

ISN Trial-List

March 2018



Once a month, the ISN-ACT (Advancing Clinical Trials) team collects and publishes a list of important nephrology trials from the latest medical literature. Each trial is reviewed in context and their risk of bias in seven key areas assessed.

Key to risk of bias assessment

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|----|------------------------------------|-----------------------------|
| R | Random sequence generation | High risk |
| A | Allocation concealment | Uncertain risk / not stated |
| BP | Blinding of participants/personnel | Low risk |
| BO | Blinding of outcome assessment | |
| CD | Complete outcome data | |
| CR | Complete outcome reporting | |
| B | No other sources of bias | |

Glomerular Diseases, Pediatric Nephrology

ISN Academy: [Glomerular Diseases](#), [Pediatric Nephrology](#)

Levamisole reduces risk of relapse in children with frequently relapsing nephrotic syndrome

A randomized clinical trial indicates that levamisole increases the time to relapse in children with steroid-sensitive idiopathic nephrotic syndrome

[Gruppen, et al. Kidney Int. 2018;93\(2\):510-518](#)

Idiopathic steroid-sensitive nephrotic syndrome in children frequently relapses leading to steroid toxicity from repeated treatment. Levamisole, originally an anti-helminth agent, has been reported to be effective in childhood nephrotic syndrome but has not been proven in a high-quality trial. Gruppen, et al. conducted an international double-blind trial of levamisole for preventing or delaying relapse in children with frequently relapsing nephrotic syndrome. One-hundred and three participants who had just achieved remission of nephrotic syndrome with steroids were randomised to levamisole (2.5mg/kg on alternate days) or placebo. Four patients (3 placebo/1 levamisole) did not receive either treatment and were excluded. In the modified intention-to-treat analysis at 12 months, 26% (13/50) of those on levamisole remained in remission compared to 6% (3/49) in the placebo group (log rank $P=0.015$). The impact of levamisole was not apparent until 100 days, prompting the authors to present time-dependent hazard ratios (HR) for relapse: <100 days HR 1.14 (95% CI 0.56-2.34) $P=0.72$; ≥ 100 days HR 0.22 (95% CI 0.11-0.43), $P=0.001$. Side effects were more common in the treatment group and included neutropenia in 12 participants (8 levamisole) which recovered with cessation of treatment or spontaneously. No patients were lost to follow up. This trial has the potential to change practice in this field and we look forward to further research to better understand the role that levamisole may play in treatment of idiopathic nephrotic syndrome.



Transplant

ISN Academy: [Transplant](#)

Bortezomib fails to impact late antibody mediated rejection in small RCT

A Randomized Trial of Bortezomib in Late Antibody-Mediated Kidney Transplant Rejection

[Eskandary, et al. J Am Soc Nephrol;29\(2\):591-605](#)

Late antibody mediated allograft rejection (ABMR) is a major cause of graft loss and is resistant to current treatments. The proteasome inhibitor bortezomib – thought to work by reducing production of pathogenic donor specific antibodies (DSA) – has shown promise in uncontrolled studies. Eskandary, et al. screened 741 patients more than 6 months post-renal transplant with an eGFR > 20 ml/min/1.73m² and identified 111 who were DSA positive. Eighty-six of these were biopsied, 52 of whom had features of ABMR. Forty-four (median time since transplant 5.0 years; median eGFR 49 vs 53ml/min/1.73m²) consented to randomization to two cycles of bortezomib (total of eight doses of 1.3mg/m²) or placebo. The primary endpoint of difference in slope of GFR decline was similar between groups (0.5ml/min/1.73m² per year [95% CI -4.8-5.8]; $P=0.86$). Nor were there significant differences in eGFR or graft loss at 2 years between bortezomib and placebo-treated participants (33 versus 42ml/min/1.73m² [$P=0.31$]; 81% versus 96% [$P=0.12$]). This study was double blinded and of relatively long duration, but limited to a single centre and had only a small sample size. Also, the placebo group had a relatively good outcome with overall graft survival of 96% and eGFR decline of only 2ml/min/1.73m² in 2 years. These results emphasise both the challenges and importance of properly conducted clinical trials in this field and highlight the ongoing need for novel therapies and collaborative research approaches to the treatment of ABMR.



Chronic Kidney Disease

ISN Academy: [Chronic Kidney Disease](#)

Single pharmacist home-visit was not able to reduce readmission in patients with CKD

Medication Therapy Management after Hospitalization in CKD: A Randomized Clinical Trial

[Tuttle, et al. Clin J Am Soc Nephrol;13\(2\):231-241](#)

Hospitalization is frequent in patients with CKD and often results in changes in medications on a background of multiple co-morbidities and polypharmacy. These are known risk factors for drug-induced adverse events and readmission to hospital. Tuttle, et al. randomized 159 hospitalized patients with CKD to a pharmacist home visit with medication review and personalised medication plan within 7 days of discharge, or to usual care. Ninety-two percent of participants in the intervention group were found to have at least one medication discrepancy or other problem addressed by the pharmacist. Despite this, the primary outcome of the number of hospital admissions, emergency department or urgent care visits within 90 days did not differ between the two groups (32/72 [44%] vs 28/69 [41%]; log rank P=0.72). The study was limited by its size, that only 120 of the 159 randomized patients completed their 90-day visit and that all participants spoke English and 70% had at least some college education. The need remains for further research, in diverse settings, aimed at reducing the burden of hospital readmission and drug-related adverse events in patients with CKD.



Anemia, Iron and Trace Elements

ISN Academy: [Anemia, Iron and Trace Elements](#)

Oral calcitriol does not suppress hepcidin in CKD but the nature of the link between vitamin D and iron metabolism remains incompletely understood

Effect of calcitriol on serum hepcidin in individuals with chronic kidney disease: a randomized controlled trial

[Panwar, et al. BMC Nephrol. 2018;19:35 doi:10.1186/s12882-018-0823-7](#)

Hepcidin is the key negative regulator of iron uptake and metabolism and its elevation in chronic kidney disease is an important cause of anaemia in these patients. Recent work in healthy subjects suggests that vitamin D suppresses hepcidin release by the liver. This inspired Panwar, et al. to investigate whether the same relationship exists in patients with CKD. They randomized 40 participants with stage 3-4 CKD (mean eGFR 38.2ml/min/m²) to calcitriol 0.5mcg daily or placebo for 6 weeks. No significant changes in hepcidin concentration (P=0.46) or in other markers of iron metabolism were identified. This study suggests that oral calcitriol may not meaningfully affect iron metabolism in unselected CKD patients. But, as the authors note, many questions remain. It is possible that an effect in CKD is dependent on 25-OH vitamin D or the presence of iron deficiency or vitamin D deficiency. Conversely, it may be that inflammation, uraemic toxins or other features of CKD are such that the relationship between hepcidin and vitamin D seen in healthy individuals is insignificant in those with CKD.



Hemodialysis

ISN Academy: [Hemodialysis](#)

Sertraline shows promise in uremic pruritis but further research is required

Sertraline can reduce uremic pruritus in hemodialysis patient: A double blind randomized clinical trial from Southern Iran

[Pakfetrat, et al. Hemodial Int. 2018;22\(1\):103-109](#)

Uremic pruritis is a common condition in ESKD and therapies based on high-quality evidence are lacking. Limited observational evidence suggests that the selective serotonin-reuptake inhibitor, sertraline, may be efficacious. Pakfetrat, et al. randomized 50 hemodialysis patients with uremic pruritis to sertraline 50mg twice daily or placebo for 8 weeks. They report a significantly greater improvement in pruritis over the study period as measured by visual analogue scale and the by the DUO pruritis scale (P=0.001 and P<0.001, respectively). While encouraging, this single centre study was limited by the lack of clarity surrounding the randomization process and the failure to report confidence intervals for the outcome measures and adverse events. Larger multicentre studies would be needed to confirm this result.

