

ISN Global Trials Focus

October 2019



The ISN-ACT (Advancing Clinical Trials) team presents this monthly showcase of randomized trials in nephrology from around the world. The trials selected are not necessarily those likely to have the highest impact. Our aim is to showcase the diversity of trials recently published and to review these in context, assessing their risk of bias in seven key areas. We hope that our efforts will drive improvement in trial quality and promote greater engagement in trial activity.

Join the debate on Twitter by following **@ISNeducation**:
 Will these trials affect your practice? Are the results valid?
 How could the trials have been improved? What further studies are needed?

If you would like to suggest any trials for inclusion in future editions, please send suggestions to research@theisn.org

Key to risk of bias assessment

Random sequence generation	High risk
Allocation concealment	Uncertain risk / not stated
Blinding of participants/personnel	Low risk
Blinding of outcome assessment	
Complete outcome data	
Complete outcome reporting	
No other sources of bias	

Contents

Sodium zirconium cyclosilicate is an effective treatment for hyperkalemia in hemodialysis patients.....	1
Vitamin C and hemodialysis AV access restenosis: pilot study hints at promise	2
A more palatable alternative for preventing renal calculi?	2
A multifaceted personal systems approach can improve medication adherence in adult kidney transplant recipients for up to 1 year	2
No benefit from peritoneal lavage in severe PD peritonitis	3
Bexagliflozin is effective in Type 2 Diabetics with CKD stage 3	3
Lower viral infections and similar graft outcomes with Everolimus in majority African-American kidney transplant cohort.....	3
Multidisciplinary and holistic approach proves a winner in Chinese PD patients	4

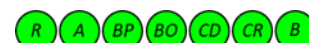
ISN Academy: [Hemodialysis](#)

Sodium zirconium cyclosilicate is an effective treatment for hyperkalemia in hemodialysis patients A Phase 3b, Randomized, Double-Blind, Placebo-Controlled Study of Sodium Zirconium Cyclosilicate for Reducing the Incidence of Predialysis Hyperkalemia (DIALIZE study)

[Fishbane et al. J Am Soc Nephrol. 2019;30\(9\):1723-1733](#)

Population	196 adults with ESKD on thrice-weekly hemodialysis, with pre-dialysis hyperkalemia (>5.4 mmol/L after long interdialytic interval, or >5.0 mmol/L after short interdialytic interval)	
Intervention vs Comparator	Sodium zirconium cyclosilicate (SZC) 5g daily vs placebo on non-dialysis days	Time 8 weeks
Outcomes	More patients in the SZC group (41% vs 1%; p<0.001) maintained a pre-dialysis K ⁺ of 4-5mmol/L during ≥3 of 4 HD treatments after the long interdialytic interval and did not require urgent rescue therapy. Few patients in either arm required rescue therapy to lower serum K ⁺ (2.1% SZC vs 5.1% placebo). Similar rates of adverse events (7.3% SZC vs 8.1% placebo) and discontinuation.	

SZC is an effective and well-tolerated treatment for hyperkalaemia in patients on chronic haemodialysis. Additional studies are required to determine long-term safety and to compare it to other potassium-binding resins such as sodium polystyrene sulfonate and patiomer.

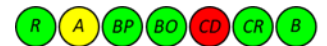


Vitamin C and hemodialysis AV access restenosis: pilot study hints at promise

A randomized feasibility study of the effect of ascorbic acid on post-angioplasty restenosis of hemodialysis vascular access
[Yang et al. Sci Rep. 2019 Jul 31;9\(1\):11095](#)

Population	93 patients on maintenance hemodialysis with successful percutaneous transluminal angioplasty (PTA) of failing AV fistula or grafts	
Intervention vs Comparator	Ascorbic acid (AA) 600mg vs AA 300mg vs placebo IV thrice weekly	Time 3 months
Outcomes	Restenosis (loss of luminal diameter between baseline [post-PTA] and follow up angiography) was lower for AA 600mg vs placebo (1.6±1.7 vs 3.2±1.7mm; P=0.006) but not for AA 300mg vs placebo (2.5±1.7 vs 3.2±1.7mm; P=0.39). Vascular access re-intervention was not different between groups (AA 600mg 30% [P=0.18 vs placebo], AA 300mg 45% [P=0.59 vs placebo] and placebo 53%).	

This small short-term study showed that AA at 600mg IV thrice weekly reduced AV access restenosis without reducing access reintervention, access failure or access thrombosis. Further studies appear warranted although the history of promising early studies followed by disappointing confirmatory trials with vitamin supplementation in cardiovascular diseases suggests caution.



ISN Academy: [Kidney Stones](#)

A more palatable alternative for preventing renal calculi?

Lime powder regimen supplement alleviates urinary metabolic abnormalities in urolithiasis patients
[Ungiaroenwathana et al. Nephrology \(Carlton\). 2019 Aug;24\(8\):791-797](#)

Population	80 patients with renal calculi requiring surgical intervention with a GFR greater than 60ml/min/1.73m ² and with no stone residue on x-ray.	
Intervention vs Comparator	Lime powder regimen (consisting of potassium, citrate, lime oil and lime juice) vs. placebo	Time 6 months
Outcomes	The increase in urine citrate (228mg/day vs. 81mg/day; P=0.013) and potassium (36mmol/day vs 22mmol/day; P=0.029) at 6 months in the lime powder group was significantly greater compared to the placebo group. However, there was no change in the urine supersaturation index, and urine pH did not differ at 6 months between groups. No patients developed new renal calculi. No adverse reactions were reported.	

Lime powder regimen improves some aspects of urine lithogenic profile. However, with only 6 months follow up, this study was unable to determine if this regimen leads to a reduction in urine calculi recurrence. A longer trial to answer this question is underway.



ISN Academy: [Transplant](#)

A multifaceted personal systems approach can improve medication adherence in adult kidney transplant recipients for up to 1 year

Improving medication adherence and outcomes in adult kidney transplant patients using a personal systems approach
 SystemCHANGE™ results of the MAGIC randomized clinical trial
[Russell et al. Am J Transplant. 2019. doi: 10.1111/ajt.15528](#)

Population	89 adult kidney transplant recipients with suboptimal medication adherence (<85%)	
Intervention vs Comparator	6 months of SystemCHANGE™ (a multifaceted intervention with in-person assessment, personalised strategies to improve medication adherence and feedback) vs. 6 months of control in-person education re healthy transplant lifestyle	Time 1 year
Outcomes	Medication adherence was higher at the end of the intervention period with SystemCHANGE™ vs. control education program (0.91 vs 0.67; difference in medians 0.24, 95% CI 0.13-0.30, P<0.001) The benefit was maintained during the post-intervention observation phase at 12 months (0.77 vs 0.60; difference in medians 0.17, 95% CI 0.06-0.33, P=0.004)	

Both groups received equivalent additional time and education beyond standard of care (90 mins over 6 months), however the problem-solving approach of SystemCHANGE™ (derived from institutional root-cause analysis and quality improvement methodologies) proved superior to control approach based on provision of education sessions.



ISN Academy: [Peritoneal Dialysis](#)

No benefit from peritoneal lavage in severe PD peritonitis

Randomized controlled trial on adjunctive lavage for severe peritonitis

[Wong et al. Perit Dial Int. 2019 Sep-Oct;39\(5\):447-454](#)

Population	40 peritoneal dialysis patients with severe bacterial peritonitis (leukocyte count >1090/mm ³ on day 3 of empiric therapy with either IP cefazolin or ceftazidime)
Intervention vs Comparator	Continuous lavage using an automated PD cyclor, with dwell volumes 2L and dwell time 2 hours, for 2-3 days with IV antibiotics vs the individual patient's usual PD schedule with IP antibiotics at doses as per ISPD guidelines.
Outcomes	Adjunctive lavage did not improve the primary outcome of treatment success: 75% vs 70% (P=0.72) Day 3 serum CRP associated with treatment failure: success versus failure 202.3± 88.2mg/L vs 301.6 ±90.5mg/L, P=0.003

In this small, single-centre trial, continuous PD lavage was not shown to improve rates of treatment success in patients with severe peritonitis. The authors suggest serum CRP can be used as an adjunct to assessing severity to peritonitis in PD patients.



ISN Academy: [Diabetes, Chronic Kidney Disease](#)

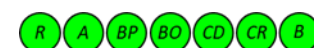
Bexagliflozin is effective in Type 2 Diabetics with CKD stage 3

Safety and Effectiveness of Bexagliflozin in Patients With Type 2 Diabetes Mellitus and Stage 3a/3b CKD

[Allegretti et al. Am J Kidney Dis. 2019;74\(3\): 328-337](#)

Population	312 participants with type 2 diabetes mellitus (HbA1c 7 to 10.5%) and eGFR 30 to 59ml/min/1.73m ²
Intervention vs Comparator	Bexagliflozin 20 mg vs. Placebo Time 24 weeks
Outcomes	Bexagliflozin lowered HbA1c by 0.37% compared to placebo (95%CI 0.20%-0.54%; P<0.001). Bexagliflozin also lowered body weight by 1.6 kg (95%CI 1.0-2.2; P<0.001), systolic BP by 3.8mmHg (95%CI 0.6-7.1; P=0.02) and albuminuria by 20.1% (geometric mean ratio reduction, 95%CI 2.5-34.6%; P=0.03). The adverse event profile was consistent with other drugs in this class.

Bexagliflozin reduces HbA1c in type 2 diabetics with CKD stage 3a/3b with similar effects on body weight, blood pressure and albuminuria to those seen in trials of other SGLT2 inhibitors. While this trial was not powered to conclude that bexagliflozin has equivalent effects on clinical endpoints as similar agents, it is generally assumed that the benefits seen in other SGLT2 inhibitor trials represent a class effect.



ISN Academy: [Transplant](#)

Lower viral infections and similar graft outcomes with everolimus in majority African-American kidney transplant cohort

Randomized controlled trial assessing the impact of everolimus and low-exposure tacrolimus on graft outcomes in kidney transplant recipients

[Taber et al. Clin Transplant. 2019 Jul 31:e13679](#)

Population	60 adult kidney transplant recipients, 57% of whom were African-American, with moderate to high immunological risk, and eGFR of at least 30ml/min/1.73m, receiving standard Tacrolimus-Mycophenolate based immunosuppressive regimen.
------------	---

Intervention vs Comparator	Three-month post-transplant transition to Everolimus (EVR) and low-exposure Tacrolimus (TAC) based regimen vs Mycophenolate (MPA) and standard exposure TAC based regimen	Duration 9 months
Outcomes	<p>At 12 months post-transplant, graft function (mean eGFR TAC/MPA 56±15 vs TAC/EVR 59±14mL/min/1.73m², P=0.47) and fibrosis scores (27.8% TAC/MPA vs 22.9% TAC/EVR, P=0.39) were similar in both treatment arms.</p> <p>Rates of acute rejection (7% TAC/MPA vs 3% TAC/EVR, P=0.55), post randomization hospitalization (20% TAC/MPA vs 27% TAC/EVR, P=0.54) and graft survival (100% in both arms) were also similar in both treatment arms. However, the TAC/EVR arm had significantly lower rates of CMV (17% TAC/MPA vs 0% TAC/EVR, P=0.02) and severe BK virus infections (13% TAC/MPA vs 0% TAC/EVR, P=0.04) as compared with those on standard immunosuppressive regimen.</p>	

Though limited by its sample size and the short follow up time, this study demonstrated that a three month post-transplant immunosuppression transition from MPA to EVR with concurrent lowering of TAC exposure is safe and effective in a majority African-American population. It may also provide the advantage of significantly lower rates of viral opportunistic infections.



ISN Academy: [Peritoneal Dialysis](#)

Multidisciplinary and holistic approach proves a winner in Chinese PD patients

Effects of Multidisciplinary Team Care Based on 5E's Renal Rehabilitation for Peritoneal Dialysis Patients in Guangxi Zhuang Autonomous Region of China: A Randomized Controlled Trial

[Luo et al. Blood Purif. 2019;48\(2\):115-123](#)

Population	146 maintenance peritoneal dialysis patients	
Intervention vs Comparator	Multidisciplinary care based on 5E's renal rehabilitation principles (a team of two physicians, two nurses, a dietician, physical therapist, social worker and psychotherapist) vs. usual care (single nurse and physician support)	Time 12 months
Outcomes	<p>At 12 months, those receiving the intervention had higher self-management scores for four of the five tested subscales.</p> <p>The rate of peritonitis was lower in the intervention group than then control group (1.5 vs. 3.4 per 100 patient-months; P=0.047)</p>	

The five E's in this program are Encouragement, Education, Exercise, Employment and Evaluation and aim to provide a holistic framework for supporting PD patients. Although this study suffers a number of shortcomings, its findings fit with the modern consensus that a focus on the whole person will improve patient experience and may improve outcomes.

