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Journal
Current Opinion in Nephrology & Hypertension, 30(1)

ISSN
1062-4821

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Publication Date
2021

DOI
10.1097/mnh.0000000000000657

Novel approaches to management of hyperkalaemia in kidney transplantation

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Purpose of review
Medications used frequently after kidney transplantation, including calcineurin inhibitors, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta blockers and antimicrobials, are considered the leading culprit for posttransplant hyperkalaemia in recipients with a well functioning allograft. Other risk factors include comorbidities such as diabetes, hypertension and heart failure; and consumption of a potassium-enriched diet. We review the mechanisms for hyperkalaemia following kidney transplantation that are addressed using nonpharmacological and pharmacological interventions. We also discuss emerging therapeutic approaches for the management of recurrent hyperkalaemia in solid organ transplantation, including newer potassium binding therapies.

Recent findings
Patiromer and sodium zirconium cyclosilicate are emerging potassium binders approved for the treatment of hyperkalaemia. Patiromer is a polymer that exchanges potassium for calcium ions. In contrast, sodium zirconium cyclosilicate is a nonpolymer compound that exchanges potassium for sodium and hydrogen ions. Both agents are efficacious in the treatment of chronic or recurrent hyperkalaemia and may result in fewer gastrointestinal side effects than older potassium binders such as sodium polystyrene sulfonate and calcium polystyrene sulfonate. Large-scale clinical studies have not been performed in kidney transplant patients. Patiromer may increase serum concentrations of tacrolimus, but not cyclosporine. Sodium zirconium cyclosilicate does not appear to compromise tacrolimus pharmacokinetics, although it may have a higher sodium burden.

Summary
Patiromer and sodium zirconium cyclosilicate may be well tolerated options to treat asymptomatic hyperkalaemia and have the potential to ease potassium dietary restrictions in kidney transplant patients by maintaining a plant-dominant, heart-healthy diet. Their efficacy, better tolerability and comparable cost with respect to previously available potassium binders make them an attractive therapeutic option in chronic hyperkalaemia following kidney transplantation.

Keywords
hyperkalaemia, kidney transplantation, management, potassium

INTRODUCTION

Metabolic derangements can occur following kidney transplantation. The most common posttransplant electrolyte and acid–base disturbances, ranked according to the likelihood of occurrence during the first several months, are hyperkalaemia, hypophosphatemia, hypomagnesemia, metabolic acidosis, hypercalcemia and hyperphosphatemia [1,2]. Hyperkalaemia is defined as a serum potassium concentration of more than 5.3 mEq/l in adults [3]. It is a common, potentially life-threatening complication following transplantation that can lead to clinical manifestations such as haemodynamic instability, central nervous system adverse events and fatal cardiac arrhythmias.

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Curr Opin Nephrol Hypertens 2021, 30:27–37

DOI:10.1097/MNH.0000000000000657

KEY POINTS

- Risk factors for hyperkalaemia in kidney transplant patients include drugs used after kidney transplantation, diabetes, hypertension, heart failure and consumption of a potassium-enriched diet.
- Management of hyperkalaemia in kidney transplant patients can be challenging.
- Patiromer and sodium zirconium cyclosilicate are emerging potassium binders approved for the treatment of hyperkalaemia.
- Patiromer may increase serum concentrations of tacrolimus, but not cyclosporine.
- Sodium zirconium cyclosilicate does not appear to impact tacrolimus drug pharmacokinetics, while it may have a higher sodium burden.

Most patients are asymptomatic or manifest nonspecific signs and symptoms, including, skeletal muscle weakness, fatigue, cardiac complications, including bradycardia or other arrhythmias, and impaired gastrointestinal motility [2].

Kidney transplant recipients are at an increased risk of developing hyperkalaemia due to both pharmacologic and pathophysiological-related mechanisms. The incidence of hyperkalaemia ranges from 25 to 44% in renal transplant recipients receiving a calcineurin inhibitor (CNI) [4,5]. Simultaneous kidney-pancreas transplant recipients with bladder drainage are more susceptible to hyperkalaemia, with one study reporting an incidence of 73% [5]. Hyperkalaemia is reported to be prevalent during the first 3 months postkidney transplantation [5].

In this review, we discuss the cause and management strategies of hyperkalaemia observed after kidney transplantation. We also discuss novel United States Food and Drug Administration (FDA) approved therapies for the management of chronic or recurrent hyperkalaemia, which appear to be well tolerated in this patient population.

CAUSES OF HYPERKALAEMIA IN KIDNEY TRANSPLANT PATIENTS

Medications using posttransplant are believed to be the major cause for posttransplant hyperkalaemia in recipients with a well functioning renal graft [2]. These include immunosuppressive medications such as tacrolimus and cyclosporine, routine antimicrobial prophylaxis such as trimethoprim/sulfamethoxazole (TMP/SMX) and pentamidine, and other nonimmunosuppressive medications, including beta-blockers (i.e. atenolol, carvedilol, metoprolol), angiotensin-converting enzyme inhibitors (ACEi) (i.e. lisinopril, quinapril, captopril), angiotensin II receptor blockers (ARBs) (i.e. valsartan, losartan, irbesartan), direct renin inhibitors (i.e. aliskiren) and potassium-sparing diuretics (i.e. amiloride, triamterene, spironolactone). Other medications that can be used in the perioperative period such as heparin, succinylcholine and NSAIDs are also associated with hyperkalaemia [6,7]. An overview of medications that can cause hyperkalaemia is presented in Table 1.

Among these medications, the CNIs are considered the main contributors to the development of hyperkalaemia in kidney transplant recipients [2]. Patients receiving tacrolimus are reported to have more frequent hyperkalaemia when compared to patients on cyclosporine [8]. CNIs can lead to both

Table 1. Medications associated with hyperkalaemia in kidney transplantation

Medications	Utility in kidney transplantation
ACEi and ARB	Hypertension
Beta-blockers (nonselective and beta 2-selective)	Hypertension
Potassium-sparing diuretics (amiloride, triamterene, spironolactone)	Hypertension
Trimethoprim, pentamidine	PCP prophylaxis
Heparin	Prevent clot formation during transplant procedure
Succinylcholine	Used in transplant recipients in need for rapid sequence intubation and rapid airway control
Calcineurin inhibitors (cyclosporine, tacrolimus)	Immunosuppressive agents
NSAIDs	Headache or pain

ACEi, angiotensin-converting-enzyme inhibitors; ARB, angiotensin II receptor blockers; NSAIDs, nonsteroidal anti-inflammatory drugs; PCP, Pneumocystis pneumonia.

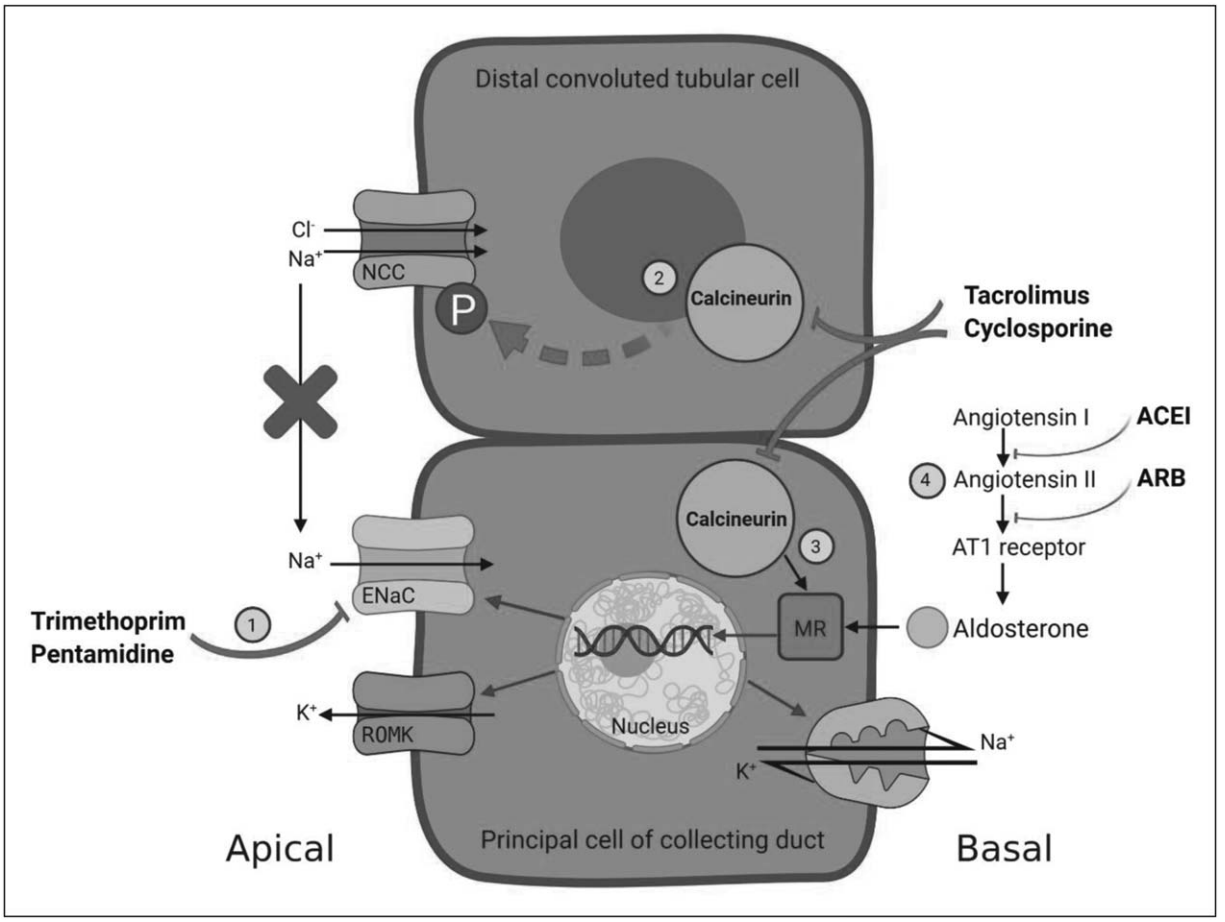

FIGURE 1. Schematic overview of the mechanisms causing hyperkalaemia in organ transplant recipients. (1) Trimethoprim and pentamidine inhibit the activity of ENaC in the late distal nephron segments and collecting duct (2) Tacrolimus and cyclosporine inhibit calcineurin, which is a phosphatase. This eventually leads to the phosphorylation and activation of the NCC, ultimately decreasing the electrical gradient for potassium secretion via ROMK channels. (3) By inhibiting calcineurin, tacrolimus and cyclosporine reduce the expression of the MR. (4) The ACEis and ARBs decrease aldosterone levels and cause potassium retention. ACEis, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; ENaC, epithelial sodium channel; ROMK, renal outer medullary potassium channel; NCC, sodium chloride cotransporter; MR, mineralocorticoid receptor.

proximal and distal RTA. Proximal RTA is characterized by bicarbonate wasting due to the toxic effects of CNIs, whereas distal RTA, also known as type IV RTA, is characterized by the inability to excrete hydrogen and potassium ions [9]. Hyperkalaemia in the kidney transplant recipient is usually seen in association with RTA [10].

Calcineurin exerts a dephosphorylating effect on the sodium-chloride cotransporter in the distal convoluted tubule [11]. Inhibition of the sodium-chloride cotransporter by CNIs leads to unopposed phosphorylation and activation of the cotransporter. In addition, CNIs are capable of inhibiting renal outer medullary K^+ channels and Na^+/K^+-ATPase in the distal tubules. Moreover, CNIs may induce the downregulation of mineralocorticoid receptor expression by inhibiting transcriptional activity of the human mineralocorticoid receptor (see Fig. 1) [12]. It has been postulated that CNIs can also cause hyperkalaemia hypertension with metabolic acidosis mimicking familial hyperkalaemic hypertension, also called Gordon syndrome or pseudohypoaldosteronism, by activating the WNK-SPAK-NCC pathway [13]. TMP/SMX and pentamidine competitively inhibit the epithelial sodium channels in the distal nephron, eventually contributing to hyperkalaemia [14].

Nonpharmacological causes of RTA in renal transplant recipients include suboptimal obstructive allograft nephropathy from ureteral stenosis at the site of anastomosis, acute and/or chronic allograft rejection, and ischemic tubular

dysfunction, especially in the early posttransplant period [15–17]. Tubular dysfunction can be due to interstitial inflammation, such as with allograft rejection, or the result of interstitial fibrosis and tubular atrophy [18]. Other risk factors for hyperkalaemia in kidney transplant recipients include older age (especially older than 70 years), diabetes mellitus and renal insufficiency [1]. Hyperkalaemia and hyperglycaemia following transplantation can also occur secondary to insulinopenia or insulin resistance leading to the decrease in translocation of potassium and glucose from the extracellular to the intracellular compartment, especially in insulin-dependent diabetic individuals [10].

NONPHARMACOLOGICAL MANAGEMENT

Haemodialysis

Haemodialysis is rarely required, especially if allograft function is preserved [19]. It is the method of choice for removing potassium when pharmacological therapies fail to sufficiently lower and eliminate potassium [20,21], and in patients with delayed graft function or allograft failure [2]. Haemodialysis is preferable over cation exchangers in cases of hyperkalaemic emergencies, and is a reasonable option in kidney transplant recipients, as these patients are likely to have dialysis access. However, if haemodialysis cannot be performed promptly (e.g. within 6 h), a gastrointestinal cation exchange therapy, preferably not sodium polystyrene sulfonate (SPS), should be used, which is then followed by haemodialysis as soon as it is available [22].

Nutrition

Dietary modification has been traditionally recommended for kidney transplant recipients with renal dysfunction who are placed on a CNI. However, it is likely rare for hyperkalaemia to occur exclusively due to excessive potassium intake, especially from a plant-dominant diet, although this has been previously demonstrated in the literature [23]. Although fresh fruits and vegetables should not be avoided given their high antioxidant vitamins and high dietary fibre content that enhances bowel movements and resolves hyperkalaemia [24–26], certain foods (e.g. dried fruits and dried vegetables especially with added potassium-based preservatives) and herbal supplements (e.g. noni juice, alfalfa, dandelion, horsetail, nettle) should be cautiously avoided during the perioperative period [27]. A potassium-restricted diet (<2 g/day) in the immediate posttransplant setting might be useful in limiting the occurrence of hyperkalaemia, although there are no convincing data to support this traditional practice. However, the benefit of restricting dietary potassium may be less that the potential harm by depriving patients from eating healthy potassium-rich foods with more fibres to lessen the risk of constipation, which can worsen hyperkalaemia [24–26].

PHARMACOLOGICAL MANAGEMENT

Acute management

Calcium, insulin and dextrose

Emergent management for hyperkalaemia starts with stabilization of the myocardium using intravenous calcium, which is indicated when the serum potassium is very high, that is more than 6.5 mEq/l [28]. Intravenous calcium gluconate is preferred over calcium chloride because it has a lower osmolality and is less irritating to the veins [28], although calcium chloride contains three time more elemental calcium than calcium gluconate (27 vs. 9 mg/ml) [29]. Insulin administration accelerates the intracellular shift of potassium into the skeletal muscle cells. Glucose is given with insulin only when serum glucose is 250 mg/dl or less.

Sodium bicarbonate

Hyperkalaemia in the setting of stable renal allograft may indicate metabolic acidosis and the need for sodium bicarbonate therapy [19]. By alkalinizing the serum, bicarbonate may indirectly cause the shift of potassium into cells via an H^+/K^+ exchange mechanism. In addition, bicarbonate may be directly transported into muscle cells along with potassium [30]. Treatment with sodium bicarbonate was successful in a 61-year-old man undergoing kidney transplantation, who developed hyperkalaemia intraoperatively [31]. Shortly after the start of surgery, an arterial blood gas revealed potassium 7.5 mEq/l, pH 7.28 and bicarbonate 18 mEq/l. Fifty mEq of sodium bicarbonate were used, followed by 25 g of dextrose, 1 g of calcium chloride and 10 units of regular insulin. Subsequent ABGs revealed potassium levels less than 5 mEq/l, and 4 l of 0.45% NaCl, each with 75 mEq bicarbonate, were given intravenously. Postoperatively, the potassium level was 3.8 mEq/l. The most likely cause of this patient's hyperkalaemia was metabolic acidosis, which is evident by his low bicarbonate level. Results of this case report suggest that the use of sodium bicarbonate can be helpful in lowering potassium levels by providing alkaline intravenous fluid to renal transplant patients with metabolic acidosis.

Beta2-agonists

When administered in a nebulizer or metered-dose inhaler, beta-agonists decrease plasma potassium levels transiently but relatively rapidly by shifting potassium intracellularly. Albuterol directly stimulates the Na^+/K^+-ATPase pump in skeletal muscles, which enhances cellular uptake of potassium. Albuterol's onset of action is usually within 15–30 min, with a peak effect between 30 and 60 min, and its effect lasts for 4–6 h [32,33]. A major concern regarding the use of albuterol is a paradoxical increase in serum potassium concentrations in the first minutes following inhalation [34,35]. Beta2-agonists may provide additive or synergistic hypokalaemic effects when combined with loop diuretics or thiazides [36].

Acute/chronic management

Diuretics

Loop diuretics are useful agents for the acute management of hyperkalaemia, whereas both loops diuretics and thiazides are also potential therapies for the chronic management of hyperkalaemia [37]. In patients with a reduced eGFR less than 45 ml/min/1.73 m^2, a loop diuretic is preferred, as thiazides become less effective at such levels of GFR, except for chlorthalidone and indapamide, which are effective to eGFR levels of 30 ml/min/1.73 m^2 [38,39]. Patients undergoing kidney transplantation are at a higher risk of developing fluid overload [40]. Volume-expanded (i.e. oedema, short-term weight gain) kidney transplant patients with hyperkalaemia can benefit from a loop diuretic, while those who manifest hyperkalaemia, hypertension and acidosis, which are symptoms consistent with sodium-chloride cotransporter activation, may also benefit from thiazides [20]. Thiazides can also be considered in kidney transplant patients with hyperkalemic hypertension and hypomagnesemia, although they increase serum magnesium when used with a CNI [41].

Fludrocortisone

Fludrocortisone has been used to treat cyclosporine-induced hyperkalaemia [4,42], and has a proven safety and efficacy in the management of tacrolimus-associated hyperkalaemia with concomitant hyponatremia in kidney transplant patients while maintaining stable tacrolimus trough concentrations [8]. Nevertheless, it is important to monitor tacrolimus levels when initiating fludrocortisone, as corticosteroids may decrease the serum concentration of tacrolimus by inducing the enzymes CYP3A4 and CYP3A5, which are responsible for tacrolimus metabolism. Conversely, tacrolimus concentrations may increase when tapering or discontinuing fludrocortisone, necessitating tacrolimus concentrations and effects to be monitored more frequently [43]. Moreover, fludrocortisone may elevate blood pressure, and its use may be somewhat challenging in hypertensive patients. Concurrent therapy with diuretics (loop and thiazide) will likely have an additive effect to fludrocortisone in inducing renal potassium wasting.

Chronic management

Sodium polystyrene sulfonate

SPS is a nonabsorbable, nonselective cation-exchange resin polymer that has been commonly used to treat chronic hyperkalaemia since the 1950s [44]. SPS exchanges potassium for sodium, but the resin is not exclusively selective for potassium; calcium and magnesium may bind as well, which can lead to overcorrection of potassium, hypocalcaemia or hypomagnesaemia. SPS should be used cautiously in transplant patients because it contains considerable amounts of sodium (100 mg per gram of the drug) and can lead to volume overload and should be used with caution in patients with severe hypertension, congestive heart failure and oedema [45]. In addition, the FDA recommends separating the dosing of SPS from other orally administered medicines by at least 3, or 6 h if the patient has gastroparesis [46].

SPS-related intestinal necrosis and other serious gastrointestinal events, which are rare, yet catastrophic, complications after renal transplantation, have been reported mainly in small case series especially when used with sorbitol as a carrier. These complications mainly appear on the ileum and colon, but can also affect the upper gastrointestinal tract to cause bleeding, ischemic colitis, focal to deep ulceration, necrosis and perforation, and faecal impaction with rectal stenosis [47,48]. Kidney transplantation and immunosuppression are considered potential risk factors for developing intestinal necrosis after SPS administration [49]. Other risk factors include history of intestinal disease, surgery, hypovolemia and renal failure [44,47]. Therefore, SPS use should be restricted to the inpatient setting excluding the immediate postoperative condition.

NOVEL THERAPIES FOR CHRONIC HYPERKALAEMIA

Patiromer

Patiromer (Veltassa; Relypsa, Inc., Redwood City, California, USA), a nonabsorbable organic polymer,

was approved by the FDA on 21 October 2015 [50]. It is a powder for suspension in water for oral administration and works by binding to potassium in the lumen of the gastrointestinal tract in exchange for calcium. Patiromer is a nonselective cation exchanger that can interact with other drugs in the gastrointestinal tract [51]. Patiromer is recommended to be initiated at 8.4 g once daily. The dose may be increased in increments of 8.4 mg at weekly intervals, with a maximum dose of 25.2 g once daily [51]. FDA labelling indicates that this agent should be separated by at least 3 h (before or after) from other medications to allow sufficient time for gastric contents to empty. Because of its nonselective cation exchanger property, patiromer can bind to magnesium in the colon and cause hypomagnesaemia in 5.3% of patients. Serum magnesium should be monitored and magnesium supplementation might be needed to avoid complications such as cardiac arrhythmias. Patiromer should be avoided in patients with severe constipation, bowel obstruction or impaction, including abnormal postoperative bowel motility disorders, because it may be ineffective and may worsen gastrointestinal conditions [51].

Rattanavich *et al.* [52] reported on two kidney transplant patients on tacrolimus who were treated with patiromer for hyperkalaemia. The study revealed that the use of patiromer is effective in treating hyperkalaemia and does not affect tacrolimus trough levels when administered at least 3 h after the tacrolimus dose. A different single-centre, retrospective study evaluated the safety, effectiveness, and tolerability of patiromer in 19 kidney transplant recipients [53]. Fifteen of these patients were previously on SPS, and 10 patients started patiromer within the first posttransplant year. Fourteen patients were started at a dose of 8.4 g/day (five required dose escalation to 16.8 g/day, one required further escalation to 25.2 g/day), three patients at 16.8 g/day (one required a dose decrease to 8.4 g/day), one patient at 8.4 g/48 h and one patient at 8.4 g 3x/week. The study reported normal potassium level (<5.2 mmol/l) following therapy with patiromer in patients who were adherent to therapy. Seven individuals required a tacrolimus dose decrease within 1–4 weeks of patiromer initiation, which may be due to the effect of SPS on tacrolimus absorption. Neither studies reported serious adverse events. In another series by Singh *et al.* [54▪], 37 solid organ transplant recipients, 73% being kidney transplants, with hyperkalaemia received patiromer at a median of 165 days after transplantation. Although serum potassium levels declined, a significant increase in mean tacrolimus concentrations, from a baseline of 6.9 to 8.3 ng/ml at 4 weeks, was observed, with 32% of patients requiring tacrolimus dose adjustments. Cyclosporine levels were not affected. A summary of these studies is outlined in Table 2 [52,53,54▪,55▪]. A clinical trial investigating the pharmacokinetics of tacrolimus and mycophenolate mofetil in kidney transplant recipients receiving patiromer has been completed, with no published results to date (NCT03229265).

Sodium zirconium cyclosilicate

Sodium Zirconium Cyclosilicate (Lokelma; AstraZeneca, Wilmington, Delaware, USA), also known as ZS-9, is an inorganic, nonabsorbed selective cation binder [56]. It works by binding potassium in the small intestine and allows for faecal excretion in exchange for sodium and hydrogen. It is a powder formulation mixed with water for oral use and was approved by the FDA in May 2019. ZS-9 is unique for being specific for potassium even in the presence of other ions [56,57]. Patiromer has a relatively delayed onset of action compared with ZS-9 (7 vs. 1 h) [51,58].

The recommended dose of ZS-9 is 10 g administered three times a day for up to 48 h. For continued treatment, the recommended dose is 10 g once daily and the dose may be uptitrated based on the serum potassium level at intervals of 1 week or longer and in increments of 5 g. In patients administered 10 g three times daily (t.i.d.), the mean serum potassium reduction was −0.7 mEq/l at 48 h, whereas the decrease in serum potassium for the placebo group was −0.2 mEq/l at 48 h. Patients with higher starting potassium levels had a greater response to ZS-9 [58]. Transplant recipients on ZS-9 should be monitored for signs of oedema because every 5 g of ZS-9 contains 400 mg of sodium. In clinical trials of ZS-9, oedema was generally mild to moderate in severity, and was reported in 4.4% of patients receiving 5 g, 5.9% of patients receiving 10 g and 16.1% of patients receiving 15 g ZS-9 compared with 2.4% of patients receiving placebo [58]. Due to its selectivity, ZS-9 does not cause other electrolyte abnormalities such as hypomagnesaemia.

There are currently no published clinical trials to assess the safety and efficacy of ZS-9 in transplant patients. In fact, renal transplant patients were excluded from all ZS-9 trials and should be the focus of future research [59–61]. A 2020 single-centre, retrospective study of 35 adult organ transplant patients assessed the effect of ZS-9 on both hyperkalaemia and immunosuppression concentrations. Of these, there were 16 kidney (45.7%), 14 liver (40%), two heart (5.7%), two combined kidney and liver (5.7%), and one combined kidney and heart transplants (2.9%). The median time from

Table 2. Clinical studies of patiromer and ZS-9 in transplant patients with hyperkalaemia

Drug	Investigators	Design	Transplant population	Endpoints	Results
Patiromer	Singh *et al.* [54▪]	Retrospective, single-centre study	37 SOT patients: kidney (73%), liver (21%), kidney-pancreas (3%), lung (3%)	Primary: Change in K^+ levels from baseline to 4, and 12 weeks; difference in tacrolimus levels at baseline, 4, and 12 weeks. Secondary: GI side effects, electrolyte abnormalities, insurance coverage of patiromer.	Statistically significant improvement in K^+ levels (baseline $K^+ = 5.44$) at week 4 ($K^+ = 4.99$) and week 12 ($K^+ = 5$). Statistically significant increase in tacrolimus levels (7.19–9.22 ng/ml) at week 4. No reported GI side effects, constipation in 8%. 81% obtained insurance coverage.
Patiromer	Lim *et al.* [53]	Retrospective, single-centre study	19 kidney transplant recipients	Safety, effectiveness, and tolerability of patiromer	All adherent patients had K^+ levels <5.2 mmol/l at last follow-up. Seven patients required tacrolimus dose reduction within 1–4 weeks of patiromer initiation; six were previously on SPS and one with prior supratherapeutic levels. No intolerable side effects; two had constipation, one had diarrhoea, one required an emergency room visit for hyperkalaemia during patiromer dose adjustment
Patiromer	Rattanavich *et al.* [52]	Not described	Two kidney transplant recipients	Effect of patiromer on treating hyperkalaemia and on tacrolimus trough levels	Patiromer use is effective in treating hyperkalaemia and does not affect tacrolimus tough levels. Patient 1: hyperkalaemia resolved within days with K^+ levels between 4.0 and 5.5 mEq/l. Patient 2: hyperkalaemia resolved but returned upon patiromer discontinuation with K^+ levels between 5.5 and 6.5 mEq/l. No need for tacrolimus dose adjustment.
ZS-9	Winstead *et al.* [55▪]	Retrospective, single-centre study	35 SOT patients: 16 kidney (45.7%), 14 liver (40%), two heart (5.7%), two kidney-liver (5.7%), one kidney-heart (2.9%)	Primary: Change in K^+ from day 0 to day 7. Secondary: Change in tacrolimus, Na^+, and bicarbonate levels from day 0 to day 7 and any reported adverse events.	K^+ levels decreased by −1.3 mEq/l from day 0 to day 7. Mean change in concentrations from days 0 to 7: tacrolimus = −0.54 ng/ml, $Na^+ = +1.7$ mEq/l, bicarbonate = +1.6 mEq/l. Two reports of mild oedema.

K+, potassium; Na+, sodium; SOT, solid organ transplant; SPS, sodium polystyrene sulfonate; ZS-9, sodium zirconium cyclosilicate.

transplant to initiation of therapy was 75 days. A t.i.d. dosing regimen was given to 12 (34%) patients with severe hyperkalaemia for a mean K^+ level of 6.2. The mean day 0 K^+ level was 5.9 mEq/l, and the mean decrease in K^+ levels from day 0 to day 7 was -1.3 mEq/l ($P \leq 0.001$). Tacrolimus drug pharmacokinetics were not significantly impacted; the mean change in tacrolimus concentrations was -0.54 nm/ml ($P = 0.82$). The mean change in sodium and bicarbonate concentrations from days 0 to day 7 was +1.70 mEq/l ($P = 0.002$) and 1.60 mEq/L ($P = 0.006$), respectively. No major adverse events were reported, although mild oedema was seen in two patients [55▪].

See Table 3 for a summary of medication therapy for hyperkalaemia. A proposed algorithm for the management of hyperkalaemia in organ transplant recipients is presented in Fig. 2.

Table 3. Nondialytic treatments for hyperkalaemia management. Cost information was obtained from Lexicomp database

Treatments	Dose	Route of administration	Onset of action	Mode of action	Common adverse events	Contraindications	Drug interactions	Cost
Membrane stabilization								
Calcium gluconate (10%)	10 ml over 10 min	i.v.	1–3 min	Antagonizes cardiac membrane excitability	Local soft tissue inflammation and necrosis, calcinosis cutis, calcification related to extravasation	Hypercalcaemia	Not significant (single dose) but may interact with aspirin, furosemide, insulin	$5.4 per 10 ml dose
Redistribution								
Regular Insulin	10 units push with 25–40 g dextrose 50% solution	i.v.	20 mins	Enhances activity of Na^+/K^+-ATPase pumps on cell membranes	Hypoglycaemia, hyperglycaemia (side effect of dextrose), hypokalaemia, local or systemic allergy, weight gain, peripheral oedema	Hypoglyacemia, hypersensitivity to regular insulin or any component of the formulation	Not significant (single dose) but may interact with aspirin, furosemide, atorvastatin	$178.4 per 10 units dose
Albuterol	10–20 mg in 4 ml of 0.9% NaCl over 10 min	Inhalation	30 min	Directly stimulates the Na^+/K^+-ATPase pump in skeletal muscles	Headache, tremor, tachycardia, pain, dizziness, pharyngitis, rhinitis.	Hypersensitivity to albuterol or any other aerosol components	Beta-blockers	$1.08–$2.08 per 10 mg dose
Elimination								
Sodium bicarbonate	50 mEq over 5 min, may repeat	i.v.	2–10 min	Shift K^+ into cells via an H^+/K^+ exchange mechanism. Bicarbonate may be directly transported into muscle cells along with K^+.	Metabolic alkalosis, tetany, hypernatremia, hypocalcaemia, hypokalaemia	Alkalosis, hypernatremia, volume overload, severe pulmonary oedema, hypocalcaemia	May precipitate when given with morphine, magnesium, calcium chloride. May deactivate sympathomimetic.	$10.5–$24 per 50 ml (50 mEq) dose
Loop diuretics	Furosemide: 40–80 mg Bumetanide: 2–4 mg	i.v.	15 min	Act on the Na^+-K^+-$2Cl^-$ symporter in the thick ascending limb of loop of Henle	Intravascular depletion, renal dysfunction, prerenal azotemia, hypotension, ototoxicity	Anuria, hypersensitivity to furosemide or any component of the formulation	In patients receiving cyclosporine, furosemide use is associated with hyperuricemia and the occurrence of gout.	Furosemide: $16.4–$112 per 40 mg dose Bumetanide: $1.26–$1.66 per 2 mg dose
Fludrocortisone	0.1 to 0.4 mg per day	Oral	Not described, but 1–2 weeks to see effects	Increases density of Na^+ channels on apical side of renal tubule cells. Increases density of Na^+-K^+-ATPase on the basolateral side	Sodium and water retention, hypertension, hyperglycaemia, osteoporosis, cardiac hypertrophy, oedema, hypokalaemia, bruising, diaphoresis, urticaria, allergic rash	Hypersensitivity to fludrocortisone or any component of the formulation, systemic fungal infections	May decrease serum concentration of tacrolimus by inducing the enzymes CYP3A4 and CYP3A5. Caution when used with strong CYP3A4 inhibitors and/or inducers	$0.75–$0.79 per tablet
Sodium polystyrene sulfonate	15–30 g in 15–30 ml	Oral, rectal	Hours to days	Exchanges sodium for potassium, calcium, ammonium and magnesium	Anorexia, nausea, vomiting, constipation, hypokalaemia, hypocalcaemia, hypomagnesemia, significant sodium retention	Hypersensitivity to sodium polystyrene sulfonate, polystyrene sulfonate resins or any component of the formulation, obstructive bowel disease, hypokalaemia	Lithium, thyroxine, nonabsorbable cation-donating antacids and laxatives (e.g. magnesium hydroxide, aluminium hydroxide)	$2.7 per 15 g dose (oral suspension), $11.1 per 30 g dose (rectal)
Patiromer	8.4–25.2 g daily	Oral	7 h	Binds to potassium in the lumen of the GI tract in exchange for calcium	Hypomagnesemia, hypokalaemia, constipation, diarrhoea, abdominal distress, flatulence, nausea	Hypersensitivity to patiromer or any component of the formulation	Significant interactions with ciprofloxacin, thyroxine, metformin.	$44 per 8.4 g packet
Sodium Zirconium Cyclosilicate	10 g three times a day for up to 48 h	Oral	1 h	Binds potassium in small intestine in exchange for sodium and hydrogen	Oedema, peripheral oedema, hypokalaemia	No contraindications listed in the manufacturer's labelling, but use with caution in patients with GI motility disorders and oedema	Furosemide, atorvastatin	$26.98 per 10 g packet

GI, gastrointestinal; i.v., intravenous; NaCl, Sodium chloride.

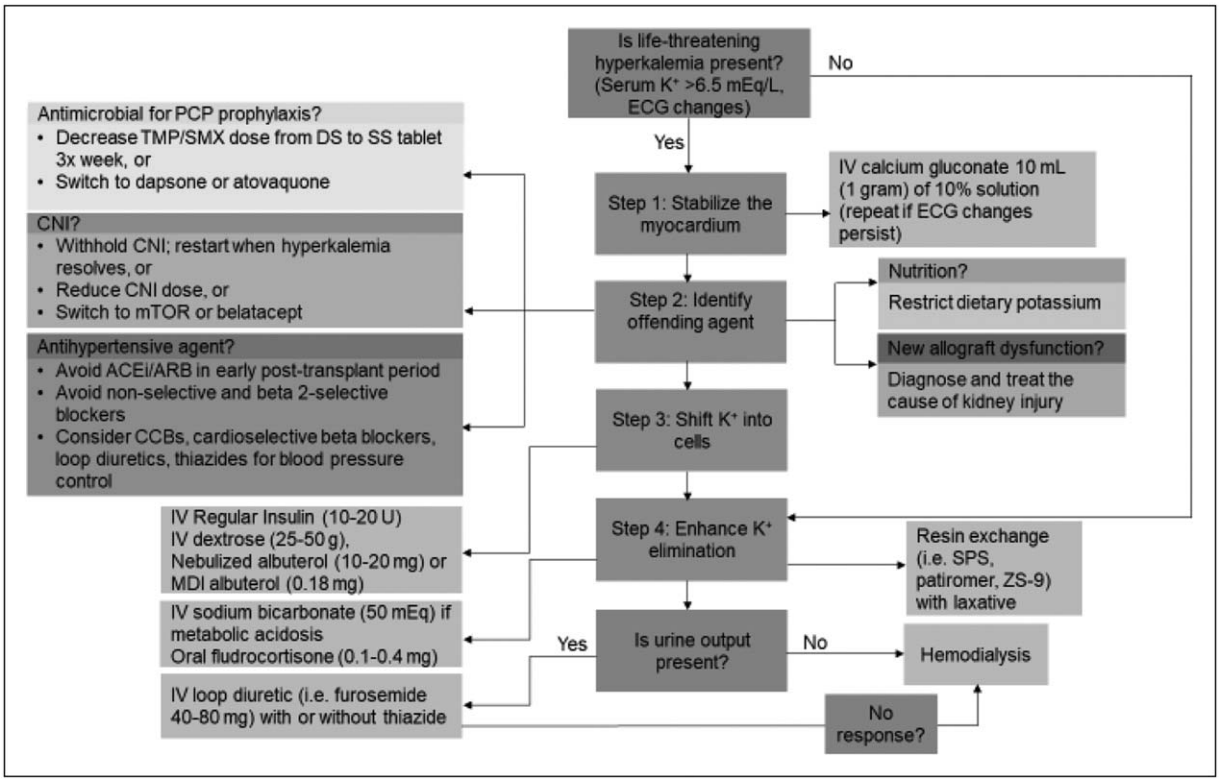

FIGURE 2. Proposed algorithm for the management of hyperkalaemia in organ transplant recipients.

CONCLUSION

Hyperkalaemia is a life-threatening complication following organ transplant that may increase the risk of mortality and can lead to increased length of stay as a barrier to patient discharge and hospital readmissions. Immunosuppressants, antimicrobials and antihypertensive drugs prescribed upon solid organ transplantation increase likelihood of hyperkalaemia. Administering insulin, glucose and calcium remain the gold standard interventions for the immediate treatment of hyperkalaemia in the acute setting. Haemodialysis is the most effective tool in removing potassium in cases of hyperkalaemic emergencies, delayed graft function or allograft failure, although a performed dialysis therapy in the first week postoperatively leads to the designation of 'delayed graft function', which is considered a less favourable outcome metric.

Patiromer and ZS-9 are new potassium binders approved for the treatment of hyperkalaemia. Their efficacy, better tolerability and comparable cost with respect to previously available potassium binders make them a pragmatic therapeutic option in chronic hyperkalaemia following solid organ transplantation. Ongoing trials are assessing drug interactions between patiromer and antirejection medications, and its efficacy in transplant recipients. Clinicians should be reminded that the new potassium binders should not be used as an emergency treatment for life-threatening hyperkalaemia because of their delayed onset of action, unless the FDA label is changed for an expanded indication.

Acknowledgements

None.

Financial support and sponsorship

The authors received no financial support for the research, authorship and/or publication of this article.

Conflicts of interest

John G. Rizk, Steven Gabardi, Youssef Rizk report they have no conflicts of interest to disclose relative to this research. David J. Quan is a consultant for Mallinckrodt Pharmaceuticals. Kamyar Kalantar-Zadeh has received honoraria and/or support from Abbott, Abbvie, ACI Clinical (Cara Therapeutics), Akebia, Alexion, Amgen, Ardelyx, ASN (American Society of Nephrology), AstraZeneca, Aveo, BBraun, Chugai, Cytokinetics, Daiichi, DaVita, Fresenius, Genentech, Haymarket Media, Hofstra Medical School, IFKF (International Federation of Kidney Foundations), ISH (International Society of Hemodialysis), International Society of Renal Nutrition

& Metabolism (ISRNM), JSDT (Japanese Society of Dialysis Therapy), Hospira, Kabi, Keryx, Kissei, Novartis, OPKO, NIH (National Institutes of Health), NKF (National Kidney Foundations), Pfizer, Regulus, Relypsa, Resverlogix, Dr Schaer, Sandoz, Sanofi, Shire, VA (Veterans' Affairs), Vifor, UpToDate, ZS-Pharma.

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