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How Dangerous Is Hyperkalemia?

John R. Montford*† and Stuart Linas*‡

*Division of Renal Disease and Hypertension, Department of Medicine, University of Colorado Anschutz Medical Campus, Aurora, Colorado; †Renal Section, Medicine Service, Veterans Affairs Eastern Colorado Health System, Denver, Colorado; and ‡Division of Nephrology, Department of Medicine, Denver Health and Hospitals, Denver, Colorado

ABSTRACT

Hyperkalemia is a potentially life-threatening electrolyte disorder appreciated with greater frequency in patients with renal disease, heart failure, and with use of certain medications such as renin angiotensin aldosterone inhibitors. The traditional views that hyperkalemia can be reliably diagnosed by electrocardiogram and that particular levels of hyperkalemia confer cardiotoxic risk have been challenged by several reports of patients with atypic presentations. Epidemiologic data demonstrate strong associations of morbidity and mortality in patients with hyperkalemia but these associations appear disconnected in certain patient populations and in differing clinical presentations. Physiologic adaptation, structural cardiac disease, medication use, and degree of concurrent illness might predispose certain patients presenting with hyperkalemia to a lower or higher threshold for toxicity. These factors are often overlooked; yet data suggest that the clinical context in which hyperkalemia develops is at least as important as the degree of hyperkalemia is in determining patient outcome. This review summarizes the clinical data linking hyperkalemia with poor outcomes and discusses how the efficacy of certain treatments might depend on the clinical presentation.

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INTEGRATED DISCUSSION

Introduction

Hyperkalemia is an electrolyte disturbance occurring with increased frequency among patients with CKD, diabetes, heart failure, and use of certain medications such as renin angiotensin aldosterone system (RAAS) inhibitors and nonsteroidal anti-inflammatory drugs.[1–4] Extracellular potassium concentration is usually kept within a narrow physiologic range by redundant and highly efficient homeostatic mechanisms that simultaneously control internal potassium redistribution while regulating net potassium excretion. Hyperkalemia occurs when rises in extracellular potassium concentration are accompanied by one, or additive, defects in these two processes. Blunted potassium redistribution typically occurs through insulin deficiency, decreases in aldosterone biosynthesis or action, diminished adrenergic signaling, and osmolar disturbances including hyperglycemia. Renal failure, and/or failure to augment distal tubular potassium secretion, is largely responsible for the maintenance of hyperkalemia. Many studies reproducibly identify common clinical risk factors that are associated with the development of hyperkalemia regardless of the clinical setting (Table 1).

The fatal consequences of rapid increases in extracellular potassium concentration have been demonstrated in the setting of acute intravenous potassium loading in animals.[5,6] Early rises in extracellular potassium concentration lower the resting cardiac membrane potential. This decreases the threshold for rapid phase-0 Na^+-dependent depolarization resulting in an increase in cardiac conduction velocity.[7] By electrocardiogram (ECG), these changes are manifested by "peaked" or "tented" T waves most prominent in the precordial (V2–V4) leads. With larger acute rises in extracellular potassium concentration, conduction delay becomes prominent in the atrioventricular node and His–Purkinje system due to action potential shortening and prolongation of phase-4 diastolic depolarization.[7,8] Indeed, prolongation of the PR interval, P-wave amplitude, and increased QRS complex width are ominous findings in patients with advanced hyperkalemia that can precede a classically described "sine-wave" pattern on ECG.[9] Thus, hyperkalemia predisposes to both cardiac hyperexcitability (ventricular tachycardia, ventricular fibrillation) and depression (bradycardia, atrioventricular block, interventricular conduction delay, and asystole), both of which can be fatal.

Despite a wealth of animal data demonstrating cardiotoxicity from acute hyperkalemia, these presentations are

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Correspondence: Dr. John R. Montford, Division of Renal Disease and Hypertension, University of Colorado Anschutz Medical Campus, Research 2, Box C281, 12700 E. 19th Avenue, Aurora, CO 80045. Email: John.Montford@UCDenver.edu

Table 1. Risk factors for the development of hyperkalemia

Clinical Risk Factor	Medication Exposure
Male sex	Potassium supplements
Non-black	Penicillin G
DM	Digoxin
CVD	NSAIDs
CHF	ACEi/ARBs
AKI	MRAs
CKD	β-adrenergic blockers
Acidosis	Heparin
Urinary obstruction	Amiloride, Triamterene
	Trimethoprim,
	Pentamidine

DM, diabetes mellitus; CVD, cardiovascular disease; NSAIDs, nonsteroidal anti-inflammatory drugs; CHF, congestive heart failure; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockade.

overall uncommon in humans. Reports of acute hyperkalemia precipitating cardiac arrest typically involve intravenous potassium loading, massive cell turnover, or shift of potassium in the setting of surgical anesthesia or critical illness.[10–14] In these cases, the measured potassium concentration was usually normal shortly before cardiopulmonary arrest; and only with rapid increases in serum potassium did the findings of tachy- and bradyarrhythmias associated with hyperkalemia become apparent. These extreme situations constitute a small minority of clinical hyperkalemia in humans which is often incidental, asymptomatic, and of unknown duration. Additionally, there are many published reports demonstrating a large disconnect between degree of hyperkalemia and expected ECG findings in humans.

The ECG was observed to be somewhat unreliable in older studies of patients with potassium levels <6.5 meq/L.[9,15] Modern studies and case reports also support that extreme hyperkalemia is accompanied by inconsistent findings. For example, a prospective study examining treatment strategies for acute hyperkalemia revealed only 46% of all patients with a serum potassium >6.0 meq/L had ascribable ECG changes.[16] In another study of hospitalized patients with serum potassium levels >6.0 meq/L, the ECG was noted to be completely insensitive at diagnosing mild-to-moderate degrees of hyperkalemia and only approached minimal predictive power with potassium levels of 7.2–9.4 meq/L.[17] In patients on hemodialysis with hyperkalemia, ECG-diagnosed T wave "tenting" did not predict the serum potassium and substantially lost its sensitivity with increasing patient age and presence of diabetes.[18] Specificity for hyperkalemia and sudden death at follow-up was improved with evaluation of the T:R wave amplitude in these patients, but sensitivity was also diminished.

Hyperkalemia has also been associated with a host of nontraditional ECG changes including T wave inversions[19] and pseudonormalizations,[20] bundle branch,[21] bifascicular,[22] sinoatrial exit,[20] and atypic bundle branch blocks,[8] and ST depressions and elevations.[15,23,24] There are even reports of profound hyperkalemia with minimal or no discernable ECG changes.[21,25,26] Additionally, metabolic acidosis,[27] left ventricular hypertrophy,[28] early benign repolarization,[29] and acute coronary ischemia[30] are known to induce T wave "tenting" in patients with normal serum potassium. Because there are currently inconsistent data supporting the utility of the ECG in predicting the degree of, and prognosis with, hyperkalemia, we must turn to published data that examines the relationship between hyperkalemia and cardiovascular outcomes.

Hyperkalemia in the Setting of Critical Illness

Compelling data link hyperkalemia with heightened adverse outcomes in the critically ill population. In a retrospective analysis of 932 hospitalized adults in two Korean medical centers, high rates of arrhythmia (in 35.2%) and cardiac arrest (in 43.3%) occurred in patients with serum potassium levels >6.5 meq/L.[31] Nonsurvivors in this cohort had a higher prevalence of comorbidities which independently predicted death including multiorgan failure (odds ratio [OR], 7.64; 95% confidence interval [95% CI], 4.00 to 14.57), malignancy (OR, 2.88; 95% CI, 1.68 to 4.96), AKI (OR, 2.17; 95% CI, 1.27 to 3.71), and need for intensive care (OR, 3.62; 95% CI, 1.79 to 7.32). Furthermore, as compared with survivors with hyperkalemia, nonsurvivors had higher increases in serum potassium preceding death (1.1 ± 1.3 versus 2.2 ± 1.5 meq/L change in serum potassium from admission, respectively). Most cases of hyperkalemia developed during hospitalization (in 60% of the cohort) with a mean admission potassium level of 5.7 ± 1.5 meq/L rising to 7.1 ± 0.7 meq/L after an average of 17 days of follow-up.

In another retrospective review of >39,000 patients admitted to the intensive care unit at two teaching hospitals in Boston, Massachusetts between 1997 and 2007, incident hyperkalemia independently predicted mortality at the time of critical care initiation.[32] This association was graded, with even minor elevations in serum potassium (to levels 4.5–5.0 meq/L) conferring an increased risk of death (OR for death within 30 days, 1.49; 95% CI, 1.38 to 1.59), and remained significant after adjusting for many potential confounders prevalent in the critical care setting (adjusted OR, 1.18; 95% CI, 1.09 to 1.27). Furthermore, failure of serum potassium to correct by >1.0 meq/L within 48 hours after initial measurement continued to predict death; whereas, this association was attenuated among patients achieving this degree of correction. Khanagavi *et al.*[33] reported on hospitalized patients with serum potassium >5.1 meq/L, finding that duration of hyperkalemia and mortality increased substantially with concomitant tissue necrosis [hazard ratio (HR) for death, 4.55; 95% CI, 1.74 to 11.90], metabolic acidosis (HR, 4.84; 95% CI, 1.48 to 15.82), and AKI (HR, 3.89; 95% CI, 1.14 to 13.26). Total duration of hyperkalemia was also associated with death, although the association was less robust (HR, 1.06; 95% CI, 1.02 to 1.09).

Data from these studies suggest that not only the absolute level, but the velocity and duration of hyperkalemia are associated with poor outcomes with critical illness. Although compelling, these studies are limited by their retrospective design and weighed down by the severity of illness in the subjects. Mortality was high

(30.7%) in the cohort by An *et al.*[31] and many patients needed cardiopulmonary resuscitation (32%), the majority for reasons unrelated to hyperkalemia. Although initial and sustained hyperkalemia predicted mortality in the study by McMahon *et al.*,[32] there are no data regarding the disease-specific clinical improvement or lack of improvement in the patients who suffered in-hospital mortality. Furthermore, these studies were unable to adequately control for the severity of patient illness due to a lack of physiologic data.

Hyperkalemia during Acute Myocardial Infarction

Hyperkalemia was not originally identified as a potential risk factor for poor outcomes during evolution of acute myocardial infarction (AMI),[34] despite the existence of strong biologic plausibility in animal models.[35,36] However, modern approaches, including percutaneous coronary intervention (PCI) and more widespread adoption of RAAS inhibitors, β-adrenergic blockers, and mineralocorticoid receptor antagonists (MRAs), have drastically improved patient survival while also predisposing the post-AMI population to more frequent hyperkalemia. One widely cited retrospective trial of 38,689 hospitalized patients with AMI treated in the modern era demonstrated an independent increase in mortality among patients with potassium levels >5.1 meq/L (OR, 3.27; 95% CI, 2.52 to 4.24) which persisted in patients with serum potassium levels of 4.5–5.0 meq/L (OR, 1.99; 95% CI, 1.68 to 2.36).[37] A subsequent analysis of this same cohort showed elevated in-hospital mortality with exposure to a higher number of hyperkalemic episodes (13.4%, 16.2%, and 19.8% increase in mortality with one, two, and three or more potassium measurements >5.0 meq/L, respectively) and maximum achieved serum potassium level (4.2%, 11.1%, 16.6%, 26.6%, and 31.7% increase in mortality with potassium levels <5.0, 5.0–5.5, 5.5–6.0, 6.0–6.5, and >6.5 meq/L, respectively).[38] Another retrospective trial analyzing 90-day mortality in 2596 Danish patients with heart failure post-AMI also supports that a serum potassium >5.1 meq/L is associated with higher risk of death (HR, 2.3; 95% CI, 1.4 to 3.6).[39]

The studies by Goyal *et al.*[37] and Grodzinsky *et al.*[38] are strengthened by use of robust adjustment models that control for baseline risk, medications, PCI use, and other pertinent factors. Nevertheless, residual confounding in very ill patients is common in retrospective analyses, and outcomes in patients with serum potassium >4.5 meq/L in the study by Goyal *et al.*[37] were ultimately driven by a small number of individuals (11%, 2%, and 0.6% of the entire cohort had potassium levels 4.5–5.0, 5.1–5.5, and >5.5 meq/L, respectively). These patients also had substantially higher comorbidities, and lower rates of PCI, aspirin, RAAS inhibitor, β-blocker, and statin usage. The analysis by Krogager *et al.*[39] suffers a similar limitation, including very few patients with serum potassium levels >5.1 meq/L. In the study by Goyal *et al.*[37] there was also a paradoxic dissociation between rates of malignant arrhythmias and rates of overall mortality in higher versus lower ranges of hyperkalemia and normokalaemia, in which both associations were more congruent. The authors hypothesized that poor coding of arrhythmias associated with extremes of hyperkalemia, such as sinus arrest and asystole, led to this discrepancy.

Hyperkalemia with CKD

One of the first studies to demonstrate an independent association of hyperkalemia and risk of subsequent death involved a large retrospective study of Japanese patients with advanced CKD presenting for dialysis initiation.[40] An initial serum potassium level >5.5 meq/L at dialysis vintage was the strongest single independent predictor of mortality after an average of 15 years of follow-up. In patients on hemodialysis, potassium levels >5.6[41] and >5.7[42] meq/L have been associated with higher mortality. This is also reflected in patients on peritoneal dialysis, with one study suggesting hyperkalemia >5.5 meq/L is associated with a heightened risk of death.[43] Potassium increases during longer intradialytic intervals, and many have attempted to link these fluctuations to the higher incidence of sudden cardiac death in patients with ESRD. In a 3-year study of community dwelling patients on hemodialysis, the presence of hyperkalemia (defined as three or more averaged serum potassium levels >6.0 meq/L over a 6-month period) was one of the strongest single predictors of sudden death (HR, 2.7; 95% CI, 1.3 to 5.9).[44]

A recently published retrospective observational trial of 52,734 patients on a Monday/Wednesday/Friday hemodialysis schedule revealed that serum potassium levels 5.5–6.0 meq/L were associated with higher risk for subsequent hospitalization, emergency department visits, and mortality within 4 days of measurement.[45] Of note, the association between hyperkalemia and hospitalization was magnified among patients entering a longer intradialytic interval (adjusted OR for hospitalization, 1.12; 95% CI, 1.0 to 1.24; OR, 1.04; 95% CI, 0.94 to 1.16; and OR, 1.68; 95% CI, 1.22 to 2.30 for patients with potassium measurements performed on Monday, Wednesday, and Friday, respectively).

The association of mortality with hyperkalemia also appears to extend to patients with earlier stage CKD. Einhorn *et al.*[2] conducted a retrospective analysis of 245,808 United States adult veterans with and without CKD, showing potassium levels of >5.5 meq/L predicted death just 1 day after measurement. In another study of 36,000 patients in the Cleveland Clinic system with an eGFR<60 ml/min per 1.73 m^2, sustained hyperkalemia (defined as an average serum potassium level >5.5 meq/L over 2.3 years) was also associated with increased all-cause mortality.[46]

However, an interesting paradox is documented in these later studies regarding the relationship between CKD stage, hyperkalemia, and mortality. In the study by Einhorn *et al.*[2] the strongest association between hyperkalemia and 1-day mortality involved patients with normal renal function (OR, 10.32 and 31.64 for serum potassium ranges ≥5.5 and <6.0

and ≥6.0 meq/L, respectively), and declined as CKD stage progressed; with stage 5 CKD associated with a much lower relative risk (OR, 2.31 and 8.02 for serum potassium ≥5.5 and <6.0 and ≥6.0 meq/L, respectively). Patients with ESRD in the study by Nakhoul *et al.*[46] also seemed to be protected with hyperkalemia relative to the entire cohort (adjusted HR for death, 1.20; 95% CI, 0.91 to 1.58 versus 1.65; 95% CI, 1.48 to 1.84, respectively). Furthermore, An *et al.*[31] showed a graded decrease in risk of death among patients with extreme levels of hyperkalemia (>6.5 meq/L) as CKD stage increased (OR for death with stage 2, 3, 4, and 5 CKD, 0.52; 95% CI, 0.35 to 0.78, 0.31; 95% CI, 0.21 to 0.46, 0.13; 95% CI, 0.06 to 0.26, and 0.17; 95% CI, 0.11 to 0.27). Similar results were observed among dialysis versus non-CKD patients with hyperkalemia and AMI in the studies performed by Goyal *et al.*[37] and Grodzinsky *et al.*[38] One prospective observational analysis of sustained hyperkalemia and outcomes in patients with creatinine clearance <50 ml/min demonstrated that hyperkalemia in the ranges of 5.0–6.0 meq/L (using an average of six measurements per patient) appeared to be well tolerated.[47]

Adaptive increases in circulating catecholamines, aldosterone, and augmentation of renal and gastrointestinal (GI) potassium elimination are thought to blunt hyperkalemia development in CKD and could partially explain this apparent disconnect in mortality relative to non-CKD patients.[48–53] However, physiologic adaptation incompletely explains why mortality risk could be diminished once hyperkalemia has already been established. Furthermore, patients with CKD might be uniquely predisposed to more not less toxicity with hyperkalemia due to a higher prevalence of metabolic derangements (*e.g.*, hypocalcemia, acidosis, and elevated uremic solutes) and structural heart disease. Left ventricular hypertrophy,[54,55] atrial fibrillation,[56,57] heart rate variability,[58] heart failure,[59] silent myocardial infarction,[60] QT abnormalities,[61] and pulmonary hypertension[62,63] are all highly prevalent in the CKD population and could lower arrhythmogenic potential with concurrent hyperkalemia. All of these factors could be further compounded by changes in individual solutes, rapid osmolar shifts, high ultrafiltration rates, and myocardial stunning during dialysis treatments. Thus, persons with CKD might be uniquely predisposed or uniquely protected from cardiotoxicity with hyperkalemia relative to other populations, and further studies should be performed with these apparent inconsistencies in mind.

Hyperkalemia with Selected Medication Exposure

Hyperkalemia that develops while exposed to certain medications could alter the threshold of cardiac toxicity. Cases of digoxin poisoning have illustrated quite dramatic rises in serum potassium with associated arrhythmias.[64] In the studies performed by Khanagavi *et al.*[33] and McMahon *et al.*[32], but not An *et al.*,[31] potassium supplementation with hyperkalemia was linked to heightened mortality. With regard to the risks of hyperkalemia while exposed to RAAS inhibitors and β-adrenergic blockers, patients in the study by An *et al.*[31] had lower observed mortality. Conversely, critically ill patients in the study by McMahon *et al.*[32] were not afforded similar protection with either agent. Unfortunately, there is no data on patient mortality stratified by exposure versus nonexposure to RAAS inhibitors and β blockers in the studies performed by Goyal *et al.*,[37] Grodzinsky *et al.*,[38] and Krogager *et al.*[39] Patients with higher mortality in these studies were less likely to be exposed to either agent. Other data indicate that RAAS inhibitor use is linked with more profound hyperkalemia and death in the elderly[65] and in patients with diabetic versus nondiabetic CKD.[66] In the randomized controlled Hypertension in Hemodialysis Patients Treated with Atenolol or Lisinopril trial,[67] lisinopril predisposed patients on dialysis to more hyperkalemia and higher cardiovascular morbidity than atenolol; although, the lack of a control group is a limitation to further generalizations that can be made from this study.

There is conflicting data regarding the outcome of patients with hyperkalemia exposed to MRAs. *Post hoc* data[68] from the Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) trial indicates that eplerenone maintains a mortality benefit in patients with CKD and eGFR<60 ml/min per 1.73 m^2 while simultaneously predisposing these patients to higher rates of hyperkalemia. Unfortunately, patients with more advanced CKD (serum creatinine >2.5 mg/dl) were excluded from both the original EPHESUS trial[69] and the earlier Randomized Aldactone Evaluation Study.[70] It is important to note that no hyperkalemia-associated deaths were reported in either of these trials. However, in an analysis of the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure, patients with serum potassium levels >5.5 meq/L had a higher risk of all-cause mortality.[71] MRA exposure was also associated with more hyperkalemia (>5.0 meq/L) and higher mortality in a study of 15,803 United States veterans with established cardiovascular disease (OR for death, 1.50; 95% CI, 0.40 to 5.64).[72] Patients with eGFR<60 ml/min per 1.73 m^2 in this study had even worse outcomes while on MRAs (OR for death, 1.74; 95% CI, 1.11 to 2.71). Another recent study examining spironolactone use in 27,213 predialysis patients in Taiwan demonstrated that exposure was independently associated with increases in hospitalizations for heart failure (adjusted HR, 1.35; 95% CI, 1.08 to 1.67), infection-related deaths (adjusted HR, 1.42; 95% CI, 1.16 to 1.73), and all-cause mortality (adjusted HR, 1.35; 95% CI, 1.24 to 1.46).[73]

Implications of Data Supporting an Association between Hyperkalemia and Mortality

To date, the published studies demonstrating an association of mortality with hyperkalemia are largely limited to retrospective analyses that do not provide evidence of causation. Much of the

published data are also cross-sectional in nature, potentially raising more questions than answers. Furthermore, there are sparse data to suggest that treatment of hyperkalemia modifies risk. In the study of critically ill patients by McMahon *et al.*,[32] the risk of mortality with hyperkalemia was attenuated in patients achieving a >1.0 meq/L decrease in serum potassium within 48 hours; although, it is unclear if this represented an actual treatment effect. Other studies suggesting that longer durations and failure to reverse hyperkalemia are associated with mortality suffer from similar limitations. Of note, An *et al.*[31] attempted to control for the effect of treatment by giving individual therapies a weighted score which was plotted against patient survival. Although increasing number of targeted interventions for hyperkalemia was associated with improved patient survival, there was no control for other treatments that were directed at reversing the underlying illness. It is interesting to note that when hemodialysis or continuous renal replacement therapy were included as treatments for hyperkalemia in this study, the improvement in patient mortality was eliminated. Extracorporeal elimination of potassium is the most efficient and definitive therapy for life-threatening hyperkalemia. Therefore, it is surprising that these therapies were not associated with improvement in mortality whereas others (withdraw of offending medicines, intravenous calcium, insulin/dextrose, *etc.*) were, especially if hyperkalemia is presumed to be the proximate cause of mortality.

Abrupt incidence and more rapid velocity of hyperkalemia are salient features in studies such as those performed by An *et al.*,[31] Goyal *et al.*,[37] and Grodzinsky *et al.*[38] More rapid development of hyperkalemia is potentially more cardiotoxic, and directed treatment might have more protective effects in this population compared with others. Nevertheless, we can find only one published attempt at protocolizing treatment of patients who develop hyperkalemia while hospitalized.[16] This study demonstrated no significant changes in patient outcome with prescribed protocols, although clinician adherence was low. We conclude that prospectively designed randomized trials of treatment for hyperkalemia should be performed with valid endpoints (*e.g.*, target potassium levels) and outcome measures (*e.g.*, mortality, arrhythmia, and health care utilization) in mind. A well designed trial using accepted therapies to lower serum potassium in noncritically ill monitored hospitalized patients with hyperkalemia would be the safest initial study to perform. Presently, we will review the common treatments for hyperkalemia and the potential pitfalls in using these agents.

Treatment of Hyperkalemia

Many reviews have been published on this topic and we will only briefly highlight these strategies. Acute treatment of life-threatening hyperkalemia necessitates infusion of intravenous calcium to protect against malignant cardiac hyperexcitability followed by agents which have been proven in humans to rapidly and effectively shift potassium into the intracellular space. Insulin appears the most well studied treatment in this regard and its rapid action to shift potassium is not dependent on receptor-ligand signaling and downstream protein synthesis. Unlike β-adrenergic agonist and bicarbonate therapy, insulin does not lose its efficacy, and might be enhanced, in the presence of renal failure.[49] Intravenous dextrose is usually given to prevent hypoglycemia and further stimulates endogenous insulin production. Studies suggest that oral glucose loading may also be an effective strategy to increase insulin and reduce serum potassium in patients on hemodialysis.[74] There is conflicting data regarding the efficacy of β-adrenergic agonists and sodium bicarbonate to reliably shift potassium; however, we observe that these agents are often used in the acute management of hyperkalemia. Ultimately, acute hemodialysis may be necessary for the extracorporeal elimination of potassium in life-threatening situations.

Diuretics are often underappreciated as an effective treatment of hyperkalemia owing to misconceptions regarding the efficacy of these drugs in patients with lower renal function. Indeed, absence of diuretic usage is associated with the development of hyperkalemia in at-risk patients.[47] Patients with CKD and patients who experience diuretic braking, in which response to a diuretic becomes blunted over time, are known to need higher diuretic doses, diuretic rotation, or combination diuretics to maintain a therapeutic effect.[75] Therapies directed at augmenting GI potassium excretion have been in use for many years, principally with sodium polystyrene sulfate (SPS). Generally, SPS has been shown to be unreliable in the acute setting although data on chronic management might support its use.[76] Newer agents, such as sodium zirconium cyclosilicate (ZS-9; AstraZeneca) and the recently Food and Drug Administration (FDA)–approved patiromer (Veltassa; Relypsa), have been demonstrated to effectively lower serum potassium when administered in patients with chronic hyperkalemia at levels <6.5 meq/L.[77–80] Furthermore, serum potassium may be rapidly lowered within hours by both ZS-9[79] and patiromer,[81] suggesting a previously unrecognized role of the upper GI tract in potassium regulation.

Correction of hypoaldosteronism by mineralocorticoid administration may be an effective therapy to reverse hyperkalemia. Data indicate that urinary losses of potassium only partially explain the treatment effect, suggesting a role for enhanced intracellular redistribution or augmented GI excretion.[82,83] This therapy has enjoyed some recent resurgence, with several reports demonstrating successful treatment of hyperkalemia due to a range of causes.[84–86] However, small randomized placebo-controlled trials using oral fludrocortisone in patients on hemodialysis with hyperkalemia have demonstrated poor efficacy[87] or modest efficacy[88] at lowering serum potassium. It is important to note that the doses used in these trials were relatively low (0.1 mg fludrocortisone daily), and older data indicate that patients with renal disease require much higher doses (up to 1.0 mg daily) to effectively reverse hyperkalemia.[82]

Perhaps the most underused of all therapies to combat hyperkalemia involves reduction of dietary potassium intake. Careful screening of the diet for potassium-rich foods is not often performed due to time-crunched clinician visits and poor dietary education given to health care providers. A careful review of potassium intake and directed counseling might prevent incident hyperkalemia and serve as an important adjunct with other therapies in the treatment of hyperkalemia. However, we can find no human data that dietary counseling is an effective strategy in the prevention or treatment of hyperkalemia. Data on the effectiveness of dietary potassium reduction in hyperkalemic individuals with advanced CKD (who often have relatively fixed levels of urinary and GI potassium excretion) is particularly needed.

Adverse Events Linked to Potassium-Lowering Therapies

Clinicians employ these therapies to patients with hyperkalemia, but to what target level? And at what cost to the patient and the health care system? It is important to highlight that many of the treatments used in management of hyperkalemia may have untoward or even unrecognized side effects. Acute infusions of elemental calcium can induce heart block in patients with digoxin-induced hyperkalemia[89] and precipitate acute dermal calcifications.[90,91] Given the higher prevalence of hyperphosphatemia in patients with CKD, intravenous calcium infusion carries the theoretic risk of creating or worsening existing metastatic vascular calcifications.

Hypoglycemia and tachycardia can accompany insulin and albuterol administration, respectively. Large intravenous infusions of sodium bicarbonate may precipitate acute hyperosmolarity,[92] including case reports of central pontine myelinolysis.[93] Sodium bicarbonate infusions also risk development of acute pulmonary edema,[94] ionized hypocalcemia,[94,95] and worsening of AKI and mortality in patients undergoing cardiac surgery.[96]

Diuretics can induce volume contraction, dysnatremias, hypomagnesemia, nephrolithiasis, and gout flares. SPS has been linked with numerous cases of intestinal necrosis,[97–99] which has given this drug a warning label by the FDA and limited its modern appeal. Newer potassium exchange resins are not without potential side effects and have been shown to induce hypomagnesemia,[78] hypercalciuria,[100] and even edema[80] at high doses. Long-term effects from these drugs are unknown and neither of these newer agents have been shown to be efficacious in patients on dialysis. Exogenous mineralocorticoids are not commonly used for hyperkalemia given concerns for precipitating volume overload and significant cardiopulmonary complications.[82]

Central line insertion for acute dialysis access can predispose to a host of periprocedural complications and trauma to the central veins that vitally feed future dialysis access creation. Very low potassium–containing dialysate solutions (<2.0 meq/L) are sometimes employed for severe cases of hyperkalemia but the consequences of achieving a rapid (within minutes) reduction in extracellular potassium concentration are unknown. Data suggest that lower potassium–containing dialysates are associated with significant morbidity and mortality[101–103]; which has largely led to abandoning this practice. Finally, unnecessary hospitalizations and clinician hypervigilance may predispose an already frail patient population to a cascade of unpredictable iatrogenic effects.

WHO IS MOST LIKELY TO BENEFIT FROM THE CORRECTION OF HYPERKALEMIA AND HOW TO ACHIEVE IT? AN OPINION-BASED SET OF RECOMMENDATIONS

Despite decades of knowledge regarding the potential risks of hyperkalemia, the high incidence and prevalence of hyperkalemia in patients with certain comorbidities and medication exposures, and the availability of effective potassium-lowering therapies, there are no guidelines to advise who should be treated. Neither the Kidney Disease: Improving Global Outcomes nor the Kidney Disease Outcomes Quality Initiative have published guidelines in the treatment of hyperkalemia. The Investigator Network Initiative Cardiovascular and Renal Clinical Trialists recently published guidelines[104] on workup of hyperkalemia and treatment strategies in patients with serum potassium >5.1 meq/L, but doesn't stipulate exactly who should be treated.

On the basis of the published data demonstrating disparate risks of hyperkalemia in different patient populations, the safety profile and reliability of agents to reduce serum potassium, and our own experience, we propose a step-wise strategy for the prevention and treatment of hyperkalemia in the following sections which is applicable in a range of clinical settings. We propose treatment on the basis of clinical presentation of the patient rather than degree of hyperkalemia, which poorly predicts cardiotoxicity in humans. Although we support a threshold for initiating therapy in certain patients, we do not support that any upper limit of hyperkalemia constitutes an "emergency" on the basis of the serum potassium concentration alone. Furthermore, we do not recommend guiding therapies on the basis of ECG findings given their inherent variability. We have found that relying on the ECG without extensive knowledge of the patient's prior cardiac history, velocity of hyperkalemia development, and baseline ECG (all are almost never present) can distract from addressing the underlying cause and interfere with appropriate targeted therapy.

Prevention and Supportive Treatment of Hyperkalemia

To reduce the incidence of hyperkalemia, at risk patients, as defined in Table 1, should be identified and managed in an anticipatory fashion, with dietary modifications, avoidance of medications which might worsen risk for hyperkalemia, and surveillance for common clinical scenarios that create additive risk. We advise all patients with existing hyperkalemia (>5.0 meq/L) to reduce potassium intake to <40 meq/d. Similar

Table 2. Strategies to urgently treat hyperkalemia

Steps	Clinical Question	Strategy
1. Increase urinary potassium losses	Is the patient volume contracted or euvolemic?	Yes, administer trial of volume expansion with or without loop diuretic
	Is the patient volume overloaded or hypertensive? a. eGFR>60 ml/min per 1.73 m^2 and diuretic-naïve b. eGFR<60 ml/min per 1.73 m^2 and diuretic-naïve c. currently taking diuretics	Yes, stratify and treat: Start low dose loop or thiazide-like diuretic Start moderate dose loop diuretic Double existing diuretic dose and/or add loop diuretic, thiazide-like diuretic, or carbonic anhydrase inhibitor
2. Increase gastrointestinal potassium elimination	Does the patient have a contraindication (recent abdominal surgery, ileus, obstipation, history of ischemic bowel) to cathartics?	No, consider a limited trial of patiromer, ZS-9, or SPS
3. Mineralocorticoid replacement	Does the patient have a contraindication (greater than stage 1 HTN, volume overload, history of heart failure) to mineralocorticoid administration?	No, consider a trial of fludrocortisone 0.1 mg daily × 3–5 d (In patients with moderately advanced CKD consider maintaining or increasing diuretics in tandem)
4. Dialysis optimization or initiation	Is the patient currently on maintenance dialysis?	Yes, optimize dialysis delivery: Assess delivered dialysis dose, duration, and frequency Screen for patient noncompliance with dialysis and patient/caregiver burnout Address any access dysfunction including poor blood flows, recirculation Assess dialysate K^+ and $HCO3^-$ concentrations No, revisit steps 1–3 and consider hospitalization and urgent dialysis initiation if hyperkalemia persists

SPS, sodium polystyrene sulfate; HTN, hypertension.

dietary reductions are advised in patients with eGFR<30 ml/min per 1.73 m^2 and in patients with eGFR>30 ml/min per 1.73 m^2 but prone to hyperkalemia. In at-risk patients with high-to-normal levels of serum potassium (4.5–5.0 meq/L), proactive dietary screening is advised to identify and mitigate large potassium loads. We readily admit these dietary recommendations are not based on evidence supporting efficacy, and they could have the adverse effect of steering patients with CKD away from more nutrient-rich foods.

Providers should seek to limit or abstain from exposing higher-risk patients to medications listed in Table 1. In cases where avoidance of these agents is not possible, close monitoring and frequent laboratory checks are advised. The data on avoidance of β-adrenergic blockers in patients prone to hyperkalemia is controversial, because β blocker usage is one of the few established therapies in CKD and non-CKD patients which is associated with lower risk of cardiovascular events. Our own practice, depending on the degree of hyperkalemia and clinical presentation, is to maintain these drugs unless other supportive measures fail to correct the hyperkalemia.

We advise cautious administration of higher RAAS inhibitor doses and MRAs in patients with diabetic CKD, advanced CKD, and those with a prior history of hyperkalemia. Combination RAAS inhibitor regimens should be avoided because these therapies place patients at special risk for hyperkalemia without proven benefit. Hyperkalemia which develops on a diuretic should prompt an investigation for factors which might cause diuretic braking and limit distal nephron sodium delivery, and thus potassium secretion.

Hyperkalemia out of proportion to changes in eGFR should prompt a rigorous investigation for urinary obstruction, insulinopenia, acidosis, and disorders which predispose to hypoladosteronism, such as adrenal insufficiency. Patients with advanced CKD, including those on dialysis, who newly develop hyperkalemia should be evaluated for new constipation or bowel obstruction. In hospitalized patients, the clinician should be attentive to the risk of incident hyperkalemia with blood product administration, sepsis, multiorgan failure, myonecrosis, and rewarming of a cooled patient. Patients on dialysis should have access interventions and other operations scheduled away from long dialytic intervals to minimize the periprocedural risk of hyperkalemia. Furthermore, monitoring postprocedural serum potassium in patients on dialysis with higher prevalent hyperkalemia is advised.

Emergency Treatment of Hyperkalemia

A "Hyperkalemia Emergency," which we define as a serum potassium >6.0 meq/L or a sudden increase in serum potassium 1.0 meq/L above 4.5 meq/L within 24 hours associated with cardiopulmonary arrest, evolving critical illness, AMI, or signs and symptoms of neuromuscular weakness, should be treated with agents that rapidly and reliably shift serum potassium into the intracellular space while preparations are made for elimination of total body potassium (TBK^+). Infusion of intravenous calcium, insulin, and

dextrose, and lastly inhaled or intravenous β-adrenergic agonist therapy should be administered only in these extreme circumstances. Consideration for sodium bicarbonate administration should be given in cases of hyperkalemia accompanying severe metabolic acidosis. Arrangements for emergent hemodialysis should be made early and proactively unless a rapidly reversible cause is identified and therapy is expedited. Our practice might require instituting hemodialysis in patients who might otherwise recover from hyperkalemia with directed treatment, yet in this demographic the failure to rapidly stabilize or reverse hyperkalemia might have fatal consequences.

Urgent Treatment for Hyperkalemia

We propose a more guarded strategy to treat hyperkalemia in less dire circumstances, which constitutes the majority of hyperkalemia cases in practice. In patients with hyperkalemia, but outside extremis, we propose adopting a four-step system aimed at maximizing elimination of TBK^+ in a prompt but safe manner: (*1*) Increase urinary potassium clearance, (*2*) augment potassium excretion through the GI tract, (*3*) administer exogenous mineralocorticoids in selected patients, and (*4*) initiate dialysis or optimize dialysis delivery (Table 2). We propose executing this strategy in patients with normal renal function with serum potassium >5.0 meq/L, patients with non-ESRD CKD and serum potassium >5.5 meq/L, and patients with ESRD on maintenance dialysis and serum potassium >6.0 meq/L who have failed supportive measures to reverse the hyperkalemia (or are deemed more at risk to fail with supportive measures alone). Utilizing one of these strategies along with supportive measures should be sufficient to reverse most cases of hyperkalemia; although, several strategies in combination can be used to maximize efficacy in patients with suspicion of multifactorial hyperkalemia.

The goals of this treatment strategy are to stabilize and gradually reduce serum potassium in low-risk patients, and more rapidly reduce serum potassium in higher-risk patients without the need to employ intravenous calcium, insulin, dextrose, β-adrenergic agonists, and bicarbonate that have little use outside emergencies and are wholly ineffective at removing TBK^+. The inclusion of mineralocorticoid administration is likely a controversial position. In our own practice, we have observed that this strategy is safe and very effective in a time-limited fashion in appropriately selected patients. Although we include dialysis initiation in cases of refractory hyperkalemia, outside patients with oligoanuric renal failure and critical illness we have found there are very few circumstances that will require the initiation of dialysis for hyperkalemia alone. We propose that a close follow-up plan should be implemented for every patient with hyperkalemia, particularly in the outpatient setting. Adopting this strategy might potentially spare patients from unnecessary emergency department visits and hospitalizations. Furthermore, employing a strategy such as this might better integrate knowledge of potassium homeostasis by the treating clinician and steer both low- and higher-risk patients with hyperkalemia into appropriate, effective, and safe treatment plans.

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