Reviews in Endocrine and Metabolic Disorders (2021) 22:1157–1170
https://doi.org/10.1007/s11154-021-09677-7

Mechanisms and management of drug-induced hyperkalemia in kidney transplant patients

John G. Rizk[1] · Jose G. Lazo Jr.[2] · David Quan[2] · Steven Gabardi[3,4] · Youssef Rizk[5] · Elani Streja[6] · Csaba P. Kovesdy[7] · Kamyar Kalantar-Zadeh[6,8]

Accepted: 16 July 2021 / Published online: 22 July 2021

Abstract

Hyperkalemia is a common and potentially life-threatening complication following kidney transplantation that can be caused by a composite of factors such as medications, delayed graft function, and possibly potassium intake. Managing hyperkalemia after kidney transplantation is associated with increased morbidity and healthcare costs, and can be a cause of multiple hospital admissions and barriers to patient discharge. Medications used routinely after kidney transplantation are considered the most frequent culprit for post-transplant hyperkalemia in recipients with a well-functioning graft. These include calcineurin inhibitors (CNIs), pneumocystis pneumonia (PCP) prophylactic agents, and antihypertensives (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta blockers). CNIs can cause hyperkalemic renal tubular acidosis. When hyperkalemia develops following transplantation, the potential offending medication may be discontinued, switched to another agent, or dose-reduced. Belatacept and mTOR inhibitors offer an alternative to calcineurin inhibitors in the event of hyperkalemia, however should be prescribed in the appropriate patient. While trimethoprim/sulfamethoxazole (TMP/SMX) remains the gold standard for prevention of PCP, alternative agents (e.g. dapsone, atovaquone) have been studied and can be recommend in place of TMP/SMX. Antihypertensives that act on the Renin–Angiotensin–Aldosterone System are generally avoided early after transplant but may be indicated later in the transplant course for patients with comorbidities. In cases of mild to moderate hyperkalemia, medical management can be used to normalize serum potassium levels and allow the transplant team additional time to evaluate the function of the graft. In the immediate post-operative setting following kidney transplantation, a rapidly rising potassium refractory to medical therapy can be an indication for dialysis. Patiromer and sodium zirconium cyclosilicate (ZS-9) may play an important role in the management of chronic hyperkalemia in kidney transplant patients, although additional long-term studies are necessary to confirm these effects.

Keywords Hyperkalemia · Potassium · Electrolyte Imbalance · Organ Transplant · Immunosuppression · PCP Prophylaxis · Antihypertensives

Abbreviations

AP	Aerosolized pentamidine
ACEI	Angiotensin-converting enzyme inhibitor
ARB	Angiotensin-II receptor blocker
CNI	Calcineurin inhibitor
CCB	Calcium channel blocker
CKD	Chronic kidney disease
ECG	Electrocardiogram
GFR	Glomerular filtration rate
PCP	Pneumocystis pneumonia
RAAS	Renin-angiotensin-aldosterone system
SPS	Sodium polystyrene sulfate
TMP/SMX	Trimethoprim/sulfamethoxazole
ZS-9	Sodium zirconium cyclosilicate

John G. Rizk and Jose G. Lazo Jr. contributed equally to this work.

✉ John G. Rizk
john.rizk@lau.edu

Extended author information available on the last page of the article

1 Introduction

Hyperkalemia, an elevated serum potassium and common electrolyte abnormality with life-threatening concerns, is not unique to the kidney transplant recipient, however can be frequently seen following transplantation [1]. The normal serum range for serum potassium is 3.5 to 5 mEq/L, with levels greater than the upper limit of normal defined as hyperkalemia. The definition and classification of hyperkalemia varies within the literature, however severity can be classified by serum potassium levels as mild (5 to < 6 mEq/L), moderate (6 to 7 mEq/L), and severe (> 7 mEq/L), and/or with electrocardiogram (ECG) changes also influencing severity definitions [2, 3]. Besides the precise potassium level value, acute hyperkalemia is considered more threatening than chronic stable hyperkalemia. This has to be taken into consideration when using fixed values for classification of the severity of hyperkalemia. Of highest concern is severe hyperkalemia which may manifest with ECG changes and cardiac arrythmias potentially leading to death if left untreated. Signs and symptoms of hyperkalemia are demonstrated in Fig. 1.

Patients with chronic kidney disease (CKD) are at increased risk for hyperkalemia. A retrospective cohort study has shown that in a patient with stage 5 CKD, the odds of hyperkalemia are 11 times more likely than in a patient with no history of CKD [4]. Prevalent comorbidities such as diabetes mellitus and hypertension treated with drugs that affect the renin–angiotensin–aldosterone system (RAAS) can also place patients at an increased risk for hyperkalemia [5]. Of note, these two disease states are common comorbidities in kidney transplant recipients, with diabetes and hypertension accounting for the top two etiologies of chronic kidney disease in adult kidney transplant recipients in 2019 at 33.9% and 22.6%, respectively [6].

Following kidney transplantation, the causes of hyperkalemia are multifactorial owing to graft function, excess potassium intake/repletion, comorbidities, and medications used in the peri- and post-operative setting [7]. The acute management of hyperkalemia has been established for years, however in the setting of nonemergent or chronic hyperkalemia, innovative therapies have been approved [8, 9]. In addition, advances in immunosuppression over the last decade also provide transplant clinicians with alternatives to lower the risk of hyperkalemia [10]. In this review, we delve into the etiology and pathophysiology of hyperkalemia in kidney transplantation and management

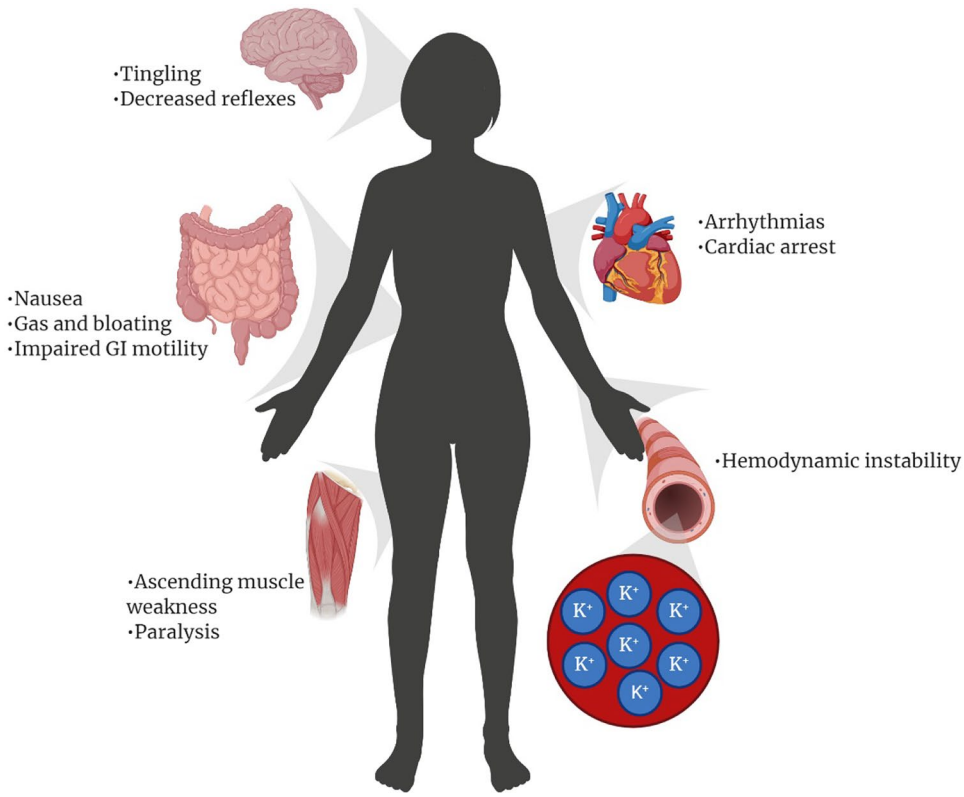

Fig. 1 Clinical manifestations of hyperkalemia. Hyperkalemia is usually asymptomatic until cardiac manifestations develop. These manifestations usually occur when the serum potassium concentration is 6.5—7 mEq/L or possibly at lower levels with an acute rise in serum potassium. Although transplant specific consequences of hyperkalemia have not yet been outlined, the most commonly affected organs are the cardiac and skeletal muscles due to an impairment of neuromuscular transmission. Hyperkalemia can cause ascending muscle weakness that begins with the legs and progresses to the trunk and arms, and rarely muscle paralysis, myopathy and paresthesia

strategies for the unique medications used for transplantation when hyperkalemia occurs.

2 Renal-mediated mechanisms of potassium homeostasis

Potassium homeostasis plays a critical role in various physiologic processes including but not limited to cell volume regulation, intracellular pH, protein and DNA synthesis, and maintaining a normal cell membrane potential. Potassium is predominantly located intracellularly, most commonly within muscles, with only 1 to 2% present in extracellular fluid [11]. This large intracellular pool of potassium allows for rapid exchange of extracellular potassium ions to maintain serum potassium within its normal range.

The renal transport pathways are crucial regulators of potassium homeostasis. In the proximal tubule, potassium reabsorption is thought to occur primarily via the paracellular pathway aided by concentration gradient [12]. Moving further along the nephron, the loop of Henle is responsible for medullary potassium recycling, Potassium is secreted into the descending thin limbs via passive diffusion from the medullary interstitium which carries a high potassium concentration [13]. Potassium is then reabsorbed along the thick ascending limb via active transport by apical $Na^+K^+2Cl^-$ (NKCC2) and a paracellular pathway. On the basolateral membrane, potassium crosses into the interstitium by potassium channels or cotransport with Cl^- or HCO_3^- [14].

The majority of filtered potassium is reabsorbed within the proximal tubules and loop of Henle, leaving the distal nephron with the role of finalizing potassium excretion. At the distal convoluted tubule, expression of renal outer medullary K + channels (ROMK) allow for potassium secretion. Within the connecting tubule and the cortical collecting duct, potassium is secreted by a small-conductance (SK) channel and a large-conductance (BK) channel found on the apical side [15, 16]. On the basolateral side, the Na^+-K^+-ATPase maintains the resting potential and functions in K^+ secretion and Na^+ absorption at the apical membrane. Within the collecting duct, potassium reabsorption may occur via apical H^+/K^+-ATPase pumps [17].

The secretion and reabsorption of K^+ is also affected by other ions such as Na^+. Aldosterone is a hormone that stimulates potassium secretion. Aldosterone increases the density of apical Na^+ channels in the connecting tubules and cortical collecting duct particularly via epithelial sodium channel (ENaC). The reabsorption of Na^+ provides a negative potential difference, which then stimulates K^+ secretion [18].

3 Mechanisms of transplant medication-induced hyperkalemia

The reported incidence of hyperkalemia is 5–40% among patients treated with a calcineurin inhibitor (CNI) such as cyclosporine or tacrolimus [19, 20]. Other immunosuppressive agents such as sirolimus, everolimus, mycophenolic acid, azathioprine, belatacept, and prednisone have not been found to be associated with hyperkalemia [21]. Given that some kidney transplant patients may have a reduced eGFR, drugs that induce hyperkalemia will manifest more profound effects on potassium levels in these patients. The exact mechanism in which CNIs induce hyperkalemia is still unclear, and there are several postulated mechanisms that describe how impaired renal potassium excretion might occur. It is hypothesized that CNIs activate the sodium-chloride cotransporter in the distal convoluted tubule through unopposed phosphorylation of the cotransporter [22]. In addition, CNIs are capable of inhibiting renal outer medullary K^+ channels, also known as ROMK, and Na–K ATPase in the distal tubules. Heering et al. showed that CNIs induce the down-regulation of mineralocorticoid receptor expression by inhibiting mineralocorticoid receptor transcriptional activity (see Fig. 2) [23]. As a result, these patients develop aldosterone resistance that manifests as hyperkalemia and metabolic acidosis, also referred to as Type 4 renal tubular acidosis [23, 24]. Cyclosporine may also have a secondary and additive effect on potassium elevation in patients concomitantly receiving a beta blocker by a mechanism that is not understood [25]. Compounding this situation further is that CNIs are inherently nephrotoxic and have been increasingly recognized as the main cause of CKD in transplant patients [26].

The trimethoprim component in trimethoprim/sulfamethoxazole (TMP/SMX) and pentamidine are structurally similar to amiloride and triamterene [27–29], causing hyperkalemia by competitively inhibiting the apical epithelial sodium channels in the distal nephron. Under normal conditions, it is through these channels that sodium reabsorption occurs, which then creates an electrical gradient that favors K^+ secretion [30]. Inhibition of epithelial sodium channels reduces the amount of potassium transported from the cell into the tubular lumen and thus into the urine. This leads to a decrease in the amount of potassium excreted in the urine and an accumulation of potassium in the serum [27].

Hyperkalemia is a rare side effect of TMP/SMX in healthy patients, although cases have been reported [31]. The side effect becomes more prominent in patients with an underlying disorder of potassium metabolism, kidney insufficiency, or if drugs known to induce hyperkalemia

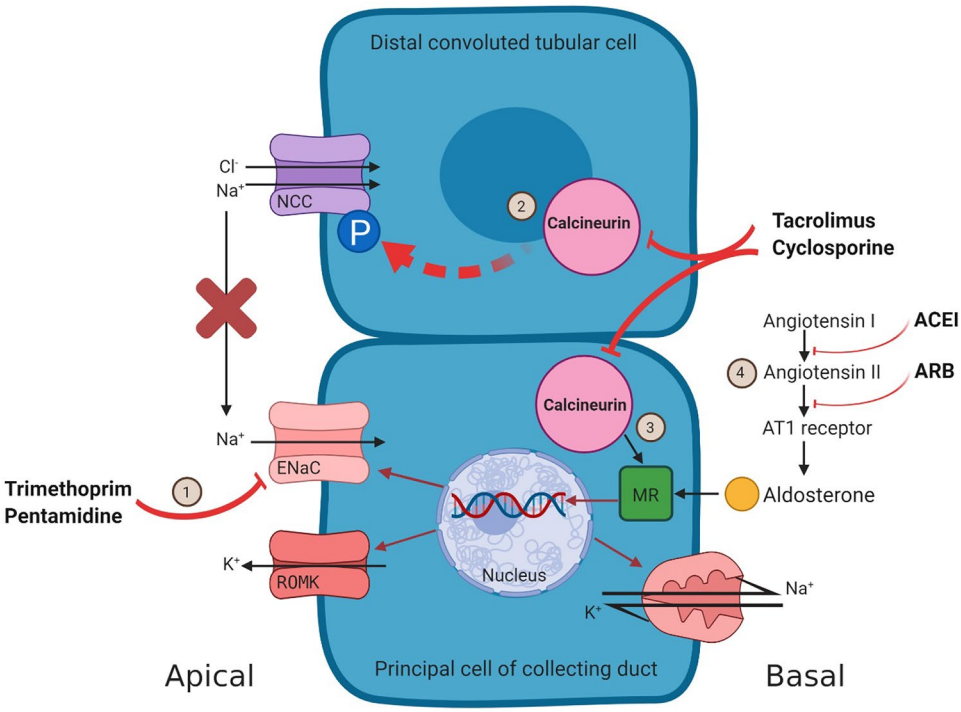

Fig. 2 Schematic overview of the mechanisms causing hyperkalemia in kidney transplant recipients. Adapted from Rizk J et al., *Curr Opin Nephrol Hypertens* 2021 Jan;30(1):27–37. Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; ENaC, epithelial sodium channel; ROMK, renal outer medullary potassium channel; NCC, sodium chloride cotransporter; MR, mineralocorticoid receptor

are given concomitantly [31]. Kidney transplant patients, in particular, are considered at high risk for the development of hyperkalemia in association with TMP therapy, and these patients should be monitored closely for the development of hyperkalemia in part because the majority of kidney transplant patients are on a combination of TMP/SMX and a CNI [32]. The risk of hyperkalemia is greater with higher doses of TMP (e.g. treatment doses of TMP/SMX for pneumocystis pneumonia), although can also be seen with standard doses. In a case report by Koc et al., two kidney transplant patients with secondary amyloidosis related to familial Mediterranean fever developed severe hyperkalemia after the administration of a standard dose of TMP/SMX [32]. Moreover, there is a major increase in the risk of hyperkalemia when TMP/SMX is used in combination with angiotensin-converting enzyme inhibitor (ACEI) or angiotensin-II receptor blockers (ARBs), and this adverse event was manifested in a lung transplant recipient who developed life-threatening hyperkalemia after treatment with the ACEI enalapril and TMP/SMX [33]. ACEIs inhibit the conversion of angiotensin I to angiotensin II, while ARBs inhibit the action of angiotensin II produced by all pathways. This results in an increase in sodium excretion and decrease in kidney loss of potassium by inhibiting the secretion of aldosterone [32].

There is limited data on the safety and efficacy of aerosolized pentamidine (AP) in solid organ transplant patients. Drug-induced hyperkalemia is common in patients receiving intravenous pentamidine [28, 34, 35]. Macesic et al. presented the largest retrospective cohort study of 56 kidney transplant recipients receiving aerosolized pentamidine [35]. Hyperkalemia was not reported in any of the patients receiving AP prophylaxis. Similarly, hyperkalemia was not observed in the retrospective study by Saukkonen et al. which examined the safety and efficacy of aerosolized pentamidine prophylaxis in 35 adult liver and kidney transplant recipients [36]. In both of these studies, no patients who received aerosolized pentamidine developed *Pneumocystis pneumonia* (PCP). AP has also been used successfully as PCP prophylaxis in adults with lung transplants and children with liver transplants [37, 38]. In contrast, pentamidine is more nephrotoxic in patients with Acquired Immune Deficiency Syndrome, and hyperkalemia has been reported in 24% (9/37) of Acquired Immune Deficiency Syndrome patients receiving a mean pentamidine dose of 255 ± 60 mg/day, either intravenously or intramuscularly [39]. The systemic absorption of AP is very low [40], about 5%, which accounts for the higher incidence of hyperkalemia with the intravenous or intramuscular forms.

4 Managing hyperkalemia by removing the offending agent

When hyperkalemia develops following transplantation, the potential offending medication may be discontinued, switched to another agent, or dose-reduced (Fig. 3). CNIs are essential to prevent acute rejection and graft loss, and post-transplant hyperkalemia should be managed despite keeping patients on these medications. A high tacrolimus

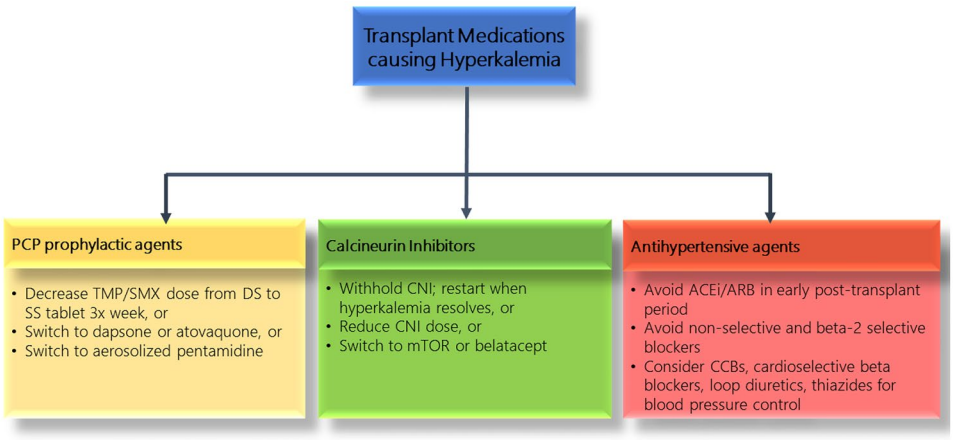

Fig. 3 Transplant medication management strategies for hyperkalemia. Abbreviations: angiotensin-converting enzyme inhibitor (ACEI), angiotensin-II receptor blocker (ARB), calcineurin inhibitor (CNI), calcium channel blocker (CCB), double strength (ds), single strength (SS), trimethoprim/sulfamethoxazole (TMP/SMX)

level (> 20 ng/mL) has been associated with an increased risk of hyperkalemia [41], thus, routine monitoring of tacrolimus trough concentrations is required especially during first three months after transplant when CNI levels have to be higher. In addition, foods high in potassium, herbal supplements, potassium-enriched salt substitutes, and drugs that contain potassium (e.g. penicillin G potassium, phosphorus replacement products containing potassium, IV solutions with potassium) should be restricted during the perioperative period, especially in patients at risk [42]. Other drugs (e.g. heparin [43], succinylcholine [9]) that can cause hyperkalemia should also be identified (see Table 1).

4.1 PCP Prophylaxis

The American Society of Transplantation considers TMP/SMX to be the first-line agent for prevention of PCP and toxoplasmosis [44]. Additionally, TMP/SMX has the potential benefit of protecting against other infectious complications in kidney transplant patients [45, 46]. Although optimal prophylaxis dosing regimens in solid-organ transplant recipients have not been fully defined, the current recommendation for TMP/SMX use ranges from single strength (80 mg TMP/400 mg SMX) to double strength (160 mg TMP/800 mg SMP) orally, either daily or three times weekly, for at least 6 to 12 months. Adverse effects of TMP/SMX include hyperkalemia, bone marrow suppression, elevated serum level of creatinine, and rash [44].

TMP-induced hyperkalemia is dose dependent [30], and these effects become more prominent when a daily double-strength regimen is used. Other prophylaxis antimicrobial agents such as atovaquone, dapsone, and inhaled pentamidine are not considered first-line agents by the American Society of Transplantation because of their narrower spectrum of activity, tolerability, cost, and efficacy [44].

Among medications used for the prevention of PCP, TMP/SMX and pentamidine are the most commonly associated with hyperkalemia [27, 28, 30, 47–49]. A single-center, retrospective cohort study examining the tolerability of TMP/SMX within the first year of kidney transplant showed that a TMP/SMX regimen of 1 single-strength tablet 3 times weekly is better tolerated in terms of adverse events than the double-strength and single-strength daily regimen [50]. Thus, a reasonable practice that can help in reducing the

Table 1 Medications associated with hyperkalemia in kidney transplantation

Medications	Utility in kidney transplantation
ACEI and ARB	Hypertension
Beta-blockers (non-selective 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

incidence of hyperkalemia is to decrease the dose of TMP/SMX from a double-strength to a single-strength tablet three times weekly when used as prophylaxis for PCP and urinary tract infections. A different retrospective single-center study showed that single-strength TMP/SMX thrice weekly is at least as effective as daily TMP/SMX for PCP prophylaxis in kidney transplant recipients, and that PCP did not occur after dose reduction at least during the rest of the first post-kidney transplant year [51]. To confirm these results, a clinical trial on transplant recipients comparing daily single strength to thrice weekly single strength TMP/SMX is needed.

Another strategy is to use dapsone or atovaquone as alternatives for PCP prophylaxis. Both of these agents are less likely to cause hyperkalemia and are potential alternate agents in patients with documented hyperkalemia secondary to TMP/SMX [52–55]. Atovaquone dosage should be 1500 mg by mouth once daily given with food, whereas dapsone is given at a dose of 50 mg twice daily or 100 mg once daily [56, 57]. Although patients who receive atovaquone instead of TMP/SMX for PCP prophylaxis have lower rates of hyperkalemia, they experience higher rates of recurrent urinary tract infections (UTIs) (33% vs 7%, $p=0.02$) [50]. Thus, routine addition of a UTI prophylactic agent for patients unable to get TMP/SMX and removal of ureteral stents within the first 30 days after transplantation is essential, particularly in kidney recipients [50, 58]. McLaughlin et al. showed that a re-challenge with TMP/SMX after switching to atovaquone was successful in a patient who previously developed TMP/SMX-induced hyperkalemia ($K^+ = 6.4$ mmol/L) [54]. Furthermore, the routine use of dapsone is not recommended given the potential for adverse hematologic events such as hemolytic anemia and methemoglobinemia [52, 59, 60].

TMP/SMX has the concurrent effect of preventing toxoplasmosis and some Gram-negative infections [61]. One double-strength TMP/SMX tablet daily confers protection against toxoplasmosis [50]. Lower doses of TMP/SMX may also provide protection against toxoplasmosis, but randomized controlled trials evaluating this option are lacking [62]. Interestingly, two single-center, retrospective cohort studies in which kidney transplant patients received single-strength TMP/SMX thrice weekly did not document any episodes of *Toxoplasma gondii* during a 1-year follow-up [50, 51].

In patients without hyperkalemia, AP is frequently used as a second-line agent for PCP prophylaxis at a dose of 300 mg/month preceded by inhaled albuterol, 180 mcg [35, 36]. It is a useful alternative for PCP prophylaxis in organ recipients given that it is administered monthly and has fewer adverse effects than other therapies [36, 37]. The most common reasons for using AP instead of TMP/SMX for PCP prophylaxis include prior sensitivity to TMP/SMX (i.e. rash, anaphylaxis, angioedema), kidney impairment, and leukopenia [35]. Macesic et al. showed that adverse reactions related to the use of AP required hospitalization and discontinuation of the drug in 5 of 56 (9%) patients; 4 patients had bronchospasm, 1 patient required intensive care admission for epinephrine infusion, but none developed hyperkalemia [35]. Thus, TMP/SMX remains the primary recommended treatment and prophylaxis regimen for PCP [63], as no patients receiving TMP/SMX required hospitalization [35]. A re-challenge with TMP/SMX was done and successful in 17 of 22 patients (77%); 3/22 (14%) and 2/22 (9%) failed the re-challenge due to leukopenia and kidney impairment, respectively.

4.2 Immunosuppressive drugs

U.S. randomized trials showed that 45% of liver transplants treated with tacrolimus develop hyperkalemia, while 31% of kidney transplant recipients receiving tacrolimus develop mild to severe hyperkalemia [64, 65]. Similarly, 26% and 32% of liver transplant and kidney transplant patients, respectively, on a cyclosporine-based immunosuppressive regimen developed hyperkalemia [64, 65]. Conversion from a CNI to other agents such as an mTOR inhibitor or belatacept can decrease the incidence of hyperkalemia, but require increased immune monitoring and may not be appropriate for all patients.

Sirolimus is a potent immunosuppressive agent approved by the FDA for kidney transplantation in 1999 [66]. Two randomized, double-blind, placebo-controlled, phase III trials assessing the safety and efficacy of sirolimus reported a low incidence of hyperkalemia in kidney transplant patients receiving sirolimus that is not dependent on the dose of the drug [67, 68]. The incidence of hyperkalemia in patients receiving sirolimus 2 mg/day was 13% in both trials, and 10–11% in patient groups receiving sirolimus 5 mg/day [67, 68]. In addition, Johnson et al. have showed previously that patients on a sirolimus-cyclosporine-steroid regimen had higher incidence of hyperkalemia than those who had cyclosporine eliminated from their regimen (2.8% vs 0%, $p=0.030$) [69]. This suggests that the early elimination of cyclosporine from a sirolimus-cyclosporine-steroid regimen can reduce the incidence of hyperkalemia. Conversion from a CNI-based immunosuppression to an everolimus-based immunosuppression may also lower the incidence of hyperkalemia. A prospective, randomized, multicenter trial revealed that only 8.3% of liver allograft recipient who started everolimus therapy with CNI reduction or discontinuation developed hyperkalemia [70]. Additionally, a post hoc analysis by Chapman et al. showed that early everolimus plus reduced-dose tacrolimus had a lower incidence of hyperkalemia than a standard tacrolimus regimen (7.7% vs 20.5%) at 12-month and 24-month follow-up [71].

Belatacept is a selective T-cell co-stimulation blocker that is frequently used as a component of a CNI-free triple drug regimen, often used in conjunction with prednisone and

mycophenolic acid. Results from BENEFIT and BENEFIT-EXT (Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial from living donor or standard criteria deceased donors, and extended criteria donors, respectively) found that the incidence of hyperkalemia was similar to cyclosporine [72, 73]. However, these studies did not specifically look at potassium levels. Belatacept may be associated with less hyperkalemia as there are no known mechanisms for this drug to induce high potassium levels, above and beyond improvements in renal function reported after conversion from CNI to belatacept that can make hyperkalemia less likely [74, 75].

4.3 Antihypertensive agents

Hypertension is the most common clinical problem among transplant patients, affecting at least 90% of this population [76]. Post-transplant hypertension occurs as a result of volume overload, CNIs, and vasoconstriction, with vasoconstriction occurring due to an increase of renin-angiotensin system, up-regulation of endothelin-1 and reduction of the bioavailability of nitric oxide [77, 78]. The use of antihypertensive agents in transplant recipients is necessary because inadequate control of post-transplant hypertension is associated with an increased risk of cardiovascular morbidity and mortality, and graft loss [79]. KDIGO guidelines recommend that blood pressure in chronic kidney disease and transplant patients should be kept below or equal of 130/85 and 125/75 in patients with proteinuria [80, 81]. There is no ideal single agent for the management of post-transplant hypertension, as there are no randomized controlled trials to support the use of one agent over another [82].

RAAS blockers may improve arterial hypertension, proteinuria, and erythrocytosis [83, 84]. There remains much debate regarding the use of these agents in kidney transplantation [83]. Two meta-analyses studies demonstrated that RAAS blockers are associated with better patient and graft survival in kidney transplant recipients, but the risk of life-threatening hyperkalemia is at least three-fold higher when compared to recipients not receiving these medications [85, 86]. Findings from a meta-analysis by Pisano et al. showed that ACEIs reduced the risk for graft loss but decreased kidney function [85]. In addition, ACEIs increased serum potassium [134 patients; mean difference (MD) 0.33 mEq/L (95% CI 0.10–0.55) as well as hyperkalemia episodes [418 patients; relative risk (RR) 3.66 (95% CI 1.13–11.80). In ARB versus placebo/routine treatment, no differences in graft loss was documented. The effect of ARBs on glomerular filtration rate (GFR) was inconclusive. Expectedly, ARBs increased the risk for hyperkalemia episodes [281 patients; RR 4.10 (95% CI 1.05–15.95)]. Pooled data drawn from ACEIs and ARBs show that the risk for graft failure was significantly reduced with respect to placebo/routine treatment, but the risk of hyperkalemia was maintained [681 patients; RR 3.42 (95% CI 1.41–8.29)] [85]. Due to the scarcity of data, the decision to use or avoid a RAAS blocker is based on clinical practice rather than scientific evidence. Patient awareness of hyperkalemia risk associated with RAAS blockers should be improved, with emphasis on pre-emptive discontinuation when an acute illness or volume depletion occurs. Beta-blockers have a demonstrated efficacy in controlling blood pressure in transplant patients [86].

Beta-blockers can increase plasma potassium levels, a cause of hyperkalemia often ignored in clinical practice. The reported incidence of beta-blocker–induced hyperkalemia is less than 5% [87], although there is little evidence that they consistently increase potassium levels. The use of non-selective beta-blockers (e.g. propranolol, nadolol, sotalol) is associated with metabolic issues, such as hyperkalemia [88]. In contrast, vasodilating beta-blockers with alpha-1 blocking properties (e.g. carvedilol, labetalol, bucindolol) may be better tolerated and may have fewer associated metabolic consequences compared with non-selective beta-blockers [88], although cases of severe hyperkalemia in kidney transplant patients taking labetalol have been reported [89, 90]. Moreover, hyperkalemia is more likely to occur in nonselective beta-blockers than cardio-selective beta-blockers (e.g. atenolol, metoprolol, bisoprolol) [91].

Calcium channel blockers (CCBs) could be the preferred first-step antihypertensive agents in kidney transplant patients, as they are associated with a lower incidence of hyperkalemia and serum potassium levels compared to RAAS blockers [274 patients; MD -0.24 mEq/L (95% CI -0.38 to -0.10)], improved graft function, and reduced graft loss, above and beyond their effect on reducing blood pressure [85]. Head to-head trials displayed that subjects randomized to CCB had improved kidney function, showing a higher GFR (+ 11 mL/min), and lower serum creatinine levels (-0.12 mg/dL) as compared with the ACEI group. Often, controlling post-kidney transplant hypertension is challenging and the majority of patients remain uncontrolled despite pharmacological management, necessitating the combination of a CCB with a RAAS blocker or diuretic/thiazide. Thus, there is an ongoing controversy regarding the routine use of RAAS blockers in the immediate post-transplant setting due to increases in serum creatinine and the risk of adverse events.

Diuretics are not routinely used as first line therapy in kidney transplant recipients, as they may cause volume depletion, electrolyte disturbances, and may worsen renal allograft function [92]. However, their use is important particularly in the peri-transplant setting. In patients with a good urinary output, loop diuretics and thiazide diuretics can be administered to increase urinary potassium elimination. The diuretic effects of thiazides were historically considered relatively weak and not comparable to the more potent actions of loop

diuretics. Because transplant patients on a CNI commonly have hyperkalemia, thiazides may increase serum magnesium when used with a CNI [92]. A longitudinal retrospective cohort study conducted in adult kidney transplant recipients showed that thiazides appear to be safe and effective in managing hypertension following transplantation, but the risk of hyperkalemia was higher in the thiazide group than the unexposed group (56% vs. 38%, $p < 0.001$) [93]. The rates of severe hyperkalemia were similar in both groups. In contrast, a more recent randomized non-inferiority crossover trial did not report a higher incidence of hyperkalemia in kidney transplant patients on thiazides compared to those on a CCB [94]. Perioperative hyperkalemia might be followed by hypokalemia due to the use of diuretics and fluid resuscitation, thus caution is warranted [95]. The use of potassium-sparing agents (e.g. amiloride, triamterene, spironolactone) should be avoided in transplant patients at risk of hyperkalemia. More RCTs are required to define the efficacy and safety of loop diuretics in kidney transplant recipients.

5 Treatment of hyperkalemia

In the immediate post-operative setting following kidney transplantation, a rapidly rising potassium refractory to medical therapy can be an indication for dialysis. In cases of mild to moderate hyperkalemia, medical management can be considered to normalize serum potassium levels and allow the transplant team additional time to evaluate the function of the graft [96]. An in-depth review on the management of acute hyperkalemia is beyond the scope of this review article however a brief overview will be provided here; readers are referred to previously published reviews for a complete review [2, 9]. Treatment for hyperkalemia can be classified into three categories: (1) antagonism of the cardiac effects of hyperkalemia; (2) redistribution of potassium into cells; and (3) removal of potassium from the body.

Administration of calcium either as calcium chloride or calcium gluconate should be used in the emergency management of hyperkalemia to stabilize the myocardial membrane from undesirable depolarization [97–99]. The administration of calcium minimally lowers serum potassium levels, if at all [7]. Following stabilization of the membrane potential, the focus shifts towards lowering serum potassium. Insulin shifts potassium intracellularly within skeletal myocytes and hepatocytes [100]. A dose of 10 units of regular insulin can be administered with a bolus or infusion of dextrose to prevent hypoglycemia. Beta2-adrenergic agonists, such as inhaled albuterol will exert its effect via Na–K ATPase to decrease serum potassium [98]. Sodium bicarbonate mediates its effect on potassium by an increase in serum pH, causing an intracellular shift of potassium via H^+/K^+ exchange [101]. Over the years, the efficacy of sodium bicarbonate for hyperkalemia has been called into question and should be avoided as monotherapy for the treatment of hyperkalemia [102].

Removal of potassium from the body can take place in the kidneys and the gastrointestinal tract. Loop diuretics are commonly used in patients' who have sufficient residual kidney function to allow for an increase in urine output [103, 104]. Loop diuretics are effective for the acute management of hyperkalemia but may be less preferred for chronic management. Mineralocorticoids have been used to treat chronic hyperkalemia in kidney transplant patients treated with calcineurin inhibitors [105, 106]. Fludrocortisone, a synthetic glucocorticoid with potent mineralocorticoid activity should be used cautiously as it may elevate blood pressure [107]. Intestinal potassium binders work through cation exchange using nonabsorbable resins. The classic agent in this class is sodium polystyrene sulfate (SPS) which exchanges Na^+ for K^+ within the colon [108]. SPS is not selective for potassium and as a result magnesium and calcium may also be eliminated potentially causing hypocalcemia or hypomagnesemia [7]. Of note, SPS carriers a risk of intestinal necrosis, particularly when used in conjunction with sorbitol and may be avoided by certain clinicians in the early post-op period, particularly now with novel agents made readily available [109, 110].

Patiromer and sodium zirconium cyclosilicate (ZS-9) are two novel potassium binders which have recently become available for the management of hyperkalemia [111, 112]. Patiromer works as a non-absorbable resin which exchanges calcium for potassium in the gastrointestinal tract [111]. Patiromer has also been shown to bind to magnesium causing hypomagnesemia in patients receiving therapy. The recommended dose is 8.4 g once daily, increasing by 8.4 g weekly up to a maximum of 25.2 g daily, titrating to the desired K^+ level. The largest study of patiromer in the solid organ transplant population was a retrospective cohort of 37 patients, 26 of which were kidney transplants, which demonstrated a statistically significant decrease in K^+ levels from 5.4 mEq/L at baseline to 4.99 mEq/L at week 4 and 5 mEq/L at week 12 [113]. ZS-9 works by exchange of hydrogen and sodium ions for potassium [112]. The recommended dose is 10 g three times daily for up to 48 h followed by a maintenance dose of 10 g daily for continued treatment. Dosing may be increased by 5 g up to 15 g once daily. Of note, every 5 g of ZS-9 contains 400 mg of sodium which places patients at risk for developing edema. ZS-9 use in the transplant population was reviewed in a retrospective cohort of 35 patients, 16 with kidney transplants, and demonstrated a mean decrease in K^+ of 1.3 mEq/L from day 0 to day 7 [114]. It is important to recognize that all of these gastrointestinal exchange agents have the potential to impact absorption and should be separated from other medications according to their respective package insert labeling, SPS and patiromer, 3 h before and after other oral medications

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

Drug	Investigators	Design	Transplant population	Endpoints	Results
Patiromer	Singh et al	Retrospective, single-center 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 to 9.22 ng/mL) at week 4. No reported GI side effects, constipation in 8%. 81% obtained insurance coverage
Patiromer	Lim et al	Retrospective, single-center 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. 7 patients required tacrolimus dose reduction within 1–4 weeks of patiromer initiation; 6 were previously on SPS and 1 with prior supratherapeutic levels. No intolerable side effects; 2 had constipation, 1 had diarrhea, 1 required an emergency room visit for hyperkalemia during patiromer dose adjustment
Patiromer	Rattanavich et al	Not described	2 kidney transplant recipients	Effect of patiromer on treating hyperkalemia and on tacrolimus trough levels	Patiromer use is effective in treating hyperkalemia and does not affect tacrolimus tough levels. Patient 1: hyperkalemia resolved within days with K^+ levels between 4.0–5.5 mEq/L. Patient 2: hyperkalemia resolved but returned upon patiromer discontinuation with K^+ levels between 5.5–6.5 mEq/L. No need for tacrolimus dose adjustment
ZS-9	Winstead et al	Retrospective, single-center study	35 SOT patients: 16 kidney (45.7%), 14 liver (40%), 2 heart (5.7%), 2 kidney-liver (5.7%), 1 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 edema

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

and ZS-9 separated 2 h before and after oral medications with clinically meaningful gastric pH-dependent bioavailability [7]. The current data on the use of these two potassium binders in the kidney transplant population is sparing and further high-quality research needs to be conducted to further characterize their effect on immunosuppressive medications. At this time, selection between the two agents should be based on safety profile or formulary restrictions within individual institutions. Table 2 provides a summary of studies that investigated the use of these two potassium binders in the transplant population.

6 Conclusion

The etiology of hyperkalemia in the kidney transplant recipients can be caused by a composite of factors [7]. CNIs, PCP prophylactic agents, and antihypertensives are prescribed almost universally in the transplant recipient [6, 82, 115]. Belatacept offers an alternative to calcineurin inhibitors however should be prescribed in the appropriate patient [10]. TMP/SMX remains the gold standard for prevention of PCP however alternative agents have been extensively studied and can be recommend in place of TMP/SMX [115]. Antihypertensives that act on the RAAS are generally avoided early after transplant however may be indicated later in the transplant course for patients with comorbidities.

Monitoring of potassium post transplantation is essential, while hyperkalemia early after transplant should be treated urgently as to prevent the need for dialysis. The agents used for treatment in the acute setting have been established, however hyperkalemia occurring in the chronic or outpatient setting can now be managed with novel intestinal potassium binders. Patiromer and ZS-9 will play a significant role in the management of chronic hyperkalemia and their use will become widespread upon addition to insurance and institutional formularies. An understanding of kidney transplantation, the elapsed time from surgery, from hour to weeks to months, and the mechanisms for medication induced hyperkalemia are all necessary to effectively manage this common electrolyte abnormality.

Declarations

Conflict of Interests JGR, JGL, DQ, SG, YR, ES report they have no conflicts of interest to disclose relative to this research. CPK is a consultant for Akebia, Ardelyx, Astra-Zeneca, Bayer, Cara Therapeutics, Reata, Tricida. KKZ has received honoraria and/or support from Abbott, Abbvie, ACI Clinical (Cara Therapeutics), Akebia, Alexion, Amgen, Ardelyx, American Society of Nephrology (ASN), Astra-Zeneca, Aveo, BBraun, Chugai, Cytokinetics, Daiichi, DaVita, Fresenius, Genentech, Haymarket Media, Hofstra Medical School, International Federation of Kidney Foundations (IFKF), International Society of Hemodialysis (ISH), International Society of Renal Nutrition and Metabolism (ISRNM), Japanese Society of Dialysis Therapy (JSDT), Hospira, Kabi, Keryx, Kissei, Novartis, OPKO, National Institutes of Health (NIH), National Kidney Foundation (NKF), Pfizer, Regulus, Relypsa, Resverlogix, Dr Schaer, Sandoz, Sanofi, Shire, Veterans' Affairs (VA), Vifor, UpToDate, and ZS-Pharma.

References

1. Jones JW, Gruessner RW, Gores PF, Matas AJ. Hypoaldosteronemic hyporeninemic hyperkalemia after renal transplantation. Transplantation. 1993;56(4):1013–5.
2. ECC Committee, Subcommittees and Task Forces of the American Heart Association. 2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Part 10.1: Life-threatening electrolyte abnormalities. Circulation. 2005;112(24 Suppl):IV121–125. https://doi.org/10.1161/CIRCULATIONAHA.105.166563
3. Clase CM, Carrero JJ, Ellison DH, Grams ME, Hemmelgarn BR, Jardine MJ, Kovesdy CP, Kline GA, Lindner G, Obrador GT, Palmer BF, Cheung M, Wheeler DC, Winkelmayer WC, Pecoits-Filho R. Conference Participants. Potassium homeostasis and management of dyskalemia in kidney diseases: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 2020;97(1):42–61.
4. Einhorn LM, Zhan M, Hsu VD, Walker LD, Moen MF, Seliger SL, Weir MR, Fink JC. The frequency of hyperkalemia and its significance in chronic kidney disease. Arch Intern Med. 2009;169(12):1156–62.
5. Kovesdy CP, Matsushita K, Sang Y, Brunskill NJ, Carrero JJ, Chodick G, Hasegawa T, Heerspink HL, Hirayama A, Landman GWD, Levin A, Nitsch D, Wheeler DC, Coresh J, Hallan SI, Shalev V, Grams ME. CKD Prognosis Consortium Serum potassium and adverse outcomes across the range of kidney function: a CKD Prognosis Consortium meta-analysis. Eur Heart J. 2018;39(17):1535–42. https://doi.org/10.1093/eurheartj/ehy100.
6. Hart A, Lentine KL, Smith JM, Miller JM, Skeans MA, Prentice M, Robinson A, Foutz J, Booker SE, Israni AK, Hirose R, Snyder JJ. OPTN/SRTR 2019 Annual Data Report: Kidney. Am J Transplant. 2021;21(Suppl 2):21–137.
7. Kovesdy CP. Management of hyperkalaemia in chronic kidney disease. Nat Rev Nephrol. 2014;10(11):653–62.
8. Bridgeman MB, Shah M, Foote E. Potassium-lowering agents for the treatment of nonemergent hyperkalemia: pharmacology, dosing and comparative efficacy. Nephrol Dial Transplant. 2019;34(Suppl 3):iii45-iii50.
9. Rizk J, Quan D, Gabardi S, Rizk Y, Kalantar-Zadeh K. Novel approaches to management of hyperkalaemia in kidney transplantation. Curr Opin Nephrol Hypertens. 2021;30(1):27–37. https://doi.org/10.1097/MNH.0000000000000657.
10. Vincenti F, Rostaing L, Grinyo J, Rice K, Steinberg S, Gaite L, Moal MC, Mondragon-Ramirez GA, Kothari J, Polinsky MS, Meier-Kriesche HU, Munier S, Larsen CP. Belatacept and Long-Term Outcomes in Kidney Transplantation. N Engl J Med. 2016;374(4):333–43.
11. Giebisch G. Renal potassium transport: mechanisms and regulation. Am J Physiol. 1998;274(5):F817–33. https://doi.org/10.1152/ajprenal.1998.274.5.F817.
12. Wilson RW, Wareing M, Kibble J, Green R. Potassium permeability in the absence of fluid reabsorption in proximal tubule of the anesthetized rat. Am J Physiol. 1998;274(6):F1109–12. https://doi.org/10.1152/ajprenal.1998.274.6.F1109.
13. Tabei K, Imai MK. Transport in upper portion of descending limbs of long-loop nephron from hamster. Am J Physiol. 1987;252(3 Pt 2):F387–92. https://doi.org/10.1152/ajprenal.1987.252.3.F387.

14. Leviel F, Borensztein P, Houillier P, Paillard M, Bichara M. Electroneutral K+/HCO3- cotransport in cells of medullary thick ascending limb of rat kidney. J Clin Invest. 1992;90(3):869–78. https://doi.org/10.1172/JCI115962.
15. Frindt G, Palmer LG. Apical potassium channels in the rat connecting tubule. Am J Physiol Renal Physiol. 2004;287(5):F1030–7. https://doi.org/10.1152/ajprenal.00169.2004.
16. Pluznick JL, Sansom SC. BK channels in the kidney: role in K(+) secretion and localization of molecular components. Am J Physiol Renal Physiol. 2006;291(3):F517–29. https://doi.org/10.1152/ajprenal.00118.2006.
17. Zhou X, Lynch IJ, Xia SL, Wingo CS. Activation of H(+)-K(+)-ATPase by CO(2) requires a basolateral Ba(2+)-sensitive pathway during K restriction. Am J Physiol Renal Physiol. 2000;279(1):F153–60. https://doi.org/10.1152/ajprenal.2000.279.1.F153.
18. Palmer LG, Frindt G. Aldosterone and potassium secretion by the cortical collecting duct. Kidney Int. 2000;57(4):1324–8. https://doi.org/10.1046/j.1523-1755.2000.00970.x.
19. Kaplan B, Wang Z, Abecassis MM, Fryer JP, Stuart FP, Kaufman DB. Frequency of hyperkalemia in recipients of simultaneous pancreas and kidney transplants with bladder drainage. Transplantation. 1996. https://doi.org/10.1097/00007890-199610270-00025.
20. Kim HC, Hwang EA, Han SY, Park SB, Kim HT, Cho WH. Primary immunosuppression with tacrolimus in kidney transplantation: Three-year follow-up in a single center. In: Transplantation Proceedings. 2004. https://doi.org/10.1016/j.transproceed.2004.08.006
21. McDermott JK, Girgis RE. Individualizing immunosuppression in lung transplantation. Glob Cardiol Sci Pract. 2018. https://doi.org/10.21542/gcsp.2018.5.
22. Hoorn EJ, Walsh SB, McCormick JA, et al. The calcineurin inhibitor tacrolimus activates the renal sodium chloride cotransporter to cause hypertension. Nat Med. 2011. https://doi.org/10.1038/nm.2497.
23. Heering PJ, Kurschat C, Vo DT, Klein-Vehne N, Fehsel K, Ivens K. Aldosterone resistance in kidney transplantation is in part induced by a down-regulation of mineralocorticoid receptor expression. Clin Transplant. 2004. https://doi.org/10.1046/j.1399-0012.2003.00154.x.
24. Deppe CE, Heering PJ, Viengchareun SAY, Grabensee B, Farman N, Lombes M. Cyclosporine A and FK506 inhibit transcriptional activity of the human mineralocorticoid receptor: A cell-based model to investigate partial aldosterone resistance in kidney transplantation. Endocrinology. 2002. https://doi.org/10.1210/endo.143.5.8821.
25. Pei Y, Richardson R, Greenwood C, Wong PY, Baines A. Extrarenal Effect of Cyclosporine A on Potassium Homeostasis in Renal Transplant Recipients. Am J Kidney Dis. 1993. https://doi.org/10.1016/S0272-6386(12)70324-4.
26. Martin EF, Huang J, Xiang Q, Klein JP, Bajaj J, Saeian K. Recipient survival and graft survival are not diminished by simultaneous liver-kidney transplantation: An analysis of the united network for organ sharing database. Liver Transplant. 2012. https://doi.org/10.1002/lt.23440.
27. Velázquez H, Perazella MA, Wright FS, Ellison DH. Renal mechanism of trimethoprim-induced hyperkalemia. Ann Intern Med. 1993. https://doi.org/10.7326/0003-4819-119-4-199308150-00008.
28. Kleyman TR, Roberts C, Ling BN. A mechanism for pentamidine-induced hyperkalemia: Inhibition of distal nephron sodium transport. Ann Intern Med. 1995. https://doi.org/10.7326/0003-4819-122-2-199501150-00004.
29. Kim YW. Antimicrobial-induced Electrolyte and Acid-Base Disturbances. Electrolyte Blood Press. 2007;5(2):111–5. https://doi.org/10.5049/EBP.2007.5.2.111.
30. Choi MJ, Fernandez PC, Patnaik A, et al. Trimethoprim-Induced Hyperkalemia in a Patient with AIDS. N Engl J Med. 1993. https://doi.org/10.1056/NEJM199303113281006.
31. Nickels LC, Jones C, Stead LG. Trimethoprim-Sulfamethoxazole-Induced Hyperkalemia in a Patient with Normal Renal Function. Case Rep Emerg Med. 2012. https://doi.org/10.1155/2012/815907.
32. Koç M, Bihorac A, Ozener CI, Kantarci G, Akoglu E. Severe hyperkalemia in two renal transplant recipients treated with standard dose of trimethoprim-sulfamethoxazole. Am J Kidney Dis. 2000. https://doi.org/10.1053/ajkd.2000.16220.
33. Bugge JF. Severe hyperkalaemia induced by trimethoprim in combination with an angiotensin-converting enzyme inhibitor in a patient with transplanted lungs. J Intern Med. 1996. https://doi.org/10.1046/j.1365-2796.1996.43869000.x.
34. Lachaal M, Venuto RC. Nephrotoxicity and hyperkalemia in patients with acquired immunodeficiency syndrome treated with pentamidine. Am J Med. 1989. https://doi.org/10.1016/S0002-9343(89)80147-0.
35. Macesic N, Urbancic K, Ierino F, Grayson ML. Is aerosolized pentamidine for pneumocystis pneumonia prophylaxis in renal transplant recipients not as safe as we might think? Antimicrob Agents Chemother. 2016. https://doi.org/10.1128/AAC.02290-15.
36. Saukkonen K, Garland R, Koziel H. Aerosolized pentamidine as alternative primary prophylaxis against Pneumocystis carinii pneumonia in adult hepatic and renal transplant recipients. Chest. 1996. https://doi.org/10.1378/chest.109.5.1250.
37. Nathan SD, Ross DJ, Zakowski P, Kass RM, Koerner SK. Utility of inhaled pentamidine prophylaxis in lung transplant recipients. Chest. 1994. https://doi.org/10.1378/chest.105.2.417.
38. Colombo JL, Sammut PH, Langnas AN, Shaw BW. The spectrum of Pneumocystis carinii infection after liver transplantation in children. Transplantation. 1992. https://doi.org/10.1097/00007890-199210000-00010.
39. Briceland LL, Bailie GR. Pentamidine-associated nephrotoxicity and hyperkalemia in patients with AIDS. Ann Pharmacother. 1991. https://doi.org/10.1177/106002809102501102.
40. Conte JE Jr, Golden JA. Concentrations of aerosolized pentamidine in bronchoalveolar lavage, systemic absorption, and excretion. Antimicrob Agents Chemother. 1988;32(10):1490–3. https://doi.org/10.1128/aac.32.10.1490.
41. Sahu MK, Singh SP, Das A, et al. High blood tacrolimus and hyperkalemia in a heart transplant patient. Ann Card Anaesth. 2017. https://doi.org/10.4103/0971-9784.203933.
42. Hollander-Rodriguez JC, Calvert JF. Hyperkalemia. Am Fam Physician. 2006. https://doi.org/10.5005/jp/books/12382_8.
43. Rizk J, Mehra MR. Anticoagulation management strategies in heart transplantation. Prog Cardiovasc Dis. 2020;63(3):210–8. https://doi.org/10.1016/j.pcad.2020.02.002.
44. Martin SI, Fishman JA. Pneumocystis pneumonia in solid organ transplantation. Am J Transplant. 2013. https://doi.org/10.1111/ajt.12119.
45. Rodriguez M, Fishman JA. Prevention of infection due to Pneumocystis spp. in human immunodeficiency virus-negative immunocompromised patients. Clin Microbiol Rev. 2004. https://doi.org/10.1128/CMR.17.4.770-782.2004
46. Higgins RM, Bloom SL, Hopkin JM, Morris PJ. The risks and benefits of low-dose cotrimoxazole prophylaxis for pneumocystis pneumonia in renal transplantation. Transplantation. 1989. https://doi.org/10.1097/00007890-198903000-00032.
47. Greenberg S, Reiser IW, Chou SY, Porush JG. Trimethoprim-sulfamethoxazole induces reversible hyperkalemia. Ann Intern Med. 1993. https://doi.org/10.7326/0003-4819-119-4-199308150-00007.
48. Alappan R, Perazella MA, Buller GK. Hyperkalemia in hospitalized patients treated with trimethoprim-sulfamethoxazole. Ann Intern Med. 1996. https://doi.org/10.7326/0003-4819-124-3-199602010-00006.
49. Perazella MA, Mahnensmith RL. Trimethoprim-sulfamethoxazole: Hyperkalemia is an important complication regardless of dose. Clin Nephrol. 1996.

50. Zmarlicka M, Martin ST, Cardwell SM, Nailor MD. Tolerability of low-dose sulfamethoxazole/trimethoprim for Pneumocystis jirovecii pneumonia prophylaxis in kidney transplant recipients. Prog Transplant. 2015. https://doi.org/10.7182/pit2015153.
51. Prasad GVR, Beckley J, Mathur M, et al. Safety and efficacy of prophylaxis for Pneumocystis jirovecii pneumonia involving trimethoprim-sulfamethoxazole dose reduction in kidney transplantation. BMC Infect Dis. 2019. https://doi.org/10.1186/s12879-019-3944-0.
52. Lee I, Barton TD, Goral S, et al. Complications related to dapsone use for Pneumocystis jirovecii pneumonia prophylaxis in solid organ transplant recipients. Am J Transplant. 2005. https://doi.org/10.1111/j.1600-6143.2005.01079.x.
53. Urbancic KF, Pisasale D, Wight J, Trubiano JA. Dapsone safety in hematology patients: Pathways to optimizing Pneumocystis jirovecii pneumonia prophylaxis in hematology malignancy and transplant recipients. Transpl Infect Dis. 2018. https://doi.org/10.1111/tid.12968.
54. McLaughlin MM, Galal A, Richardson CL, et al. Switch to atovaquone and subsequent re-challenge with trimethoprim-sulfamethoxazole for Pneumocystis prophylaxis in a kidney transplant population. Transpl Infect Dis. 2017. https://doi.org/10.1111/tid.12769.
55. Goto N, Oka S. Pneumocystis jirovecii pneumonia in kidney transplantation. Transpl Infect Dis. 2011. https://doi.org/10.1111/j.1399-3062.2011.00691.x.
56. Mepron [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020500s017lbl.pdf (Accessed 5 Jun 2020).
57. Dapsone [package insert]. , Barnstaple, EX32 8NS, UK: Accord; 2019. https://www.medicines.org.uk/emc/files/pil.5768.pdf (Accessed 5 Jun 2020).
58. Giullian JA, Cavanaugh K, Schaefer H. Lower risk of urinary tract infection with low-dose trimethoprim/sulfamethoxazole compared to dapsone prophylaxis in older renal transplant patients on a rapid steroid-withdrawal immunosuppression regimen. Clin Transplant. 2010. https://doi.org/10.1111/j.1399-0012.2009.01129.x.
59. Plotkin JS, Buell JF, Njoku MJ, et al. Methemoglobinemia associated with dapsone treatment in solid organ transplant recipients: A two-case report and review. Liver Transplant Surg. 1997. https://doi.org/10.1002/lt.500030207.
60. Mitsides N, Green D, Middleton R, et al. Dapsone-induced methemoglobinemia in renal transplant recipients: More prevalent than previously thought. Transpl Infect Dis. 2014. https://doi.org/10.1111/tid.12161.
61. Bodro M, Paterson DL. Has the time come for routine trimethoprim-sulfamethoxazole prophylaxis in patients taking biologic therapies? Clin Infect Dis. 2013. https://doi.org/10.1093/cid/cit071.
62. AIDSinfo. Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. March 28, 2019. AIDSinfo. 2019.
63. Limper AH, Knox KS, Sarosi GA, et al. An official American Thoracic Society statement: Treatment of fungal infections in adult pulmonary and critical care patients. Am J Respir Crit Care Med. 2011. https://doi.org/10.1164/rccm.2008-740ST.
64. Prograf [package insert]. Deerfield, IL: Astellas Pharma US; 2009. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/050708s027,050709s021lbl.pdf (Accessed 10 Jul 2019).
65. Pirsch JD, Miller J, Deierhoi MH, Vincenti F, Filo RS. A comparison of tacrolimus (FK506) and cyclosporine for immunosuppression after cadaveric renal transplantation. Transplantation. 1997. https://doi.org/10.1097/00007890-199704150-00013.
66. Rapamune Oral Solution and Tablets [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals Inc. https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021110s058lbl.pdf Accessed 4 Jun 2019.
67. Kahan BD, Steinberg S, Bartlett S, et al. Efficacy of sirolimus compared with azathioprine for reduction of acute renal allograft rejection: A randomised multicentre study. Lancet. 2000. https://doi.org/10.1016/S0140-6736(00)02480-6.
68. MacDonald AS. A worldwide, phase III, randomized, controlled, safety and efficacy study of a sirolimus/cyclosporine regimen for prevention of acute rejection in recipients of primary mismatched renal allografts. Transplantation. 2001. https://doi.org/10.1097/00007890-200101270-00019.
69. Johnson RWG, Kreis H, Oberbauer R, Brattstrom C, Claesson K, Eris J. Sirolimus allows early cyclosporine withdrawal in renal transplantation resulting in improved renal function and lower blood pressure. Transplantation. 2001. https://doi.org/10.1097/00007890-200109150-00007.
70. De Simone P, Metselaar HJ, Fischer L, et al. Conversion from a calcineurin inhibitor to everolimus therapy in maintenance liver transplant recipients: A prospective, randomized, multicenter trial. Liver Transplant. 2009. https://doi.org/10.1002/lt.21827.
71. Chapman WC, Brown RS, Chavin KD, et al. Effect of Early Everolimus-Facilitated Reduction of Tacrolimus on Efficacy and Renal Function in de Novo Liver Transplant Recipients: 24-Month Results for the North American Subpopulation. Transplantation. 2017. https://doi.org/10.1097/TP.0000000000001524.
72. Durrbach A, Pestana JM, Pearson T, et al. A phase III study of belatacept versus cyclosporine in kidney transplants from extended criteria donors (BENEFIT-EXT Study). Am J Transplant. 2010. https://doi.org/10.1111/j.1600-6143.2010.03016.x.
73. Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression (BENEFIT) (BENEFIT). Retrieved from: https://clinicaltrials.gov/ct2/show/study/NCT00256750
74. Rostaing L, Massari P, Garcia VD, et al. Switching from calcineurin inhibitor-based regimens to a belatacept-based regimen in renal transplant recipients: a randomized phase II study. Clin J Am Soc Nephrol. 2011;6(2):430–9. https://doi.org/10.2215/CJN.05840710.
75. Gupta G, Regmi A, Kumar D, et al. Safe Conversion From Tacrolimus to Belatacept in High Immunologic Risk Kidney Transplant Recipients With Allograft Dysfunction. Am J Transplant. 2015;15(10):2726–31. https://doi.org/10.1111/ajt.13322.
76. Carpenter MA, John A, Weir MR, et al. BP, cardiovascular disease, and death in the folic acid for vascular outcome reduction in transplantation trial. J Am Soc Nephrol. 2014. https://doi.org/10.1681/ASN.2013040435.
77. Kaufeld J, Schiffer M, Chatzikyrkou C. Pathogenesis and Management of Hypertension after Kidney Transplantation. Curr Hypertens Rev. 2012. https://doi.org/10.2174/157340212804546062.
78. Severova-Andreevska G, Danilovska I, Sikole A, Popov Z, Ivanovski N. Hypertension after kidney transplantation: Clinical significance and therapeutical aspects. Open Access Maced J Med Sci. 2019. https://doi.org/10.3889/oamjms.2019.264.
79. Rigatto C, Parfrey P, Foley R, Negrijn C, Tribula C, Jeffery J. Congestive heart failure in renal transplant recipients: Risk factors, outcomes, and relationship with ischemic heart disease. J Am Soc Nephrol. 2002.
80. Kasiske BL, Zeier MG, Chapman JR, et al. KDIGO clinical practice guideline for the care of kidney transplant recipients: A summary. Kidney Int. 2010. https://doi.org/10.1038/ki.2009.377.
81. Hamdani G, Nehus EJ, Hanevold CD, et al. Ambulatory blood pressure, left ventricular hypertrophy, and allograft function in children and young adults after kidney transplantation. Transplantation. 2017. https://doi.org/10.1097/TP.0000000000001087.
82. Weir MR, Burgess ED, Cooper JE, et al. Assessment and management of hypertension in transplant patients. J Am Soc Nephrol. 2015. https://doi.org/10.1681/ASN.2014080834.

83. Ponticelli C, Cucchiari D. Renin-angiotensin system inhibitors in kidney transplantation: a benefit-risk assessment. J Nephrol. 2017;30(2):155–7. https://doi.org/10.1007/s40620-017-0378-x.
84. Rizk JG, Kalantar-Zadeh K, Mehra MR, Lavie CJ, Rizk Y, Forthal DN. Pharmaco-Immunomodulatory Therapy in COVID-19. Drugs. 2020;80(13):1267–92. https://doi.org/10.1007/s40265-020-01367-z.
85. Pisano A, Bolignano D, Mallamaci F, et al. Comparative effectiveness of different antihypertensive agents in kidney transplantation: a systematic review and meta-analysis. Nephrol Dial Transplant. 2019. https://doi.org/10.1093/ndt/gfz092.
86. Hausberg M, Barenbrock M, Hohage H, Müller S, Heidenreich S, Rahn KH. ACE inhibitor versus β-blocker for the treatment of hypertension in renal allograft recipients. Hypertension. 1999. https://doi.org/10.1161/01.HYP.33.3.862.
87. Hahn L, Hahn M. Carvedilol-induced hyperkalemia in a patient with chronic kidney disease. J Pharm Pract. 2015. https://doi.org/10.1177/0897190014566306.
88. Weir MR, Salzberg DJ. Management of hypertension in the transplant patient. J Am Soc Hypertens. 2011. https://doi.org/10.1016/j.jash.2011.07.003.
89. McCauley J, Murray J, Jordan M, Scantlebury V, Vivas C, Shapiro R. Labetalol-induced hyperkalemia in renal transplant recipients. Am J Nephrol. 2002. https://doi.org/10.1159/000065225.
90. Arthur S, Greenberg A. Hyperkalemia associated with intravenous labetalol therapy for acute hypertension in renal transplant recipients. Clin Nephrol. 1990.
91. Hawboldt J, McGrath D. Possible metoprolol-induced hyperkalemia. J Pharm Pract. 2006. https://doi.org/10.1177/0897190007300728.
92. Tantisattamo E, Molnar MZ, Ho BT, et al. Approach and Management of Hypertension After Kidney Transplantation. Front Med (Lausanne). 2020;7:229. Published 2020 Jun 16. https://doi.org/10.3389/fmed.2020.00229
93. Taber DJ, Srinivas TM, Pilch NA, et al. Are thiazide diuretics safe and effective antihypertensive therapy in kidney transplant recipients? Am J Nephrol. 2013. https://doi.org/10.1159/000355135.
94. Moes AD, Hesselink DA, van den Meiracker AH, Zietse R, Hoorn EJ. Chlorthalidone Versus Amlodipine for Hypertension in Kidney Transplant Recipients Treated With Tacrolimus: A Randomized Crossover Trial. Am J Kidney Dis. 2017. https://doi.org/10.1053/j.ajkd.2016.12.017.
95. Hultin S, M. Hawley C, W. Johnson D, S. Francis R. Perioperative Care for Kidney Transplant Recipients. In: Perioperative Care for Organ Transplant Recipient. 2019. https://doi.org/10.5772/intechopen.84388
96. de Vries BCS, Berger SP, Bakker SJL, de Borst MH, de Jong MFC. Pre-Transplant Plasma Potassium as a Potential Risk Factor for the Need of Early Hyperkalaemia Treatment after Kidney Transplantation: A Cohort Study. Nephron. 2021;145(1):63–70.
97. Alvestrand A, Wahren J, Smith D, DeFronzo RA. Insulin-mediated potassium uptake is normal in uremic and healthy subjects. Am J Physiol. 1984;246(2 Pt 1):E174–80.
98. Beeler GW Jr, Reuter H. Membrane calcium current in ventricular myocardial fibres. J Physiol. 1970;207(1):191–209.
99. Davey M, Caldicott D. Calcium salts in management of hyperkalaemia. Emerg Med J. 2002;19(1):92–3.
100. Allon M, Copkney C. Albuterol and insulin for treatment of hyperkalemia in hemodialysis patients. Kidney Int. 1990;38(5):869–72.
101. Allon M, Shanklin N. Effect of bicarbonate administration on plasma potassium in dialysis patients: interactions with insulin and albuterol. Am J Kidney Dis. 1996;28(4):508–14.
102. Blumberg A, Weidmann P, Shaw S, Gnädinger M. Effect of various therapeutic approaches on plasma potassium and major regulating factors in terminal renal failure. Am J Med. 1988;85(4):507–12.
103. Sebastian A, Schambelan M, Sutton JM. Amelioration of hyperchloremic acidosis with furosemide therapy in patients with chronic renal insufficiency and type 4 renal tubular acidosis. Am J Nephrol. 1984;4(5):287–300.
104. Suki WN. Use of diuretics in chronic renal failure. Kidney Int Suppl. 1997;59:S33–5.
105. Furuya R, Kumagai H, Sakao T, Maruyama Y, Hishida A. Potassium-lowering effect of mineralocorticoid therapy in patients undergoing hemodialysis. Nephron. 2002;92(3):576–81.
106. Marfo K, Glicklich D. Fludrocortisone therapy in renal transplant recipients with persistent hyperkalemia. Case Rep Transplant. 2012;2012:586859.
107. Kaisar MO, Wiggins KJ, Sturtevant JM, et al. A randomized controlled trial of fludrocortisone for the treatment of hyperkalemia in hemodialysis patients. Am J Kidney Dis. 2006;47(5):809–14. https://doi.org/10.1053/j.ajkd.2006.01.014.
108. Scherr L, Ogden DA, Mead AW, Spritz N, Rubin AL. Management of hyperkalemia with a cation-exchange resin. N Engl J Med. 1961;19(264):115–9.
109. McGowan CE, Saha S, Chu G, Resnick MB, Moss SF. Intestinal necrosis due to sodium polystyrene sulfonate (Kayexalate) in sorbitol. South Med J. 2009;102(5):493–7.
110. Rashid A, Hamilton SR. Necrosis of the gastrointestinal tract in uremic patients as a result of sodium polystyrene sulfonate (Kayexalate) in sorbitol: an underrecognized condition. Am J Surg Pathol. 1997;21(1):60–9.
111. Veltassa (patiromer for oral suspension) prescribing information. Redwood City, CA: Relypsa Inc.; 2020. https://www.veltassa.com/pi.pdf (17 Mar 2021, date last accessed)
112. Lokelma (sodium zirconium cyclosilicate for oral suspension) prescribing information. Wilmington, DE: AstraZeneca; 2020. https://www.azpicentral.com/lokelma.pdf (17 Mar 2021, date last accessed)
113. Schnelle K, Winters H, Pesavento T, Singh P. Largest Experience of Safety and Efficacy of Patiromer in Solid Organ Transplant. Transplant Direct. 2020;6(9):e595.
114. Winstead RJ, Demehin M, Yakubu I, Song C, Brown A, Levy M, Gupta G. Sodium zirconium cyclosilicate use in solid organ transplant recipients and its effect on potassium and immunosuppression. Clin Transplant. 2020;34(3):e13791.
115. Fishman JA, Gans H. AST Infectious Diseases Community of Practice. Pneumocystis jiroveci in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019;33(9):e13587.

Authors and Affiliations

John G. Rizk[1] · Jose G. Lazo Jr.[2] · David Quan[2] · Steven Gabardi[3,4] · Youssef Rizk[5] · Elani Streja[6] · Csaba P. Kovesdy[7] · Kamyar Kalantar-Zadeh[6,8]

1 Arizona State University, Edson College, Phoenix, AZ, USA

2 UCSF Medical Center, University of California San Francisco, San Francisco, CA, USA

3 Department of Transplant Surgery, Brigham and Women's Hospital, Boston, MA, USA

4 Department of Medicine, Harvard Medical School, Boston, MA, USA

5 Department of Internal Medicine, Division of Family Medicine, Lebanese American University Medical Center – St. John's Hospital, Beirut, Lebanon

6 Department of Medicine, Division of Nephrology, Hypertension and Kidney Transplantation, School of Medicine, University of California, CA, Irvine, Orange, USA

7 Division of Nephrology, University of Tennessee Health Science Center, Memphis, TN, USA

8 Department of Epidemiology, University of California, UCLA Fielding School of Public Health, Los Angeles, CA, USA