Review: Management of Hyperkalemia in Kidney Transplant Recipients

Bassem Almalki[1], Kathleen Cunningham[1], Michelle Kapugi[1], Clare Kane[1], and Akansha Agrawal[1]

[1]Northwestern Memorial Hospital

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Abstract

Hyperkalemia is a frequent complication among kidney transplant recipients that can lead to fatal arrhythmias. The causes of hyperkalemia post kidney transplant are multifactorial and often are drug-induced, and include decreased glomerular filtration rate, tubular dysfunction, and impaired sodium delivery in the distal nephron. This review will discuss pathophysiology and management of both acute and chronic hyperkalemia in kidney transplant recipients.

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Authors : Bassem Almalki[1], Kathleen Cunningham[1], Michelle Kapugi[1], Clare Kane[1], Akansha Agrawal[2]

Affiliations : [1]Department of Pharmacy[2] Department of Nephrology; Northwestern Memorial Hospital, Chicago, IL, United States

Abstract

Hyperkalemia is a frequent complication among kidney transplant recipients that can lead to fatal arrhythmias. The causes of hyperkalemia post kidney transplant are multifactorial and often are drug-induced, and include decreased glomerular filtration rate, tubular dysfunction, and impaired sodium delivery in the distal nephron. This review will discuss pathophysiology and management of both acute and chronic hyperkalemia in kidney transplant recipients.

Methods

This review is based on an English language literature search that was performed using the PubMed and Google Scholar databases. The keywords 'Hyperkalemia', 'Management' and 'Kidney Transplantation' were used for the search. The last search was done in 15 June 2020. Due to the lack of publications in kidney transplantations, all papers that evaluated hyperkalemia were selected for a further analysis.

Introduction

Kidney transplant (KT) is an established treatment option for patients with end-stage renal disease (ESRD). Electrolyte imbalances are a common consequence of ESRD that often normalize after successful KT. However, electrolyte imbalances, including hyperkalemia, may persist after KT for various reasons including tubular dysfunction caused by acute and/or chronic rejection, direct drug-induced tubular toxicity, and drug-induced enhanced sodium delivery in the distal nephron. Moreover, KT recipients are more prone to electrolyte abnormalities compared to non-kidney transplant recipients with the same level of kidney function.[1]

The prevalence of hyperkalemia ranges from 25-44% in KT recipients on calcineurin inhibitors (CNIs). [2] The time course of hyperkalemia is not well defined after KT. In a small study, hyperkalemia occurred on an average around 100 days post-transplant. [3]

There is no consensus definition of hyperkalemia but generally potassium levels greater than 5.5 mmol/L require immediate intervention. [4 5] Hyperkalemia in the general population is usually asymptomatic but if left untreated may lead to muscle weakness or paralysis, cardiac arrhythmias, and death. [6] The exact consequences of untreated hyperkalemia after KT have not yet been established.[7] However, data from the general and chronic kidney disease (CKD) populations highlights the importance of maintaining normal serum potassium concentrations.[6 8 9] Despite the high incidence and potentially life-threatening consequences of hyperkalemia, there is a lack of consensus on the management in KT recipients. The purpose of this article is to review the pathophysiology, dietary considerations, and management of acute and chronic hyperkalemia with a focus on kidney transplant recipients.

Pathophysiology of hyperkalemia in kidney transplant

With an intracellular concentration of 150 mmol/L compared to 4 mmol/L in the extracellular compartment, potassium is the most abundant intracellular cation. Potassium intake, distribution between intracellular and extracellular compartments, and renal excretion help determine serum potassium concentration. In the distal nephron segments and mediated by aldosterone, potassium secretion takes place in response to distal sodium delivery which triggers sodium reabsorption via the epithelial sodium channel (ENaC). This action creates an electrical gradient that favors potassium secretion. [10] Medications used in KT are considered to be the major cause of hyperkalemia in a functioning graft.[7]

CNIs such as tacrolimus and cyclosporine are the core maintenance immunosuppressants in KT due to superior graft survival. They can, however, induce hyperkalemia by various mechanisms, with tacrolimus posing a significantly higher risk than cyclosporine.[11] These mechanisms include impaired function of the sodium-chloride cotransporter (NCC) in the distal convoluted tubule as well as downregulation of mineralocorticoid expression via RAAS suppression leading to hyperkalemic type 4 renal tubular acidosis. [12] In addition, supratherapeutic CNI concentrations can result in afferent renal arteriolar vasoconstriction and acute kidney injury resulting in impaired potassium elimination. [13-15] These mechanisms offer insight into unique treatment options for hyperkalemia.

Trimethoprim/Sulfamethoxazole (TMP/SMX) is an antimicrobial that is commonly used post-transplant to prevent pneumocystis pneumonia and urinary tract infections. Trimethoprim can cause hyperkalemia by blocking the epithelial sodium channel (ENaC) in the distal nephron, thereby impairing potassium elimination. [16] Of note, the incidence of hyperkalemia is relatively lower with a regimen consisting of one single strength tablet three times weekly compared to full dose (1-2 double strength tablets twice daily) regimens. [7]

Finally, the Renin-Angiotensin-Aldosterone-System (RAAS) inhibitors appeal for the management of hypertension as they have been shown to decrease proteinuria and decrease mortality in patients with CKD. However, RAAS inhibitor use post-transplant has been associated with a 2.2-fold increased risk for life-threatening hyperkalemia (defined as a K >6mmol/L), limiting their routine use. [17] Nevertheless, the introduction of the new potassium binders (patiromer and sodium zirconium cyclosilicate) may allow for the continuation of RAAS inhibitors in patients with compelling indications. [18]

Dietary considerations in kidney transplant

Many potassium-rich foods are considered part of a healthy diet. In non-dialysis, normo-kalemic patients with CKD, the National Kidney Foundation suggests an unrestricted potassium intake. [19] However, in a nonfunctioning graft or elevated serum potassium concentration, a low potassium diet with potassium intake 1 - 3 g/day should be encouraged. [20] Healthcare providers play an important role after KT in educating KT recipients about their potassium and nutritional management. Table 1 contains examples of food rich in potassium content ([?] 300 mg). [21]

Management of hyperkalemia in kidney transplant

Stabilization of the cardiac membrane

Calcium

Calcium directly antagonizes the toxic myocardial effects of hyperkalemia by reducing the threshold potential of cardiac myocytes leading to stabilization of the membrane potential, with or without changing the serum potassium concentration. [22] It is indicated when serum potassium concentration is $>$ 6.5 mmol/L or when it is $>$ 6.0 mmol/L with EKG changes. [23] Calcium for injection is available as the chloride or gluconate salt. Calcium gluconate is the preferred agent due to the potential for extravasation with calcium chloride. [24] The suggested dose of calcium gluconate is 1,000 mg (10 mL of a 10 % solution) infused over 2 to 3 minutes, with constant cardiac monitoring. The dose can be repeated in 5 to 10 minutes if EKG changes persist. The use of intravenous calcium to treat arrhythmias in the setting of hyperkalemia is not based on robust evidence. It was shown to be effective in animal experiments and case reports. [25-27] However, administration of intravenous calcium is believed to be an important and life-saving approach in hyperkalemia with life-threatening EKG changes. [28 29] Peripheral vasodilation, hypotension, bradycardia, and arrhythmias are noted adverse reactions with intravenous calcium administration.[30]

Redistribution of potassium

Insulin-glucose

Insulin temporarily reverses hyperkalemia by shifting sodium out of the cell in exchange for potassium via the activation of sodium–potassium ATPase pump. Bolus insulin is recommended to be administered as 10 units of regular insulin intravenously given along with an intravenous bolus of dextrose 25-50 g. This regimen when given to anephric adult patients resulted in a reduction of serum potassium concentrations by about 0.6 mmol/L in $<$15 minutes. This effect can last between 30 and 60 minutes after a single bolus followed by a gradual serum potassium rebound. [31 32] Caution should be used when administering IV insulin to patients with kidney dysfunction, as insulin is renally eliminated. Hypoglycemia can occur for up to 6 hours after IV insulin administration, therefore frequent blood glucose monitoring is advised for the first 4-6 hours after administration. [33 34] The sensitivity to insulin varies with diabetes severity and current renal function. A prospective observational study of 72% of patients with CKD found that 17% of patients who received insulin-glucose therapy developed symptomatic hypoglycemia. [33] Various studies have explored different insulin dosing strategies in the setting of renal dysfunction. LaRue et al [34] and Pierce et al [35] found that patients with kidney failure who received 10 or 5 units of regular insulin achieved similar rates of serum potassium reduction and hypoglycemia. Conversely, one study reported that an insulin dose of 5 units significantly reduced the risk of hypoglycemia compared with 10 units, with an increase in serum creatinine being associated with an increased risk for hypoglycemia. [36] Farina et al [37] concluded that the use of 50 g of dextrose instead of 25 g did not reduce hypoglycemia incidence. It should be noted that the evidence is limited by small cohort sizes and retrospective design. The KDIGO guidelines recommend the administration of 5 units regular insulin along with 25g of dextrose in patients with CKD. [23]

Beta-2 Agonists

Beta-2 adrenergic receptor agonists work by promoting the activation of sodium–potassium ATPase pumps resulting in intracellular potassium shifting.[38] Salbutamol, intravenously or by nebulization, has been shown to be an effective agent in treating hyperkalemia. The nebulized route is preferred due to the ease of administration and fewer side-effects. [39-41] With a dose dependent effect, the onset of action of salbutamol is 30 minutes with a peak effect within 60 minutes.[42] It reduced serum potassium levels by approximately 1 mmol/L, and the effect persisted for at least 2 hours. Salbutamol via nebulizer can be given in doses of 10 or 20 mg.[32 43 44]. Albuterol is another beta-2 agonist commonly used in the treatment of hyperkalemia in the United States (US). When albuterol was given as 10 mg nebulization, the serum potassium concentration was lowered by a mean of 0.62 mmol/L, and 20 mg reduced serum potassium by 0.98 mmol/L after 2 hours. [42] Administration of these relatively high doses of beta-2 agonists may lead to tremor, tachycardia, and

headache. In KT recipients on tacrolimus, tremors and headaches caused by beta-2 agonists can be confused with tacrolimus toxicity.

Sodium bicarbonate

By raising extracellular bicarbonate levels, an increase in sodium–potassium ATPase pump activity results in an increase in uptake of intracellular potassium. [10] The use of bicarbonate infusion fails to lower serum potassium acutely and therefore has fallen out of favor.[43 45] However, in a case series of patients with metabolic acidosis (pH $<$ 7.35), a decrease in serum potassium concentration (1.5–3.0 mmol/L) in response to sodium bicarbonate was observed. [46-48] Sodium bicarbonate should be avoided in hypervolemic patients due to the risk of sodium overload and pulmonary edema. [49 50] In general, oral sodium bicarbonate (3-5g/day) should not be used as a first line treatment, and should be considered only in patients with concomitant metabolic acidosis (HCO3 $<$ 22mmol/L). However, it appears less effective in lower serum potassium levels in patients with advanced CKD [23 51]

Elimination of potassium from the body

Potassium binding agents. Table 2 includes a detailed comparison of existing potassium binding agents.

Sodium polystyrene sulfonate (SPS)

With higher affinity for potassium than sodium or calcium, cation-exchange resins including SPS, work by competitively exchanging cations for secreted potassium in the colon, where the most potassium excretion takes place. [52] Each gram of resin binds approximately 0.65 mmol of potassium *in vivo* . [53] In patients with CKD and mild hyperkalemia (5.0–5.9 mmol/L), the results of a double-blind randomized controlled trial showed that 30 g daily of SPS for 7 days was superior to placebo in reducing serum potassium concentration.[54] This study reported an absolute reduction of serum potassium concentration of 1.25 mmol/L ($p<0.001$) with SPS. More subjects in the SPS group achieved normokalemia, although the difference was not statistically significant ($p=0.07$). Common adverse reactions of SPS include diarrhea, abdominal bloating and cramps, vomiting, and electrolyte imbalance.[54 55] SPS can cause serious adverse gastrointestinal (GI) events including bowel necrosis and consequent death. In a systematic review, SPS use was associated with 58 cases of bowel necrosis and 33% mortality. [56] SPS occasionally is mixed with sorbitol, a polyalcohol sugar, to induce faster passage through the digestive system. Sorbitol is thought to be the reason for these serious GI adverse events, but the findings of 2 recent large observational studies refuted that notion. Serious adverse GI events were twice as high among those treated with SPS (without sorbitol) compared to the non-SPS groups. [57 58] It should be noted that SPS should be avoided in patients who are not having consistent bowl movements as well as in KT recipients in the immediate post-operative phase. The use of SPS in clinical practice is controversial due to its unestablished safety and efficacy profiles.[59 60] In the acute setting, SPS utilization should be limited to patients with mild to moderate hyperkalemia without electrocardiography (EKG) changes as the onset of action may take up to 3 days. [55 61] Nevertheless, SPS continues to be routinely used due to its accessibility and lower cost. [18] Limited data in using SPS in the management of hyperkalemia in kidney transplant recipients.

Patiromer

Patiromer is an organic, non-absorbable potassium-binding polymer. It is formulated with calcium as the exchange ion, leading to less excessive sodium absorption and potentially less volume overload compared to SPS. The drug is active throughout the GI tract but mostly in the colon with an onset of action ranging from 4 – 7 hours. [62] PEARL-HF was a double-blinded, placebo-controlled study evaluating the role of patiromer in heart failure patients with CKD.[63] The patiromer group (15g twice daily) had a mean potassium reduction of –0.22 mmol/L from baseline to week 4 compared to an increase of 0.23 mmol/L in the placebo group (mean difference –0.45 mmol/L, $p<0.0001$). The proportion of patients with potassium $>$ 5.5 mmol/L at any time during the study was 7% in the patiromer group vs 25% in the placebo group ($p=0.015$). The use of patiromer allowed the dose of spironolactone to be increased from 25 mg/day to 50 mg/day in 91% of patiromer patients compared to 74% of placebo patients ($p=0.019$). Patiromer was also

evaluated in patients with CKD on RAAS inhibitors. (Weir, 2015) Patiromer was dosed based on serum potassium as 4.2g twice daily (serum K+ 5.1 – 5.4 mmol/L) or 8.4g twice daily (serum K+ level 5.5 – 6.4 mmol/L). Mean change in serum potassium concentration at week 4 (phase 1) was -1.01 ± 0.03 mmol/L (P<0.001). After 8 weeks, more patients in the patiromer group (94% vs. 44%) were maintained on RAAS inhibitors. The AMETHYST-DN study was designed to establish the safety, efficacy, and optimal dosing of patiromer in patients with hyperkalemia and diabetic nephropathy. [64] Patiromer dose varied from 4.2g – 16.8g twice daily. In the maintenance phase, the proportion of patients with normal potassium at each visit through week 52 was 83.1%–92.7% in the mild-hyperkalemia group (5.1-5.5 mmol/L) and 77.4%–95.1% in the moderate-hyperkalemia group (5.6-5.9 mmol/L). The lowest starting dose was selected to be 8.4 g/day for mild hyperkalemia and 16.8 g/day for moderate hyperkalemia. PEARL-HF Extension study was an 8-week open-label follow-up study to the PEARL-HF trial to determine the effectiveness of patiromer 8.4 g twice daily. In 90.5% of patients, serum potassium concentrations between 3.5 – 5.5 mmol/L were reached with mean potassium reduction -0.13 mmol/L at the end of study. [65]

Patiromer is generally well tolerated with common adverse effects including constipation and hypomagnesemia.[62 66 67] Patiromer was shown to bind to half of tested oral medications in vitro. When tested in humans, patiromer did not impact the bioavailability of 14 drugs when administration was separated by 3 hours, however, the bioavailability of ciprofloxacin was decreased (90% CI) for maximum concentration 83%–133.8%, exceeding the 80%–125% limit. [62] Hypercalcemia, though uncommon, has been reported in patients receiving patiromer as a result of systemic absorption of calcium released from the patiromer polymer. [68] Patients with more advanced CKD are thought to be more prone to this adverse effect. [69]

In KT recipients, there is limited data regarding the safety and efficacy of patiromer when taken with anti-rejection medications. In a retrospective study of 19 KT recipients, patiromer, when administered 3 hours apart from tacrolimus, was shown to be effective in reducing serum potassium concentration without having a significant impact on tacrolimus trough concentrations. [70 71] A pharmacokinetic study is currently underway to evaluate the significance of the drug-drug interaction between patiromer and tacrolimus or mycophenolate mofetil. [72] With the limited available evidence, spacing out patiromer 3 hours from anti-rejection medications should be considered. Patiromer has become a valuable treatment option for chronic hyperkalemia as it has demonstrated a better safety and efficacy profile when compared to SPS. While chronic patiromer use can be costly (a 30 day supply of patiromer 8.4 g is $850), it was associated with a reduction in hospitalization costs related to hyperkalemia in heart failure patients. [73]

Sodium zirconium cyclosilicate (ZS9)

ZS9 is the newest potassium binder that received an initial FDA approval for the treatment of hyperkalemia in 2018. ZS9 is a non-absorbable potassium binder that exchanges hydrogen and sodium for potassium and ammonium ions throughout the entire GI tract with an onset of action within 1 hour after ingestion. [74] Unlike patiromer, ZS9 does not affect magnesium levels, but does increase bicarbonate levels, which is an advantage in the context of hyperkalemia. In a multicenter randomized, double-blind, placebo-controlled clinical trial, patients with mean serum potassium concentration 5.3 mmol/L were randomized to receive ZS9 (1.25g – 10g by mouth 3 times daily) or placebo for 48 hours.[75] A significant dose-dependent reduction in serum potassium concentration was observed in the ZS9 groups. Following the initial 48 hour phase, patients who received a maintenance dose of ZS9 (5 or 10 g daily) remained normokalemic for 12 days. Similar outcomes were seen when the maintenance phase was extended to 28 days and 12 months. [76 77] It important to note that KT recipients were excluded from all of the previous studies, except in the study by Spinowitz et al. where only 1% of included patients were KT recipients (n=9). [77]

In a recent retrospective study of 35 transplant patients (16 kidney recipients), the effect of ZS9 on both hyperkalemia and immunosuppression concentrations was evaluated. The mean decrease in serum potassium concentration from day 0 to day 7 was -1.3 mmol/L (p= <0.001) without a significant impact on tacrolimus drug pharmacokinetics (the mean change in tacrolimus concentrations was -0.54 ng/mL). [78] ZS9 is generally well tolerated when compared to SPS. The most common adverse effects are hypokalemia and edema. [74]

The drug-drug interaction profile of ZS9 has not been established, however, it is reasonable to separate ZS9 from other medications to prevent chelation and decreased absorption. Due to its relatively fast onset of action, ZS9 is the only potassium binder shown to be effective in the setting of acute hyperkalemia. Cost may be a barrier in the US, a 30 day supply of ZS9 can cost $656 USD. The cost-effectiveness of ZS9 is questionable when compared to the other potassium binders. [79]

Fludrocortisone

The role of fludrocortisone in the management of hyperkalemia is due to its mineralocorticoid properties as well as its ability to enhance potassium secretion in the GI tract. [80] Fludrocortisone, when given for 3 months to patients with CKD on dialysis showed no benefit in decreasing serum potassium concentrations. [81] In kidney transplant, most data are from case reports. Marfo et al. reported 3 cases of successful hyperkalemia management when fludrocortisone 0.1 mg/day was used in the setting of acute and chronic hyperkalemia. [82] Its role was also described in tacrolimus-induced aldosterone resistance. [13] In 2 case reports, normokalemia was achieved in 2 days when fludrocortisone 0.1 mg/day was initiated in KT recipients.[83 84] Signs and symptoms of fluid retention need to be monitored in patients receiving fludrocortisone.

Diuretics

Loop and thiazide diuretics enhance potassium excretion by increasing delivery of sodium to the collecting ducts. [10 85] Loop diuretics are the most common diuretic class used in hyperkalemia because they promote urinary potassium excretion even in patients with moderate renal impairment. There are no data in using loop diuretics in acute hyperkalemia. Loop diuretics can be considered in the setting of mild chronic hyperkalemia in patients with CKD and volume overload. [10] Generally, the use of thiazides should be avoided in kidney transplant recipients due to increase the risk of developing potassium disturbances. [86] The role of diuretics in acute hyperkalemia is uncertain, but in patients with chronic hyperkalemia who are normovolemic or hypervolemic, diuretic therapy can be considered. [28]

Dialysis

Dialysis is the ultimate treatment for severe hyperkalemia (serum potassium concentration [?] 6.0 mmol/L with EKG changes or [?] 6.5 mmol/L) in patients with ESRD. [23] Potassium removal can be effected by dialysate concentrations of potassium and bicarbonate, as well as a dialyzer blood flow. Using a low potassium and glucose dialysate can enhance potassium removal, however, it may reduce the efficiency of urea clearance and aggravate ventricular arrhythmias. [87-89] The use of high bicarbonate dialysate can also accelerate the drop in the serum potassium concentration. [90] However, the safety of this approach has not been established. Lastly, potassium clearance can be enhanced by increasing the dialysis blood flow resulting in maximizing the potassium gradient between the blood and the dialysate. [91]

Author Recommendations for Management of Acute and Chronic Hyperkalemia in Kidney Transplant Recipients

Management of Acute Hyperkalemia in Kidney Transplant Recipients

Hyperkalemia may manifest as an acute or chronic condition. A logical 5-step approach to treat acute hyperkalemia should be followed (Figure 1). In patients with a serum potassium concentration $>$ 6.5 mmol/L or $>$ 6.0 mmol/L with EKG changes, calcium gluconate should be administered to stabilize cardiomyocyte membranes. The dose should be repeated if there is no effect within 5-10 minutes. Second, shift potassium into cells using intravenous insulin 5-10 units along with dextrose 25 g +- a nebulized beta-2 agonist. Consider sodium bicarbonate if acidosis is present without volume overload. Third, remove potassium from the body with a potassium binder +- diuretics. ZS9 is the preferred potassium binder in acute hyperkalemia due to its relatively fast onset of action. Drug-drug interactions with anti-rejection medications and cost should be evaluated when ZS9 is chosen. Fourth, monitor serum potassium concentration at 1 - 2 hours after the initiation of treatment and blood glucose, if insulin-glucose therapy is used, hourly for up to six hours. Fifth, prevent recurrence by initiating a low potassium diet ($<$ 1-3 g/day), discontinuing medications known to cause hyperkalemia (when possible), and/or continuing a potassium binder. Dialysis should serve as the

last resort when hyperkalemia does not respond to the above therapies or when rapid potassium removal is deemed necessary.

Management of Chronic Hyperkalemia in Kidney Transplant Recipients

Patients with chronic hyperkalemia warrant a review of medications and dietary intake. Metabolic acidosis should be corrected with sodium bicarbonate and initiation of a potassium binder or loop diuretics may be helpful. Patients with a serum potassium concentration [?] 6.5 mmol/L may require hospital admission for emergency treatment.

Concluding Remarks

Hyperkalemia is a common electrolyte abnormality after KT with an incidence ranging from 25-44% in KT recipients on CNIs.[2] In KT patients, factors such as tubular dysfunction and various drug classes may increase the risk of hyperkalemia. Limited data exist in the kidney transplant population on the management of hyperkalemia. Our recommendations are mainly based on data from studies in patients with CKD. Nevertheless, KT patients by definition have CKD and the approach to treating hyperkalemia should be generally the same. Understanding the pathophysiology, treatment options, as well as limitations are all key to the successful treatment and prevention of hyperkalemia post-kidney transplant.

Disclosers

The authors report no conflicts of interest in this work

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Table 1. Food Rich in Potassium Content

Source	Serving size (>300 mg of potassium)
Milk	1 cup
Banana	1 medium
Cantaloupe	1 cup
Chicken	3 ounces
Fish	3 ounces
Carrot	1 large
Celery	1 stalk
Spinach	$\frac{1}{2}$ cup
Potato, baked	1 medium
Sweet potato	$\frac{1}{2}$ cup
Tomato	1 large

Table 2. Comparison of Existing Potassium Binders

	SPS	Patiromer	ZS9
Mechanism of action	Cation-exchange resin, exchanges sodium for H^+ in stomach, then exchange for H^+ for other cations in large intestine	Nonabsorbed organic polymer, binds potassium in the colon	Inorganic polymer; negative charge to framework enables cation exchange

	SPS	Patiromer	ZS9
Dosing	Oral: 15 g 1 to 4 times daily Rectal: 30 to 50 g every 6 hours	Oral: Initial: 8.4 g once daily; adjust dose at [?]1-week intervals in increments of 8.4 g; maximum dose: 25.2 g/day	Oral: Initial: 10 g 3 times daily for up to 48 hours; maintenance: 10 g once daily (range: 5 g every other day to 15 g once daily); maximum maintenance dose: 15 g/day
Onset of action	Variable	7 hours	1 hour
Efficacy	Reduces serum potassium concentration by 0.82 and 1.14 mmol/L	Mean reduction in serum potassium concentration at week 4: -1.01 mmol/L	Mean initial reduction in serum potassium (48 hr) -0.46 to -1.1; 98% achieved normokalemia within 48 hr
Safety	Risk of acute bowel necrosis, diarrhea, and gastrointestinal intolerance	Constipation and hypomagnesemia	Hypokalemia and edema

Figure 1. Management of Acute Hyperkalemia