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Hyperkalemia treatment standard

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ABSTRACT

Hyperkalemia is a common electrolyte disturbance in both inpatient and outpatient clinical practice. The severity and associated risk depends on the underlying cause and rate of potassium (K^+) increase. Acute hyperkalemia requires immediate attention due to potentially life-threatening manifestations resulting from the rapid increase in plasma K^+ concentration. Treatment is initially focused on stabilizing the cardiac membrane, followed by maneuvers to shift K^+ into the cells, and ultimately initiating strategies to decrease total body K^+ content. Chronic hyperkalemia develops over a more extended period of time and manifestations tend to be less severe. Nevertheless, the disorder is not benign since chronic hyperkalemia is associated with increased morbidity and mortality. The approach to patients with chronic hyperkalemia begins with a review of medications potentially responsible for the disorder, ensuring effective diuretic therapy and correcting metabolic acidosis if present. The practice of restricting foods high in K^+ to manage hyperkalemia is being reassessed since the evidence supporting the effectiveness of this strategy is lacking. Rather, dietary restriction should be more nuanced, focusing on reducing the intake of nonplant sources of K^+. Down-titration and/or discontinuation of renin–angiotensin–aldosterone inhibitors should be discouraged since these drugs improve outcomes in patients with heart failure and proteinuric kidney disease. In addition to other conservative measures, K^+ binding drugs and sodium–glucose cotransporter 2 inhibitors can assist in maintaining the use of these drugs.

Keywords: acute and chronic hyperkalemia, dietary potassium restriction, patiromer, renin–angiotensin–aldosterone system (RAAS) inhibitors, SGLT2 inhibitors, zirconium cyclosilicate

IN A NUTSHELL

- Acute hyperkalemia develops rapidly and often presents with more pronounced and potentially life-threatening symptoms due to the rapid increase in plasma K^+ levels.
- Treatment of acute hyperkalemia proceeds along the following sequence: 1) provide intravenous calcium to antagonize the effect on hyperkalemic depolarization, 2) promote cellular uptake of K^+ with the use of insulin and β_2-receptor agonists, 3) initiate therapy to decrease total body K^+ and 4) identify and manage the underlying etiology.
- Chronic hyperkalemia develops over an extended period, persisting for weeks, months or longer and, in a graded fashion, is associated with increased morbidity and mortality.
- Treatment of chronic hyperkalemia should include the following: 1) reassess the need for drugs known to interfere in kidney K^+ secretion, 2) restrict dietary K^+, but in a more nuanced manner, 3) ensure effective diuretic therapy, 4) correct metabolic acidosis if present and 5) consider the use of K^+-binding drugs.
- Down-titration and/or discontinuation of drugs that interfere in the renin–angiotensin–aldosterone axis should be discouraged; the use of sodium–glucose cotransporter 2 inhibitors and K^+-binding drugs can be useful in this setting.

INTRODUCTION

Hyperkalemia is commonly defined as a plasma potassium (K^+) concentration >5.0 or 5.5 mEq/l, with the upper limit of normal varying among different guidelines and publications [1–3]. While it is infrequent in individuals with normal kidney function, its occurrence in patients with chronic kidney disease (CKD) ranges from 5 to 50% [4]. The primary cause of hyperkalemia is the loss of kidney function; however, in clinical practice, this electrolyte disorder often results from a combination of factors that limit kidney K^+ excretion, superimposed on kidney dysfunction. This situation is evident in patients with diabetes mellitus, where diminished mineralocorticoid activity is frequently an early manifestation due to hyporeninemic hypoaldosteronism. Similarly, in advanced stages of heart failure, along with reductions in distal Na^+ delivery, the concurrent use of drugs that interfere with the renin–angiotensin–aldosterone system (RAAS) contributes to hyperkalemia. In these scenarios, hyperkalemia is prevalent and can develop even with mild or moderate reductions in the glomerular filtration rate.

ACUTE VERSUS CHRONIC HYPERKALEMIA

The severity of hyperkalemia and its associated risks depend on the underlying cause and rate of K^+ increase. Acute hyperkalemia develops rapidly and often presents with more pronounced and potentially life-threatening symptoms due to the rapid increase in plasma K^+ levels. Manifestations may include muscle weakness, paralysis, palpitations and potentially life-threatening cardiac arrhythmias. Common causes of acute hyperkalemia include rapid release of K^+ from cells (e.g. trauma, burns,

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rhabdomyolysis), acute kidney injury, excessive intake of K^+ in the setting of impaired excretion or certain medications (e.g. K^+-sparing diuretics).

Chronic hyperkalemia develops over a more extended period, often persisting for weeks, months or even longer. Chronic hyperkalemia may be asymptomatic, and symptoms, if present, are generally milder compared with acute hyperkalemia. Long-term elevation of K^+ levels can lead to complications such as cardiac arrhythmias and muscle weakness. There is a graded increase in the risk of mortality, cardiovascular morbidity, progression of CKD and hospitalization as the plasma level of K^+ increases in patients with chronic hyperkalemia, especially in those with CKD, diabetes mellitus and congestive heart failure [5, 6]. Chronic hyperkalemia is often associated with underlying medical conditions such as CKD, certain endocrine disorders (e.g. Addison's disease) or the use of medications that affect K^+ balance. The disorder frequently reoccurs after successful lowering of plasma K^+ since the underlying causes are often not readily correctable.

TREATMENT STANDARD

Emergent treatment of hyperkalemia

After excluding patients with pseudohyperkalemia, the initial step in management is determining who is in need of emergent therapy. Emergent treatment of acute hyperkalemia involves prompt intervention to lower elevated K^+ levels and prevent potentially life-threatening complications, especially cardiac arrhythmias (Fig. 1). Increases in plasma K^+ concertation initially increase cardiac conduction velocity by lowering the resting cardiac membrane potential and decreasing the threshold for rapid phase 0 sodium (Na^+)-dependent depolarization [7]. Electrocardiographic manifestations of these changes are peaked or 'tented' T waves. With further increases in plasma K^+ concentration, cardiac conduction system delays develop due to action potential shortening and prolongation of diastolic depolarization. These changes give rise to prolongation of the PR interval, widening of the QRS complex and a decrease or loss of P waves and ultimately what has classically been described as a sine-wave pattern. It should be emphasized that the electrocardiogram (ECG) is not a reliable indicator of hyperkalemia in that the ECG may remain normal with severe degrees of hyperkalemia even when interpreted by a cardiologist [8]. In addition, a hyperkalemic patient can rapidly evolve from a normal ECG to manifestations of cardiac hyperexitability (ventricular tachycardia and/or fibrillation) or depression (atrioventricular block, asystole). For these reasons, any patient with ECG abnormalities related to hyperkalemia should undergo emergent treatment. In addition, strong consideration for emergent therapy should be given to patients with a plasma K^+ value >6.0 mEq/l, even in the absence of ECG changes. Factors to consider in this situation include the presence of underlying cardiac conduction system disease, muscle weakness, level of kidney function and degree of adaptation to hyperkalemia expected to have occurred and the rate of change in plasma K^+, and whether near-term increases are expected, as in rhabdomyolysis or sepsis.

Stabilization of the cardiac membrane with administration of calcium salts

Intravenous (IV) calcium is the initial treatment of choice in cases of severe hyperkalemia with or without ECG changes or symptoms of muscle weakness. Calcium does not alter the plasma K^+ concentration but antagonizes the destabilizing electrical effects of hyperkalemia on the heart. Two mechanisms may account for the salutary effect of calcium in stabilizing the cardiac membrane [9, 10]. First, deposition of divalent calcium on the extracellular surface of the cell creates a surface charge effect resulting in partial repolarization of the cardiac membrane, thereby stabilizing voltage-gated channels that have been previously depolarized. Second, calcium deposition may bind to and directly cause closure of voltage-gated Na^+ channels, allowing repolarization of the membrane potential and effectively antagonizing the effect on hyperkalemic depolarization.

Calcium is available as IV calcium gluconate or calcium chloride, but the former is preferred since it can be administered through a peripheral vein and is less irritating to the vasculature and surrounding tissues in case of extravasation. The usual dose is 10 ml of a 10% calcium gluconate solution (93 mg of elemental calcium). Favorable effects on the ECG are expected within minutes, but if no response is observed, the dose can be repeated after 5 min. The effects may last 30–60 min, which allows enough time for implementation of maneuvers to lower the plasma K^+ concentration. Caution is needed when giving repeated doses of calcium to patients taking cardiac glycosides, because hypercalcemia may precipitate digitalis toxicity.

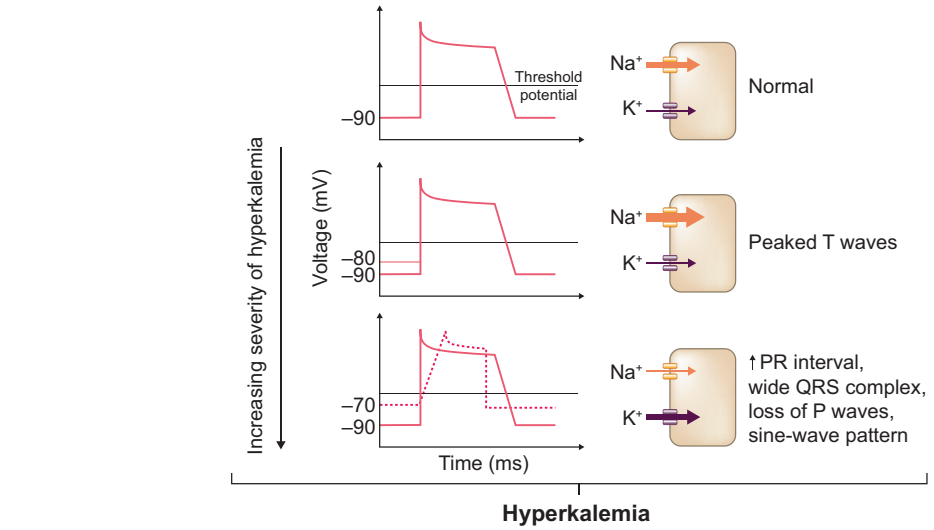
Lowering plasma K^+ concentration by promoting cellular uptake

Insulin therapy

Following stabilization of the cardiac membrane with calcium, therapy is focused on reducing extracellular K^+ concentration by promoting the cellular uptake of K^+. Insulin binds to cell surface receptors and triggers an increase in activity of the Na^+-K^+-ATPase, facilitating the movement of K^+ from the extracellular to the intracellular space. IV regular insulin exhibits an onset of action within 15 min, peaks at 30–60 min and has a duration of approximately 4 h. In contrast, subcutaneous regular insulin shows an onset at ≈30 min, a peak at 3 h and a duration of 8 h. The IV route of administration is preferred due to the shorter onset of action. IV glucose in the form of dextrose in water (50 ml of 50% dextrose solution) is given with IV regular insulin in patients who are not hyperglycemic (blood glucose level <250 mg/dl) to assist in preventing hypoglycemic events. Studies utilizing a regimen of 10 units of IV regular insulin and 25 g of IV dextrose report a reduction in plasma K^+ ranging from 0.65 to 1.14 mEq/l, accompanied by hypoglycemia rates ranging from 11 to 75% [11–13]. A Kidney Disease: Improving Global Outcomes (KDIGO) controversies conference recommends 5 units of IV regular insulin; however, the group acknowledges the data supporting this recommendation are limited [1]. Given the risk of hypoglycemia, careful monitoring of the blood glucose level is required. The 2020 UK Renal Association Guidelines recommend 10 units of IV regular insulin with 25 g of IV glucose, followed by an IV infusion of 10% glucose at 50 ml/h for 5 h in patients with a pretreatment blood glucose <126 mg/dl to prevent hypoglycemia [2].

β-adrenergic receptor agonists

Catecholamines induce cellular uptake of K^+ through β_2-receptor-mediated activation of the Na^+-K^+-ATPase pump. Inhaled albuterol (also known as salbutamol) is given as a 10–20 mg dose in 4 ml of saline delivered by nebulizer, a dose several-fold higher than that used in the treatment of reactive airway disease. The onset of action is usually within 30 min, with a peak effect occurring at 90–120 min. The reduction in plasma K^+ ranges from 0.6 to 1.0 mEq/l; however, the response rate is much lower (≈40–50%) in patients with end-stage-kidney



ECG changes and/or rapid rise in K^+, K^+ > 6 mEq/L

Emergent treatment indicated

Stabilize myocardial cell membrane
(calcium gluconate,10 mL of 10% IV)

Cell shift (redistribution)
Insulin: (10 units regular insulin IV with 1 amp (50ml) D50 IV)
Albuterol: (20 mg in 4 ml nebulized)

Decrease total body K^+

- Oliguria or ESKD → Hemodialysis
- Hypervolemic (non-oliguric) → Diuretics
- Metabolic acidosis → Sodium bicarbonate

Consider K^+ binding drugs as an adjunct to above emergent therapies

Non-emergent treatment

Dietary K^+ counseling, avoid salt substitutes

Discontinue drugs (if possible) that interfere in kidney K^+ secretion
Inquire about use of over-the-counter NSAIDs and herbal preparations

Ensure effective diuretic therapy (loop diuretics with eGFR < 30 ml/min)

Oral $NaHCO_3$ to treat metabolic acidosis

Avoid down-titration or discontinuation of RAAS inhibitor if possible

Initiate SGLT2 inhibitor if indicated

	Sodium polystyrene sulfonate	Patiromer	Sodium zirconium cyclosilicate
Mechanism of action	Na^+-K^+ exchange resin often given with sorbitol Non-selectively binds K^+, Ca^{2+}, Mg^{2+}	Exchanges Ca^{2+} for K^+, also binds Mg^{2+}	Binds K^+ in exchange for H^+ and Na^+
Time of onset (hours)	Variable (hours to days)	7	1
Binding site	Colon	Colon	Entire intestinal tract
Commonly reported adverse reactions and precautions	Diarrhea, metabolic alkalosis, hypernatremia, volume overload, rarely colonic necrosis. Must separate dose from other oral drugs by at least 3 hours	Constipation, diarrhea, flatulence, hypomagnesemia. Must separate dose from other oral drugs by at least 3 hours	Constipation,diarrhea, edema. Can increase gastric pH potentially interfering with drugs having pH-dependent solubility

Figure 1: Emergent and non-emergent therapy of hyperkalemia. Hyperkalemia initially causes cell membrane depolarization, bringing the resting membrane potential closer to the threshold potential and thereby facilitating activation of fast Na^+ channels. This change is reflected by peaking of the T wave and indicates increasing excitability and conduction velocity of the myocardium. With an increasing severity of hyperkalemia, there is both inactivation of voltage-dependent Na^+ channels and activation of inwardly rectifying K^+ channels causing decreased conduction velocity and cell refractoriness to excitation. See the text for a detailed discussion of treatment options for patients deemed to have indications for emergent versus non-emergent therapy.

disease [14]. Potential complications include tachyarrhythmias and myocardial ischemia in patients with coronary artery disease. Inhaled albuterol should not be used as monotherapy, given the inconsistent effect of the drug, but may provide additional lowering of plasma K^+ when coadministered with insulin [11, 15].

IV sodium bicarbonate

Sodium bicarbonate therapy can be considered as an additional treatment for hyperkalemia in the presence of concomitant metabolic acidosis, although data on its effectiveness are conflicting. In the absence of metabolic acidosis, any lowering effect of bicarbonate is largely explained by dilution secondary to expansion of extracellular fluid volume [16]. Potential complications include volume overload, development of hypernatremia, reductions in ionized calcium concentration and carbon dioxide retention. Given the effectiveness of treatments discussed above and the potential adverse side effects, sodium bicarbonate use in hyperkalemia management should be limited to those patients who also have severe metabolic acidosis. As an example, administration of sodium bicarbonate as an isotonic solution is useful in a hyperkalemic patient with volume depletion and metabolic acidosis.

Maneuvers to decrease total body K^+ content

Assuming an increase in total body K^+ content, the ultimate therapy of hyperkalemia requires maneuvers that remove K^+ from the body. The three routes available for elimination of K^+ are the use of diuretics to promote kidney K^+ excretion, the use of cation exchange drugs to promote gastrointestinal loss and utilization of an extracorporeal circuit using dialysis.

Diuretics

Loop diuretics alone or in combination with a thiazide diuretic can be effective in lowering total body K^+ content. The effectiveness of this approach as an emergent therapy is often limited since many patients who develop acute hyperkalemia have significant reductions in functioning nephron mass, rendering the drugs ineffective. Preexisting volume depletion can be made worse with diuretics, limiting any kaliuretic effect. In general, the use of high-dose diuretics for purposes of lowering total body K^+ content should be reserved for patients with mild–moderate hyperkalemia who are volume overloaded and have preserved kidney function.

Gastrointestinal loss using K^+-binding drugs

For >50 years, the main drug utilized to promote gastrointestinal K^+ loss was sodium polystyrene sulfonate, usually in combination with a cathartic such as sorbitol. The drug contains 4 mEq of Na^+ per gram and binds K^+ in exchange for Na^+ primarily in the colon. An oral dose of 30 g of the drug can be expected to remove up to 36 mEq of K^+ in association with a Na^+ load of 60–90 mEq. The drug reaches the site of action after 2 h and has a peak effect at 4–6 h and may continue for 24 h. When given as a retention enema, the drug binds about half as much K^+ per gram dose as compared with oral administration. With the advent of new K^+-binding drugs and the risk of gastrointestinal toxicity, such as colonic necrosis, the use of sodium polystyrene sulfonate both as an acute and chronic therapy has fallen out of favor [17].

Patiromer is an oral polymer that binds K^+ in exchange for calcium, creating a favorable gradient for K^+ movement from blood into the gastrointestinal tract. A single oral dose of 8.4 grams lowers plasma K^+ by 0.23 mEq/l within 7 hours of administration [18]. Sodium zirconium cyclosilicate (SZC) has a high-capacity crystalline lattice structure that binds K^+ in exchange for sodium and hydrogen. The drug lowers K^+ by 0.4 mEq/l at 1 h and 0.7 mEq/L at 4 h following administration of a 10-g dose [19]. Both drugs have been proven to be safe and effective in patients with hyperkalemia; however, current labeling indicates the drugs should not be used as an emergent treatment of life-threatening hyperkalemia because of the delayed onset of action. While not a replacement for calcium, insulin and glucose, or β_2-receptor agonists, the National Institute for Health and Care Excellence (NICE) has approved both drugs as an option in the treatment of acute life-threatening hyperkalemia when used as an adjunct along with the standard of care [2].

Hemodialysis (HD)

In severe cases or when other measures are ineffective, HD may be used to directly remove K^+ from the bloodstream. This is particularly important in cases of kidney failure. Emergent HD is indicated in patients with hyperkalemia who demonstrate an inadequate response to standard medical therapy, such as persistent ECG changes or a plasma K^+ level >6.0 mEq/l. Plasma K^+ concentration decreases rapidly in the early stages of HD, but as the plasma K^+ level declines, removal becomes less efficient since movement from the intracellular space to the extracellular space becomes a limiting factor.

The plasma K^+ level decreases by 1 mEq/l in the first hour of treatment and then 1 mEq over the next 2 h before finally reaching a steady state during the last hour of a 4-h treatment [20]. In total, approximately 70–90 mEq of K^+ is removed from the body. This amount exhibits considerable variability and is influenced by changes in acid–base status, changes in glucose and insulin concentration, catecholamine activity and changes in tonicity [21]. For example, K^+ removal in acidotic patients is lower than in normal subjects due to net addition of base causing a shift of K^+ into the cells. A glucose-free dialysate causes greater amounts of K^+ removal compared with a standard glucose-containing bath since insulin levels are lower, causing less of a shift of K^+ into cells. Dialytic K^+ removal is lower in patients treated with nebulized albuterol prior to the procedure due to a shift of K^+ into cells and a reduced concentration of K^+ in the extracellular space. While there are no studies addressing the issue, acutely increasing the tonicity of the extracellular fluid with hypertonic saline or mannitol is expected to increase K^+ removal since increased tonicity shifts K^+ from the cells into the extracellular space. Given the tendency for plasma K^+ to increase in the immediate post-dialysis time period, the most efficient way to remove excess K^+ stores is to prescribe 2- to 3-h periods of dialysis separated by several hours. A dialysate K^+ of 2 mEq/l should be used in patients with plasma K^+ levels up to 8 mEq/l [2]. The dialysate can be reduced to 1.0 mEq/l with higher K^+ levels but should be increased to 2 mEq/l once the plasma K^+ level decreases to <7.0 mEq/l, since use of a 1.0 mEq/l dialysate is associated with an increased rate of arrhythmias. Telemetry and close monitoring of plasma K^+ during the course of the procedure is essential.

Management of chronic hyperkalemia

The treatment of chronic hyperkalemia focuses on managing elevated K^+ levels over the long term and addressing the underlying causes. While early intervention is crucial in acute cases to minimize the risk of severe complications, individuals with chronic

hyperkalemia require ongoing monitoring and management to prevent recurrence [22].

Accurately assess the level of kidney function to better define the risk of hyperkalemia

Chronic hyperkalemia is infrequent in CKD until the estimated glomerular filtration rate (eGFR) falls below 15–20 ml/min due to adaptive changes in remaining nephrons leading to increased capacity for K^+ secretion. Changes in serum K^+ concentration and mineralocorticoids independently contribute to this response by inducing functional and structural changes in the distal nephron to include amplification of the basolateral membrane area, increased activity of the Na^+-K^+-ATPase pump, heightened Na^+ delivery and enhanced apical Na^+ transport [23, 24]. Increased colonic K^+ secretion mediated by increased expression of high-conductance K^+ channels and Na^+- K^+-ATPase pump sites on the apical and basolateral surface, respectively, of colonic epithelial cells also provides a defense against development of hyperkalemia as kidney function declines [25]. Development of hyperkalemia with more modest declines in eGFR (40–60 ml/min/1.73 m^2) implicate one or more of the following superimposed disturbances: decreased distal Na^+ delivery (decompensated congestive heart failure, acute glomerulonephritis), direct injury to the distal nephron (tubulointerstitial disease, urinary obstruction) and abnormalities of the renin–angiotensin–aldosterone cascade [26] (Fig. 2).

Reassess the need for drugs known to interfere with kidney K^+ secretion

The use of prescribed or over-the-counter non-steroidal anti-inflammatory drugs should be discouraged. Inhibition of prostaglandin synthesis inhibits renin release from juxtaglomerular cells in the kidney and interferes with the stimulatory effect of angiotensin II on adrenal gland release of aldosterone. These drugs also predispose to hyperkalemia by augmenting Na^+ reabsorption in the thick ascending limb of Henle, thereby decreasing distal delivery [27]. In the absence of a specific indication, β-blockers should be avoided since these drugs lower plasma renin levels by interfering in the stimulatory effect of sympathetic nerves on juxtaglomerular cells. These drugs can also worsen hyperkalemia associated with exercise and fasting due to unopposed stimulation of α-adrenergic receptors signaled by afferent nerve activity originating in diseased kidneys [28]. Salt substitutes and herbal medication can be a hidden source of dietary K^+. For example, noni juice, derived from the fruit of the noni tree (*Morinda citrifolia*), contains 56 mEq/l of K^+. The Chinese herb *chan su* contains an extract of toad skin that mimics the toxicity of digitalis, potentially resulting in hyperkalemia [29].

Dietary modifications

Early observational studies demonstrating a high risk of hyperkalemia following the administration of K^+ salts in patients with reduced kidney function have led to the common practice of recommending the restriction of foods high in dietary K^+, including fruits and vegetables, as a management strategy for hyperkalemic CKD patients. It is now recognized this management strategy lacks evidence and has the potential to be harmful because by restricting foods high in dietary K^+, healthy nutrients are inadvertently restricted [30]. Diets incorporating K^+-rich foods are rich sources of vitamins, minerals and fiber, which provide multiple health benefits. There are recent data from observational studies demonstrating no association between diets that include fruits and vegetables and elevations in plasma K^+ levels in CKD patients. Unlike K^+ salts, dietary K^+ in plant sources is less available for absorption, as it remains in cell walls and is excreted in stool [31]. The high fiber content of plant foods increases gastrointestinal transit time and reduces the risk of constipation, further decreasing the risk of hyperkalemia. A more useful strategy in dietary management of hyperkalemia is to focus on restricting dietary K^+ from highly processed foods and additives where the bioavailability of K^+ is significantly higher [32, 33].

Effective diuretic therapy

Diuretics are an effective strategy to minimize hyperkalemia. Diuretics acting proximal to the collecting duct enhance K^+ excretion by increasing flow and delivery to the K^+ secretory portion of the distal nephron. Initiation of effective diuretic therapy provides additional blood pressure and volume control often required in CKD patients with hyperkalemia. Loop diuretics are preferred and continue to be effective in patients with an eGFR <30 ml/min/1.73 m^2, while thiazide diuretics tend to be much less effective at this level of kidney function. Chlorthalidone may be an exception to this rule, as it has shown efficacy in blood pressure control in stage 4 CKD patients [34].

Correct acidosis if present

The 2012 KDIGO guidelines recommend oral bicarbonate therapy to maintain plasma bicarbonate levels within the normal range in patients with values <22 mEq/l [35]. Correction of acidosis is effective in decreasing plasma K^+ concentration by promoting a shift of K^+ into cells and increasing kidney K^+ excretion through increases in distal Na^+ delivery. Concurrent effective diuretic therapy lessens the risk of volume overload with the administration of this salt.

Maintain optimal dosing of RAAS inhibitors whenever possible

Hyperkalemia poses a therapeutic dilemma in patients receiving RAAS inhibiters since patients at highest risk for this complication are the same patients who derive the greatest amount of cardiovascular benefit. Down-titration of the dose or discontinuation altogether is a common management strategy, but data show this comes at the expense of worse outcomes. In a retrospective analysis of an extensive database, the development of hyperkalemia resulted in discontinuation in 30% and down-titration in 50% of individuals receiving submaximal and maximal doses of RAAS inhibitors, respectively [36]. This approach led to a more rapid progression of CKD, cardiovascular events and mortality in those who discontinued or underwent dose reductions compared with patients receiving maximally tolerated doses. In a separate retrospective cohort study involving two distinct populations, the authors investigated the association between discontinuing RAAS inhibitors due to hyperkalemia and primary outcomes such as all-cause mortality, as well as secondary outcomes including cardiovascular mortality, fatal and non-fatal cardiovascular events and initiation of dialysis [37]. Discontinuation of these drugs was linked to higher all-cause mortality, cardiovascular mortality and an increased risk of dialysis initiation. While submaximal doses were associated with a lower risk of all-cause and cardiovascular mortality compared with therapy discontinuation, individuals receiving maximal doses of RAAS inhibitors experienced the highest survival benefits. The consistency of these studies supports

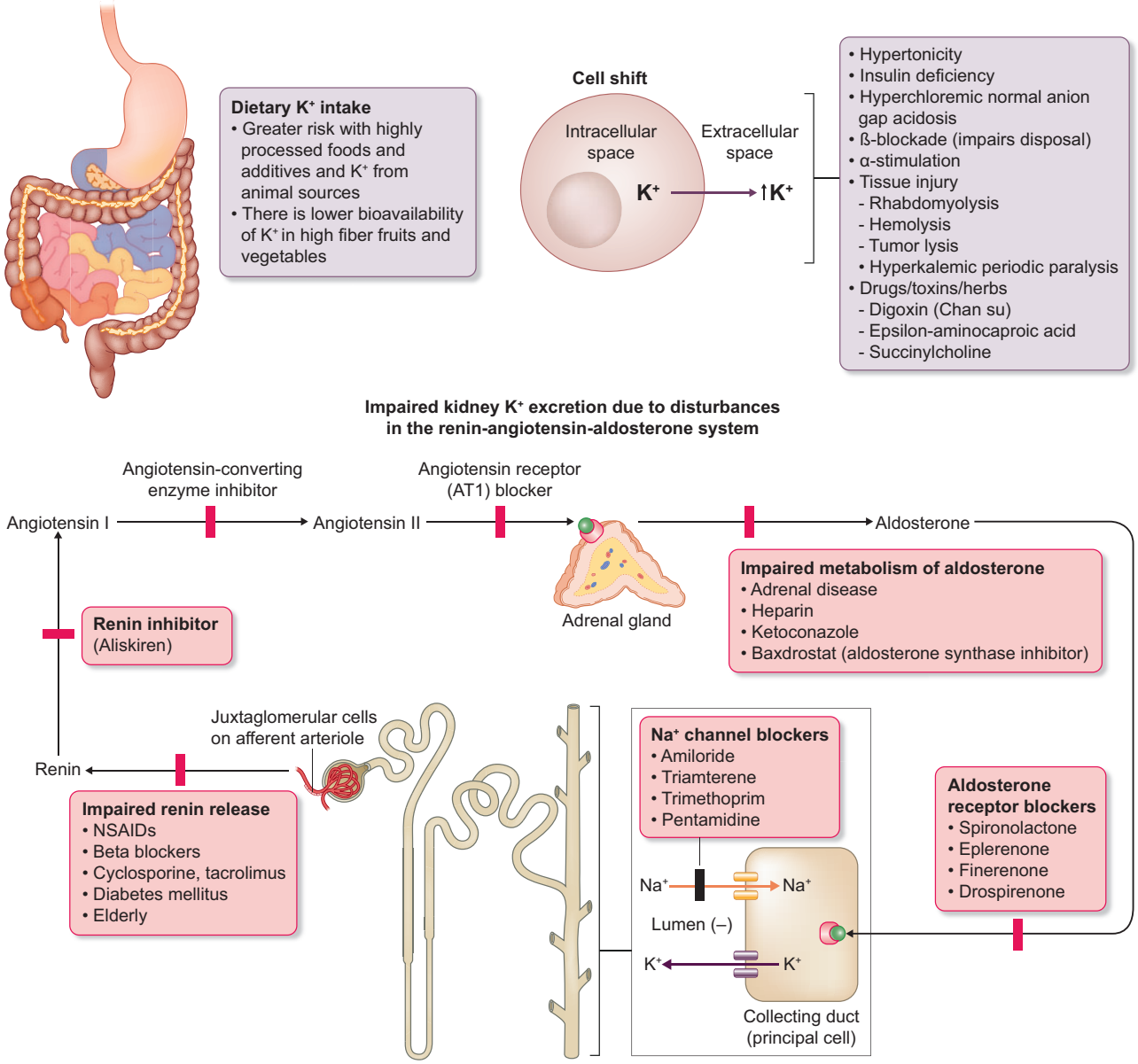


Figure 2: Selected causes of hyperkalemia. Dietary intake of K^+ as a cause of hyperkalemia only occurs in the setting of reduced kidney function since the normal kidney has a prodigious capacity for K^+ secretion. Hyperkalemia due to cell shift causes acute hyperkalemia and, by itself, is not a cause of chronic hyperkalemia. Adaptations in remaining nephrons serve to minimize the development of hyperkalemia until the GFR decreases to <20–25 ml/min/1.73 m^2. Development of hyperkalemia with mild–moderate decreases in GFR (40–60 ml/min) should prompt the search for conditions and/or medications that interfere in the renin–angiotensin–aldosterone system. Not shown in the figure is decreased distal Na^+ delivery or kidney disease targeted to the distal nephron as additional factors to consider in this later situation.

the recommendation to maintain RAAS inhibitors at target doses whenever possible following an episode of hyperkalemia [38]. In addition to the conservative measure discussed above, two additional therapies can be implemented to enable the use of RAAS inhibitors.

K^+-binding drugs: patiromer or SZC

Initiation and use of either patiromer or SZC can allow for the continuation and optimization of RAAS inhibitor therapy in patients with hyperkalemia. Both drugs have demonstrated the ability to sustain normokalemia for 52 weeks despite ongoing use of RAAS inhibitors in patients with diabetes and CKD, including those with heart failure [39, 40]. Numerous guideline organizations [European Society of Cardiology (ESC), American College of Cardiology, KDIGO and NICE] advocate for use of K^+-binding drugs for the management of hyperkalemia to enable the use of RAAS inhibitors [41–43]. An expert consensus document by the Working Group on Cardiovascular Pharmacotherapy of the ESC suggests the following strategy: when plasma K^+ is between 5.0 and 6.5 mEq/l, a K^+ binder should be initiated followed by up-titration of the RAAS inhibitor [44]. The inhibitor should only be reduced or discontinued if plasma K^+ is >6.5 mEq/l. In this later situation, K^+-binder therapy should be initiated and plasma K^+ remeasured after 1 week. If the target K^+ is achieved, then up-titration or reinitiation of the RAAS inhibitor should be considered.

Consider the use of sodium–glucose cotransporter 2 (SGLT2) inhibitors

Pharmacologic inhibition of SGLT2 in the proximal tubule has paradoxical implications for kidney K^+ excretion [45]. Despite theoretical predictions of both increased and decreased K^+ elimination, clinical data reveal minimal impact on plasma K^+ concentrations in patients with normal kidney function. SGLT2 inhibitors exhibit a protective effect against hyperkalemia in individuals with reduced kidney function receiving RAAS blockade [46]. While not indicated for this purpose, many patients on RAAS inhibitor therapy also have indications for the utilization of SGLT2 inhibitors, allowing them to capitalize on the beneficial effect these drugs have on limiting the development of hyperkalemia.

CONCLUSION

The treatment standard for hyperkalemia depends on the severity of the condition, its duration and the underlying cause. Immediate measures are required for patients with acute hyperkalemia demonstrating clinical manifestations of toxicity or plasma K^+ concentrations >6.0 mEq/l. Identifying and addressing the underlying cause is also of critical importance. Recommended approaches to this condition include a detailed dietary history assessing for consumption of potassium additives, salts and homeopathic remedies that may provide a source of highly bioavailable potassium along with utilization of K^+ binding drugs and SGLT2 inhibitors to maintain optimal dosing of RAAS inhibitors.

AUTHORS' CONTRIBUTIONS

The authors contributed equally to the writing of this article.

DATA AVAILABILITY STATEMENT

No new data were generated or analyzed in support of this research.

CONFLICT OF INTEREST STATEMENT

B.F.P. participated in advisory boards for AstraZeneca and Bayer Health Care Pharmaceuticals.

D.J.C. provided consultation to AstraZeneca regarding dietary potassium management in CKD patients.

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