocyte globulin; **RCT** = randomised controlled trial; **SARS-CoV-2** = severe acute respiratory syndrome coronavirus 2; **SGLT2** = sodium-glucose cotransporter-2; **UACR** = urine albumin creatinine ratio.

Welcome to the latest issue of Nephrology Research Review.

In this issue, we review a pair of studies exploring response to mRNA vaccines in haemodialysis patients, examine a large observational study casting doubt on the benefit of chlorthalidone over hydrochlorothiazide, explore important secondary analyses from trials of roxadustat and dapagliflozin, review a cohort study highlighting the potential for donor-derived cell-free DNA and gene expression profiling to detect kidney transplant rejection, and see that the importance of religion to one's outlook on life clearly influence decisions around end-of-life care – although perhaps it is not as strong a predictor as some might assume.

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

Kind Regards,

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Humoral and cellular responses to mRNA-1273 and BNT162b2 SARS-CoV-2 vaccines administered to hemodialysis patients

Authors: Broseta JJ et al.

Summary: This prospective study examined seroconversion among 205 haemodialysis recipients at three Spanish dialysis units. Patients received mRNA-1273 (Moderna) or BNT162b2 (Pfizer-BioNTech) vaccines. Humoral response was defined by detection of immunoglobulin (Ig)G anti-receptor binding domain of the S1 spike antigen (anti-S1-RBD) and cellular response by a positive cytokine stimulation assay. Of the 175 patients who were seronegative at baseline and who received both doses (57% Moderna, 43% Pfizer), a humoral and/or cellular response was seen in 97.7% of patients (98% with Moderna, 92% with Pfizer). Age was an important predictor of response, with the median antibody level of over 150 U/ml (the upper limit of detection) in those aged 20 to 67 years, compared with 104 U/ml in the 68 to 80 age group, and 59 U/ml in those aged over 80 ($p<0.001$). Other predictors of poor response were current immunosuppressive treatment and low serum albumin. A more robust humoral response was observed in the 24 patients who were seropositive at baseline, with higher antibody levels even after a single vaccine dose. Infection with SARS-CoV-2 was identified after vaccination in 3 patients, one of whom had severe disease.

Comment: This study confirms an immunological response to both Moderna and Pfizer vaccines in haemodialysis patients. Unsurprisingly, age and immunosuppression were associated with less robust response to vaccination. Although limited to description of short-term immunological response and lacking data on the durability of response and clinical efficacy, this study is useful in the Australian context where both Moderna and Pfizer are now available for haemodialysis recipients.

Reference: Am J Kidney Dis 2021;78(4):571-81
Abstract

Evaluation of the SARS-CoV-2 antibody response to the BNT162b2 vaccine in patients undergoing hemodialysis

Authors: Yau K et al.

Summary: This single-centre study from Canada investigated humoral responses to the BNT162b2 (Pfizer-BioNTech) vaccine in 142 haemodialysis recipients and 35 health care workers acting as controls. Among 66 patients who had antibody levels measured after 1 dose, seroconversion (detectable antibodies) at 28 days occurred for anti-spike protein in 53 (80%) patients and for anti-receptor binding domain (anti-RBD) in 36 (55%). In the 72 patients who received 2 doses, seroconversion at 14 days was evident in 69 (96%) for anti-spike, and 63 (88%) for anti-RBD. By 2 weeks after the second dose, 52 (72%) of these patients exceeded the median antibody level seen in convalescent plasma for anti-spike antibodies, and 43 (60%) reached this target for anti-RBD antibodies. All of the health care workers seroconverted, with antibody levels exceeding the median level seen in convalescent plasma for both antibody types.

Comment: This study appears to have been prompted by local health care guidance advising delaying second doses of the Pfizer vaccine (as a means to increase first-dose coverage in the setting of shortages). The data presented here demonstrate a poor response to a single dose of Pfizer in haemodialysis patients, suggesting that this vulnerable group should be prioritised for second doses. Fortunately, Australia is no longer in this situation, although it is a challenge still faced by many dialysis providers worldwide. Of more relevance to the current Australian situation: despite the high rate of seroconversion following 2 doses, approximately one-third of dialysis patients in this study failed to mount a robust antibody response, suggesting suboptimal protection. A small French study published last month in *Am J Kidney Dis* suggests that a minority of dialysis patients who do not respond to 2 doses of the Pfizer vaccine will respond to a third. They also noted that all patients with a weak antibody response to 2 doses demonstrated a substantial increase in antibody levels with a third dose. The ATAGI advice recommending a third dose for immunocompromised patients and those receiving dialysis could not be more timely.

Reference: JAMA Netw Open 2021;4(9):e2123622
Abstract

Comparison of clinical outcomes and safety associated with chlorthalidone vs hydrochlorothiazide in older adults with varying levels of kidney function

Authors: Edwards C et al.

Summary: Using administrative data collected in the Canadian province of Ontario, this study compared kidney and cardiovascular outcomes in older adults commencing chlorthalidone or hydrochlorothiazide. Using propensity score matching, the investigators identified 12,722 new users of chlorthalidone or hydrochlorothiazide (in a 1:4 ratio) aged over 65 years. Commencing chlorthalidone was associated with a 24% greater risk of a decline in eGFR of 30% or more (HR 1.24, 95% CI 1.13–1.36) and a 12% greater risk of cardiovascular events (HR 1.12, 95% CI 1.04–1.22). It was also associated with a higher risk of hypokalaemia, although no difference was noted in the risk of dialysis or kidney transplantation, death, or hyponatraemia. These findings were similar across strata defined by eGFR, with the exception that the excess risk of hypokalaemia was less pronounced among those with lower eGFR (<45 ml/min/1.73m^2).

Comment: Use of chlorthalidone in preference to hydrochlorothiazide is, at least anecdotally, seen as an archetypal nephrologist move. The choice tends to be made with the air of a connoisseur selecting a Châteauneuf-du-Pape over chateau-de-cardboard. This study follows two earlier large retrospective cohort studies which found no evidence of superior outcomes with chlorthalidone, and a greater risk for adverse events. The present study raises the possibility of harm. However, these studies are at odds with network meta-analyses suggesting chlorthalidone further reduces the risk of cardiovascular events compared to hydrochlorothiazide. Both types of study suffer potential biases. Fortunately, a randomised study comparing both agents is underway in the US Veterans' Affairs network and is aiming to enrol over 13,000 participants. Given the widespread use of hydrochlorothiazide for hypertension, the results of this study may have implications far beyond the claims of nephrologists to an expert palate.

Reference: JAMA Netw Open 2021;4(9):e2123365
Abstract

Efficacy and cardiovascular safety of roxadustat for treatment of anemia in patients with non–dialysis-dependent CKD

Authors: Provenzano R et al.

Summary: This meta-analysis pooled data from three closely related phase III studies of roxadustat versus placebo in people with non-dialysis dependent CKD (ANDES, ALPS, and OLYMPUS). There was no difference in the rate of the primary cardiovascular safety end-point (a composite of myocardial infarction, stroke, and all-cause mortality), with 10.6 and 10.3 events per 100 patient-years in the roxadustat and placebo arms, respectively (HR 1.10, 95% CI 0.96–1.27). Roxadustat effectively increased haemoglobin and reduced the need for transfusion.

Comment: Hypoxia-inducible factor (HIF)-prolyl hydroxylase inhibitors offer similar efficacy to erythropoiesis-stimulating agents but without requiring injection. They have been shown to be safe in patients already receiving dialysis. However, a recent study of vadadustat vs darbepoetin failed to demonstrate non-inferiority to darbepoetin on the important issue of cardiovascular safety. The present study, meta-analysing 3 similar RCTs comparing roxadustat to placebo (and which were not designed as non-inferiority studies) did not detect a statistically significant difference in the rate of major adverse cardiovascular events (MACE). Nevertheless, with the point estimate of the hazard ratio for the composite MACE outcome (1.10) favouring placebo, and the upper bound of the confidence interval exceeding the 1.25 margin for non-inferiority used in the vadadustat study, caution regarding the use of these agents in the non-dialysis population may remain.

Reference: Clin J Am Soc Nephrol 2021;16(8):1190-1200
Abstract

Effects of dapagliflozin in stage 4 chronic kidney disease

Authors: Chertow GM et al., for the DAPA-CKD Trial Committees and Investigators

Summary: This prespecified subgroup analysis of the DAPA-CKD study examined outcomes in the 624 participants with baseline eGFR between 25 and 30 ml/min/1.73m^2. This study enrolled patients with albuminuric CKD, regardless of diabetes status. Those who received 10mg per day of dapagliflozin had a 27% relative reduction (HR 0.73, 95% CI 0.53–1.02) in risk of the primary composite outcome of kidney failure, renal or cardiovascular death, or ≥50% decline in eGFR compared to those receiving placebo. Although not statistically significant in itself, this reduced risk of kidney and cardiovascular outcomes was consistent with the effect seen in those participants with an eGFR >30 ml/min/1.73m^2. In addition, the reductions in each of the components of the composite outcome were similar to that seen in those with higher levels of baseline kidney function. There were no differences in the rates of adverse events.

Comment: This analysis demonstrates that the beneficial effects of dapagliflozin extend even to those with early stage 4 CKD, with no increased risk of adverse events. These findings may be tentatively extended to both diabetic and non-diabetic patients with albuminuric (i.e. UACR >30 mg/mmol) CKD, who were eligible for the DAPA-CKD study and were similarly represented in this subgroup analysis. Although this study is still limited by its status as a secondary analysis, its findings are nevertheless consistent with previous analyses of the CREDENCE and DAPA-CKD studies showing similar renal benefits from SGLT2 inhibitors across the spectrum of eGFR down to 25–30 ml/min/1.73m^2.

Reference: J Am Soc Nephrol 2021;32(9):2352-61
Abstract

Combining blood gene expression and cellfree DNA to diagnose subclinical rejection in kidney transplant recipients

Authors: Park S et al.

Summary: Using a cohort of kidney transplant patients undergoing both kidney biopsy and collection of blood gene expression profile and donor-derived cell-free DNA (cfDNA), this study compared the accuracy of the non-invasive tests in the detection of subclinical rejection in 428 paired biopsy and blood samples from 208 patients. Only patients with stable graft function undergoing surveillance biopsies were included. The area under the receiver operating curve for diagnosis of subclinical rejection was 0.75 with the gene expression profile, 0.72 with donor-derived cfDNA, and 0.81 when both tests were combined. The negative predictive value when both tests were negative was 88%, and the positive predictive value when both were positive was 81%.

Comment: The non-invasive identification of subclinical rejection is an important focus of research in transplant medicine. It offers the potential to permit more nuanced individualisation of transplant immunosuppression, which may then lead to important improvements in long-term graft function and reduction in recipient morbidity. This study paired a microarray panel analysing expression patterns of 120 genes with analysis of donor-derived cfDNA (as a proportion of all cfDNA) identified by screening both recipient and donor for a panel of approximately 70,000 single nucleotide polymorphisms. Both approaches have garnered interest in recent years, but their proper place in management is not yet established. The present study shows that using a combination of non-invasive approaches to diagnose rejection may improve accuracy. Further studies in varied cohorts will be required to better understand the use of these tools in clinical practice.

Reference: Clin J Am Soc Nephrol 2021;16(10):1539-51
Abstract

Association between self-reported importance of religious or spiritual beliefs and end-of-life care preferences among people receiving dialysis

Authors: Scherer JS et al.

Summary: As part of a survey of the treatment preferences of people with kidney failure, haemodialysis and peritoneal dialysis recipients at 31 US dialysis units were asked to respond to the statement 'My religious or spiritual beliefs are what really lie behind my whole approach to life'. Responses were 'definitely true', 'tends to be true', 'tends not to be true', and 'definitely not true'. Of the 1431 patients approached, 937 (70%) participated, of whom 46% rated the statement 'definitely true'. After adjusting for demographic and educational factors, those with strong religious or spiritual identification were more likely to wish to be resuscitated and less likely to have thought or spoken about stopping dialysis. They were, however, no less likely to have unmet palliative care needs, nor to differ in their views on documentation of end-of-life treatment preferences, assignment of a surrogate decision maker, or to value life prolongation over relief of pain and discomfort.

Comment: We are all likely to carry expectations, informed by experience but also by preconceptions, of the influences of particular spiritual beliefs on end-of-life care. This study found a clear association between religious or spiritual beliefs and a wish to be resuscitated, but no differences in willingness to engage with advanced care planning generally. The study may suffer some limitation in generalisability, for example owing to the location in two US cities and the need for English-language fluency to participate. In addition, stated preferences may be distinct from actions taken in the end-of-life situation. It is also notable that the differences between the most and least religious respondents (after adjustment for available confounders) were typically quite small. For example, a preference for CPR was expressed by 69.8% of those who assigned most importance to religion or spirituality, and by 60.8% of those who assigned it no importance. This study finds that many of our patients place great weight on religion or spiritual beliefs, but also emphasises the importance of open discussion of end-of-life preferences as one cannot make assumptions about what are highly personal and individual decisions.

Reference: JAMA Netw Open 2021;4(8):e2119355
Abstract

Early postoperative basal insulin therapy versus standard of care for the prevention of diabetes mellitus after kidney transplantation

Authors: Schwaiger E et al.

Summary: To determine if more aggressive use of insulin in the immediate post-transplant period would reduce the incidence of new-onset diabetes after transplantation (NODAT), Schwaiger et al. randomised 263 kidney transplant recipients receiving standard immunosuppression with corticosteroids, tacrolimus and mycophenolate, to a proactive insulin strategy or a reactive strategy. The proactive strategy comprised use of intermediate acting insulin, with the introduction of a morning dose of isophane insulin if early afternoon glucose exceeded 140 mg/dL (7.8 mmol/L), subsequently targeting an early afternoon glucose of 110 mg/dL (6.1 mmol/L) and continued on discharge if persisting treatment was required. For the reactive strategy, only fasting morning glucose was routinely measured and more frequent monitoring and treatment initiated if glucose exceeded 200 mg/dL (11.1 mmol/L) with a sulphonylurea commenced if persisting treatment was required. 88% of those in the proactive arm were discharged on insulin, whereas only 16% of those in the reactive arm received any treatment for hyperglycaemia. There was no statistically significant difference in the number of participants with NODAT (based on a positive oral glucose tolerance test) at 12 or 24 months (17 vs 7 [OR 0.40, 95% CI 0.16–1.01], and 19 vs 15 [OR 0.71, 95% CI 0.34–1.49], respectively).

Comment: This study found no clear evidence that a proactive insulin strategy reduced the incidence of NODAT. The strength of this study was the 2-year follow-up. The authors performed a number of post-hoc analyses in the per protocol study population, finding a significant reduction in NODAT after adjusting for a baseline imbalance in polycystic kidney disease. Further studies to determine the optimal management of hyperglycaemia post-transplant are clearly warranted.

Reference: J Am Soc Nephrol 2021;32(8):2083-98
Abstract

Independent commentary by Dr Brendan Smyth

Brendan Smyth is a Staff Specialist at St George Hospital, Postdoctoral fellow at the NHMRC Clinical Trials Centre, and Research Fellow at The George Institute for Global Health. His research focus is clinical trials and research methodology, with a particular interest in haemodialysis. He has experience in clinical trial development, implementation and analysis; and is a leading member of the International Society of Nephrology Advancing Clinical Trials (ISN-ACT) group, including driving the creation of the ISN-ACT Clinical Trials Toolkit. In addition to journal publications, he has contributed textbook chapters and designed and delivered nephrology teaching courses at a masters level. He is a Fellow of the Royal Australasian College of Physicians and is an active early career researcher and trialist.

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Primary results of the randomized trial of metformin administration in polycystic kidney disease (TAME PKD)

Authors: Perrone RD et al.

Summary: This phase II study randomised 97 participants with autosomal dominant polycystic kidney disease (ADPKD) and an eGFR >50 ml/min/1.73m^2 to twice daily metformin or placebo. The primary outcome of safety and tolerability opened the way to a larger study, with 77 (79%) participants remaining on their allocated treatment at 2 years, with a similar rate of serious adverse events in the 2 groups. The average rate of decline in eGFR was not significantly different (–1.71 vs –3.07 ml/min/1.73m^2 per year in the metformin and placebo groups respectively, mean difference 1.37 ml/min/1.73m^2 per year [95% CI –0.70 to 3.44]).

Comment: The ability of metformin to reduce cyst growth in preclinical models has aroused much interest given the potential of a cheap and generally well-tolerated drug to preserve kidney disease in those with ADPKD. The numerical difference in eGFR slope seen in this study is tantalising, but in this small study the confidence intervals around this estimate were wide. Further studies are underway, including a planned study in over 1000 participants led by an Australian research team that is aiming to commence recruitment soon.

Reference: Kidney Int 2021;100(3):684-96
Abstract

Belatacept for simultaneous calcineurin inhibitor and chronic corticosteroid immunosuppression avoidance

Authors: Kaufman DB et al., for the BEST Study Group

Summary: This study reported the 2-year follow-up of participants in the Belatacept Early Steroid withdrawal Trial (BEST), which randomised 316 low-risk kidney transplant recipients to three immunosuppression strategies: belatacept with alemtuzumab induction, belatacept with rATG induction, or tacrolimus with rATG induction. All patients received mycophenolate. Corticosteroids were used in the induction period and were withdrawn after day 5. There was no statistically significant difference in the occurrence of the primary composite end-point of death, graft loss, or eGFR <45 ml/min/1.73m^2 between the belatacept groups (alemtuzumab 11/107, rATG 13/104) and the tacrolimus group (22/105; p=0.99 and p=0.66 for each comparison). However, the incidence and severity of rejection was higher in the belatacept groups (alemtuzumab 20/107, rATG 26/104) than in the tacrolimus group (7/105; p=0.009 and p<0.001 for each comparison). Kidney function was similar in all groups (median eGFR 66, 63, and 64 ml/min/1.73m^2, respectively). There was no difference in *de novo* donor-specific antibodies.

Comment: This intriguing study failed to show superiority of a strategy of calcineurin inhibitor-avoidance with co-stimulation blockade in kidney transplant patients treated with corticosteroid-free maintenance therapy. Reliance on belatacept without calcineurin-inhibition was clearly linked to a higher risk of acute rejection, particularly in the first year post-transplant. However, it is notable that the proportion of participants with an eGFR <45 ml/min/1.73m^2 at two years was lower in the belatacept groups (although median eGFR did not differ and eGFR slope was not presented). Ultimately, this study shows a belatacept-based strategy to be feasible, but without a clear advantage over the traditional calcineurin-inhibitor regimens. Longer-term studies may be needed to determine if calcineurin-inhibitor avoidance can protect graft function in the longer term.

Reference: Clin J Am Soc Nephrol 2021;16(9):1387-97
Abstract

