HYPERKALEMIA: ADVANCING CARE IN THE EMERGENCY DEPARTMENT AND INTENSIVE CARE UNIT

PROCEEDINGS MONOGRAPH FROM THE EMCREG-INTERNATIONAL MULTIDISCIPLINARY HYPERKALEMIA CONSENSUS PANEL NOVEMBER 17, 2018




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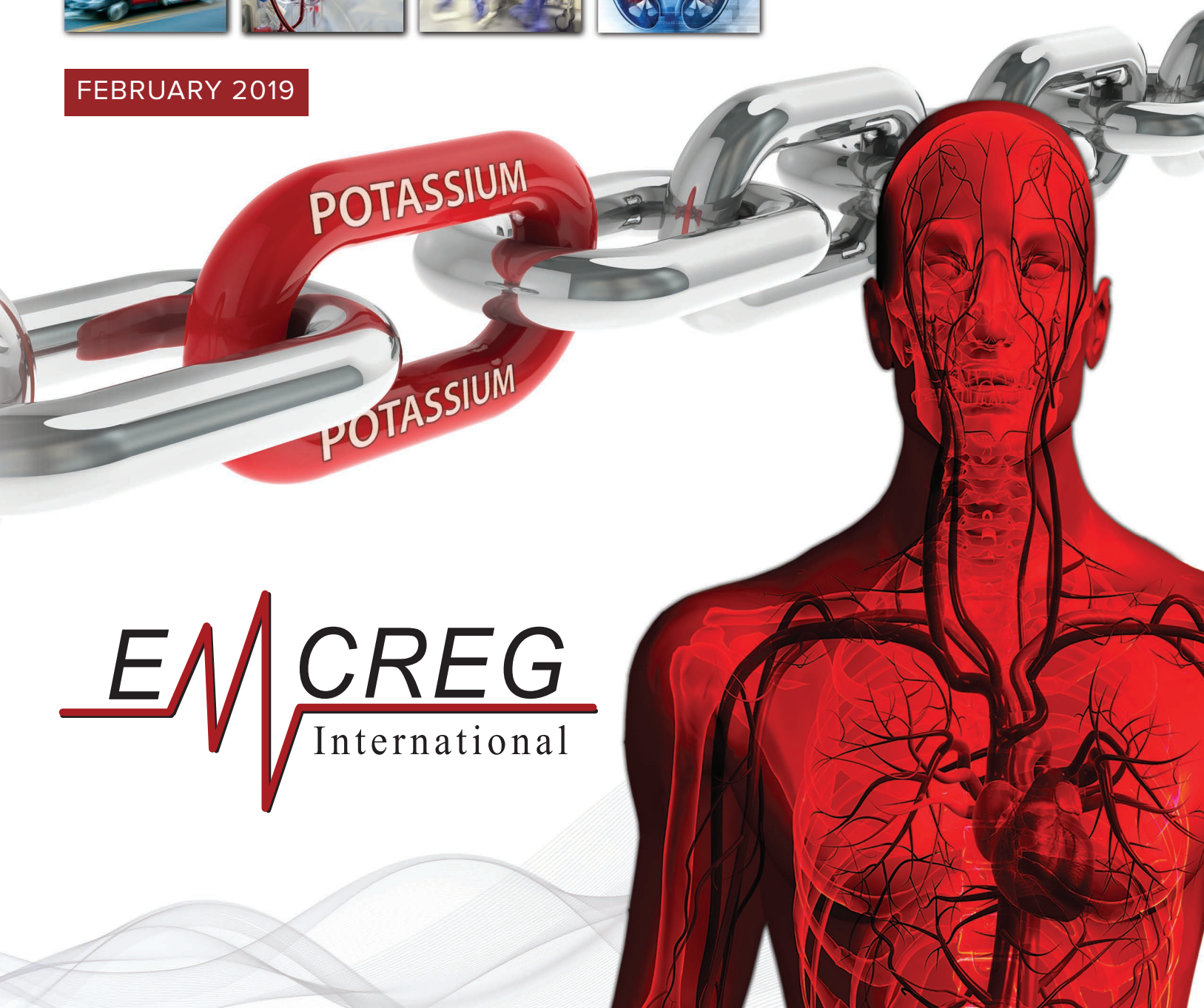

EMCREG International

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Proceedings Monograph from the
EMCREG-International Multidisciplinary HYPERKALEMIA CONSENSUS PANEL
November 17, 2018

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Dear Colleagues, FEBRUARY 2019

In this February 2019 EMCREG-International Proceedings Monograph from the November 17, 2018 EMCREG-International Multidisciplinary Consensus Panel on Hyperkalemia held in Orlando, Florida, you will find a detailed discussion regarding the treatment and disposition of patients with hyperkalemia. For emergency physicians, critical care physicians, hospitalists, and cardiologists, the current approach to hyperkalemia in the Emergency Department or Intensive Care Unit has remained essentially unchanged over the last several decades. Patients with hyperkalemia have a potentially life-threatening condition which must be rapidly addressed and effectively treated by the acute care physician. In the Emergency Department, the emergency physician typically administers treatment for patients with hyperkalemia designed to shift extracellular potassium ions into the intracellular compartment, resulting in effective, albeit transient, improvement in electrocardiographic findings as well neurologic symptoms. If the serum potassium level is significantly elevated, electrocardiographic dysrhythmias are present, or renal function is compromised through acute kidney injury or chronic kidney disease, potassium can be eliminated rapidly from the body by hemodialysis. While very effective in treating hyperkalemia, it is often difficult for hemodialysis to be arranged off hours even in major tertiary care medical centers. New FDA approved oral therapies such as sodium zirconium cyclosilicate and patiromer, two cation exchange compounds, use the gastrointestinal tract to eliminate potassium ions from the body providing acute care physicians an additional treatment option.

This EMCREG-International Proceedings Monograph contains multiple sections reflecting critical input from experts in Emergency Cardiovascular and Neurovascular Care, Prehospital Emergency Medical Services, Emergency Medicine Operations, Nephrology, Hospital Medicine, Neurocritical Care, Cardiology, Medical Critical Care, and Trauma and Surgical Critical Care discussing the treatment of hyperkalemia in an approach we hope the reader will find extremely practical and clinically useful. These expert specialists will describe the implications of managing hyperkalemia in their field with patients in the Emergency Department, Critical Care Units, and the Cardiology Clinic. Finally, an EMCREG-International Hyperkalemia Consensus Panel algorithm for the approach to management of patients with life-threatening hyperkalemia is provided for the clinician and can be expanded in size for use in a treatment area such as the Emergency Department or Critical Care Unit.

For background, the Emergency Medicine Cardiac Research and Education Group (EMCREG)-International was established in 1989 as an emergency medicine cardiovascular and neurovascular organization led by experts from the United States, Canada, and across the globe. We now have Steering Committee members from the US, Canada, Australia, Belgium, Brazil, France, Netherlands, New Zealand, Japan, Singapore, Sweden, and the United Kingdom. Now in our 30th anniversary year, we remain committed to providing you with the best educational programs and enduring material pieces possible. In addition to our usual Emergency Physician audience, we now reach out to our colleagues in Cardiology, Internal Medicine, Family Medicine, Hospital Medicine, and Critical Care with our EMCREG-International University of Cincinnati College of Medicine Office of Continuing Medical Education (CME) accredited symposia and enduring materials.

Finally, through this EMCREG-International Multidisciplinary Hyperkalemia Consensus Panel Proceedings Monograph, clinicians can receive state of the art information which can significantly impact the care of their patients. It is our sincere hope that you will find this enduring material educational piece on the care of patients with hyperkalemia useful to you in your daily practice as an emergency physician, intensive care physician, hospitalist, cardiologist, internist, and family physician. Instructions for obtaining CME credit from the University of Cincinnati College of Medicine Office of Continuing Medical Education are available at the conclusion of this February 2019 EMCREG-International Multidisciplinary Hyperkalemia Consensus Panel Proceedings Monograph. We hope you visit our website (www.emcreg.org) to see the full complement of EMCREG-International capabilities, to download previous educational monographs and complete CME tests for credit, and to obtain information regarding future educational events and publications. Thank you very much for your interest in EMCREG-International educational initiatives.

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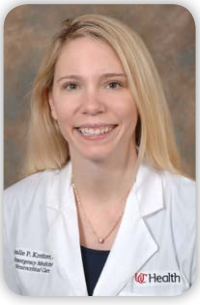

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LEARNING OBJECTIVES

1. Discuss normal renal potassium handling and the adaptations that serve to maintain potassium homeostasis in patients with chronic kidney disease.
2. Describe the relationship between guideline-directed medical therapies for heart failure, including renin-angiotensin-aldosterone system inhibitors, mineralocorticoid receptor antagonists and beta blockers, and hyperkalemia.
3. Describe the clinical manifestations and electrocardiographic changes that may be associated with hyperkalemia.
4. List the existing treatments for hyperkalemia and describe the gaps in current therapy.
5. Describe the unique challenges associated with treatment of hyperkalemia in the prehospital setting.
6. Discuss the issues that surround emergent dialysis of patients with hyperkalemia in the emergency department (ED), including indications, catheter placement, and complications.
7. Identify the types of delays encountered in the ED setting that impact treatment of patients with potentially life-threatening hyperkalemia.
8. Describe the major determinants of potassium removal with hemodialysis.
9. Describe the advantages of sodium zirconium cyclosilicate compared to sodium polystyrene sulfonate and patiromer as a means of potassium excretion for acute medical critical care conditions.
10. List the particular issues of hyperkalemia in neurocritical patients, including the risk of cerebral edema with dialysis and special concerns with targeted temperature management and succinylcholine and mannitol administration.
11. Define a step-wise approach to treating hyperkalemic urgency and emergency in acute care and critical care settings.
12. Define the surgical and neurocritical patient populations at greatest risk for hyperkalemia and determine appropriate therapy for their management.
13. Discuss the discharge criteria and continuum of care for patients with hyperkalemia.

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INTRODUCTION

Hyperkalemia is a potentially life-threatening electrolyte abnormality that is frequently encountered in the acute care setting. In this monograph, the mechanisms of development of hyperkalemia are reviewed, particularly as they pertain to patients with acute kidney injury (AKI), chronic kidney disease (CKD), and heart failure. Strategies for management of the patient with hyperkalemia are discussed, from cardiac stabilization and shifting potassium into the cells to removal of potassium from the body. The development of new pharmacologic agents has facilitated the ability to eliminate potassium through the gastrointestinal (GI) tract. Reliable GI excretion of potassium has the potential to reduce hyperkalemic events in susceptible patients, avoid cardiovascular complications, obviate or delay the need for dialysis in some critically ill patients, and improve clinical outcomes. The currently available GI agents are discussed along with other temporizing and elimination strategies for the treatment of hyperkalemia, with particular focus on the challenges faced in the emergency department (ED) and inpatient critical care.

MECHANISMS OF DEVELOPMENT OF HYPERKALEMIA

Hyperkalemia is typically defined as a serum potassium concentration of >5.0 or >5.5 mEq/L, with the upper limit of normal varying across guidelines and publications. It is relatively uncommon to find hyperkalemia in individuals with normal renal function; however, in patients with CKD, the incidence ranges from 5% to 50%.[1] Although loss of kidney function is the single most important cause of hyperkalemia, in clinical practice this electrolyte disorder is usually the result of a combination of factors that limit renal potassium (K^+) excretion superimposed on renal dysfunction (Table 1). Such is the case in diabetics, in whom decreased mineralocorticoid activity is often an early finding due to hyporeninemic hypoaldosteronism, or in advanced stages of heart failure with accompanying reductions in distal delivery of sodium (Na^+) combined with concurrent use of drugs that interfere with the renin-angiotensin-aldosterone system (RAAS). In these settings, hyperkalemia is common and can develop with only mild or moderate reductions in the glomerular filtration rate (GFR); see Table 2.

TABLE 01 Causes of Hyperkalemia

- **Pseudohyperkalemia**
- **Cellular redistribution**
  - Metabolic acidosis
  - Cell shrinkage (hypertonicity)
  - Deficiency of insulin
  - Beta blockers
  - Hyperkalemic periodic paralysis
  - Cell injury
- **Excess intake (very rare)**
  - Potassium supplementation
- **Decreased renal excretion**
  - Decreased distal delivery of sodium (oliguric renal failure)
  - Mineralocorticoid deficiency
  - Defect of cortical collecting tubule
  - Renin-angiotensin-aldosterone system blockade

TABLE 02 Risk Factors for Hyperkalemia

- Chronic kidney disease: risk is inversely related to glomerular filtration rate and increases substantially below an estimated GFR of 30 ml/min/1.73 m^2
- Diabetes mellitus*
- Decompensated congestive heart failure
- Medications:
  - Inhibition of renin release from juxtaglomerular cells
    - Non-steroidal anti-inflammatory drugs
    - Beta blockers
    - Calcineurin inhibitors: cyclosporine, tacrolimus
  - Inhibition of aldosterone release from the adrenal gland
    - Heparin
    - Ketoconazole
  - Mineralocorticoid receptor blockade
    - Spironolactone
    - Eplerenone
  - Blockade of epithelial sodium channel blocker in the renal collecting duct
    - Amiloride
    - Triamterene
    - Trimethoprim
- Potassium supplements, salt substitutes, certain herbs, and potassium enriched foods in the setting of impaired renal excretion

*A spectrum of abnormalities in the renin-angiotensin-aldosterone system have been described in patients with diabetes mellitus to include hyporeninemic hypoaldosteronism as well as normal renin release but a diminished capacity to release aldosterone. Hypoaldosteronism combined with dysfunction of collecting ducts due to diabetic nephropathy and treatment with ACEI or ARB's make these patients at particularly high risk for hyperkalemia.

Normal Renal Potassium Handling

The normal kidney has a large capacity to excrete potassium. Accumulation of potassium in the interstitium following increased intake exerts an inhibitory effect on the thick ascending limb and, to a lesser extent, proximal tubular sodium chloride (NaCl) reabsorption, which results in increased flow and sodium delivery to the distal nephron.[2] High potassium intake modulates flow and sodium delivery through direct effects in the distal convoluted tubule (DCT1). Elevations in plasma potassium are registered by cells in the initial portion of the DCT1, which leads to decreased activity of the thiazide-sensitive Na^+-Cl^- co-transporter.[3] In consequence, flow and sodium are delivered increasingly to the adjacent aldosterone-sensitive distal nephron (DCT2 and collecting duct) where electrogenic and flow-mediated potassium secretion is enhanced. A gastric-kidney reflex also provides an inhibitory effect on the Na^+-Cl^- co-transporter and is initiated when potassium enters the stomach. Lastly, a circadian rhythm facilitates potassium secretion during the day when potassium intake is highest. These mechanisms, which underlie the prodigious capacity of the normal kidney to excrete potassium, evolved in response to the diet of prehistoric man that contained a four-fold higher potassium content. High potassium intake has health benefits, suggesting the evolutionary design of the kidney was to maintain potassium homeostasis in the setting of high potassium intake.[4]

Potassium Homeostasis in Acute Kidney Injury

A number of characteristic features of AKI make hyperkalemia particularly common. When the cause is acute tubular necrosis or tubulointerstitial renal disease, widespread injury to the late distal tubule and collecting duct often occurs and leads to direct injury of the cells responsible for potassium secretion. Often AKI is associated with severe reductions in the GFR (<10 ml/min) that become rate limiting for potassium secretion. The rapidity of renal function loss precludes sufficient time for normal renal and extrarenal adaptive mechanisms to adequately develop. In patients with more severe injury manifested clinically by oligo-anuria, there is a marked reduction in distal delivery of salt and water which contributes to decreased distal potassium secretion. In non-oliguric acute kidney injury, hyperkalemia tends to be less common since distal delivery of salt and water is plentiful. Patients with AKI are more likely to have severe acidosis, increased catabolism, and tissue breakdown, all leading to release of intracellular potassium into the extracellular compartment. This release of potassium in the setting of impaired renal potassium secretion makes life-threatening hyperkalemia a common occurrence in patients with AKI.

Potassium Homeostasis in Chronic Kidney Disease

Chronic kidney disease is more complicated than AKI. In addition to the decreased GFR and secondary decrease in distal delivery, there is nephron dropout and a smaller number of collecting ducts to secrete potassium. This is counterbalanced by an adaptive process in which the remaining nephrons develop an increased ability to excrete potassium. As a result, hyperkalemia (potassium >5.5 mEq/L) is uncommon in patients with chronic kidney disease until the GFR falls below 15-20 ml/min.

The nature of the adaptive process that facilitates potassium excretion in patients with CKD is thought to be similar to the adaptive process that occurs in response to high dietary potassium intake in normal subjects.[5,6] Chronic potassium loading in animals augments the secretory capacity of the distal nephron so that renal potassium excretion is significantly increased for any given plasma potassium level. Increased potassium secretion under these conditions occurs in association with structural changes characterized by cellular hypertrophy, increased mitochondrial density, and proliferation of the basolateral membrane in cells in the distal nephron and principal cells of the collecting duct. Increased serum potassium and mineralocorticoids independently initiate the amplification process, which is accompanied by an increase in Na^+-K^+-ATPase activity.

With advancing CKD, a significant proportion of daily potassium excretion occurs via the GI tract. The GI losses are important in maintaining potassium balance in chronic dialysis patients because hemodialysis removes approximately 80-100 mEq/treatment (300 mEq/week), yet dietary potassium intake is usually 400–500 mEq/week.[7] Data are consistent with increased expression of colonic potassium channels as the mechanism for the adaptive increase in potassium secretion in patients with end-stage

renal disease (ESRD). Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) have both been reported to cause hyperkalemia in patients treated with hemodialysis and peritoneal dialysis.[8] The development of hyperkalemia with these drugs may be due to decreased colonic potassium excretion resulting from lower circulating levels of aldosterone or decreased activity of angiotensin II.

Summary

Adaptive increases in renal and GI excretion of potassium help to prevent hyperkalemia in patients with CKD as long as the GFR remains >15-20 ml/min. Once the GFR falls below these values, the impact of factors known to adversely affect potassium homeostasis are significantly magnified. Impaired renal potassium excretion can be the result of conditions that severely limit distal sodium delivery, decreased mineralocorticoid levels or activity, or a distal tubular defect. In clinical practice, hyperkalemia is usually the result of a combination of factors superimposed on renal dysfunction.

HYPERKALEMIA ASSOCIATED WITH RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM INHIBITORS AND THE ROLE OF GASTROINTESTINAL POTASSIUM EXCRETION IN PATIENTS WITH HEART FAILURE

There are 6.5 million individuals with heart failure in the United States and tens of millions more worldwide.[9] Patients with heart failure are at substantially increased risk for conduction abnormalities, dysrhythmias, and mortality.[9] Heart failure patients, by virtue of their disease state, comorbid conditions, and use of guideline-directed medical therapies, are at increased risk for hyperkalemia.[10] Hyperkalemia can occur with relatively high frequency in patients with acute and chronic heart failure.[10] Elevation in potassium levels can affect the activity of myocardial potassium channels, resulting in more rapid membrane depolarization and slower myocardial electrical conduction. These changes can, in turn, increase the risk for both serious tachyarrhythmias and bradyarrhythmias. Potassium levels >5.5 mEq/L in patients with heart failure have been associated with increased risk of mortality in multiple studies.[10]

Patients with heart failure are at particularly high risk for developing hyperkalemia, which is in part reflective of their medical comorbidities, including diabetes mellitus and CKD.[10] In addition, guideline-directed medical therapies for heart failure contribute to the increased risk of hyperkalemia.[9,10] The cornerstones of guideline-directed medical therapies for heart failure with reduced ejection fraction that increase the risk of hyperkalemia include the following: 1) RAAS inhibitors, including ACEIs and ARBs with or without neprilysin inhibition (ARNI); 2) mineralocorticoid receptor antagonists (MRAs, spironolactone and eplerenone); and 3) beta blockers.[9] Renin elevation due to renal hypoperfusion in heart failure leads to the excretion of potassium by stimulating the synthesis of aldosterone, whereas ACEIs, ARBs, ARNIs, and MRAs decrease potassium excretion by limiting formation of aldosterone or blocking its effects on the kidney. These agents are associated with an increased risk of hyperkalemia, particularly when administered in combination. In addition, excess dietary intake of foods high in potassium or sodium supplements containing high potassium content can also contribute to hyperkalemia in patients with heart failure.[10]

As the use of guideline-directed medical therapy for heart failure has become more common, especially in combination, hyperkalemia in heart failure has also become more common.[10] The use of ACEI or ARB therapy has been associated with the development of hyperkalemia in a reported 10% to 38% of patients hospitalized with heart failure.[10] Hyperkalemia in outpatients with heart failure has been reported in up to 10% to 20% of patients receiving RAAS inhibitor therapy within one year of follow-up.[11-13] Heart failure patients with impaired renal function and those with diabetes are at even higher risk of hyperkalemia.[11,14] In the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure (PARADIGM-HF) trial, despite renal function and potassium-based eligibility criteria and a run-in period, it was reported that approximately 15% of patients in both the sacubitril/valsartan and the enalapril arms developed hyperkalemia over a median 27 months of follow-up.[12] In a study of 19,194 outpatients with heart failure, it was reported that 11.3% of patients had hyperkalemia (incidence of 2.90/100 person-years; 95% confidence interval [CI], 2.78 to 3.02) during a mean follow-up of 3.9 years.[13] In a large population-based cohort of 31,649 patients

with a new diagnosis of heart failure between 2000 and 2012, hyperkalemia with at least one potassium level > 5.0 mEq/L occurred in 39% of patients over a mean follow-up of 2.2 years.[14] After an index hyperkalemia event, close to half of the patients had a subsequent hyperkalemic event during follow-up. Heart failure patients with hyperkalemia were at an increased risk of re-hospitalization (6-month hazard ratio, 2.75; 95% CI, 2.65–2.85) and death (hazard ratio, 3.39; 95% CI, 3.19–3.61) when compared with matched heart failure patients without incident hyperkalemia. Prior analyses of clinical trials and population-based studies suggest that independent risk factors for the development of hyperkalemia in patients with heart failure include severity of renal dysfunction, type 2 diabetes mellitus, and use/dosing of ACEIs, ARBs, and MRAs.[10,11,14]

The increased risk of hyperkalemia in patients with heart failure has significant influence on the treatment of this disease state. Whether as a consequence of a real or perceived risk of hyperkalemia, multiple studies in the hospital and outpatient settings have demonstrated that guideline-directed medical therapies are underused, and when they are used, there is suboptimal dose titration to guideline-recommended target doses.[10,15] Hyperkalemia in patients with heart failure remains a major dilemma in clinical practice.[10]

The recent development of GI agents that can reliably reduce serum potassium levels may provide physicians with the opportunity to effectively titrate evidence-based therapies in patients with heart failure. Patiromer is a cation exchange polymer that exchanges calcium for potassium in the intestinal lumen. In patients with CKD and hyperkalemia who were receiving RAAS inhibitors, patiromer decreased serum potassium levels a mean of -1.01±0.03 mEq/L (P<0.001) after 3 days and reduced the recurrence of hyperkalemia as compared to placebo.[16] In a phase II study of patients with diabetes, CKD and hyperkalemia who were treated with RAAS inhibitors, patiromer significantly reduced potassium levels and demonstrated continued efficacy over a 52-week treatment period.[17] Significant reduction in serum potassium occurs by 7 hours after the first dose of patiromer, and there have been no serious adverse events noted with its use.[16-18]

Another cation exchange agent, sodium zirconium cyclosilicate (SZC), has also been developed as a treatment for hyperkalemia. In a large double-blind, placebo-controlled clinical trial, 753 patients with hyperkalemia (potassium levels 5.0-6.5 mEq/L), which included patients with heart failure, diabetes and CKD and patients receiving ACEIs, ARBs, or MRAs, were randomized to receive one of four doses of SZC (1.25 g, 2.5 g, 5 g or 10 g) or placebo, administered three times daily for the initial 48 hours (acute phase).[19] The primary endpoint of this study was the rate of change in serum potassium from baseline throughout the 48-hour acute phase. Results from the acute phase showed significant, rapid, and dose-dependent reductions in serum potassium at the 2.5 g, 5 g, and 10 g doses. The trial met the primary efficacy endpoint for the acute phase at the 2.5 g, 5 g, and 10 g doses compared with placebo (P=0.0009, P<0.0001, and P<0.0001, respectively). Mean serum potassium reduction was -0.73 mEq/L at the 10 g dose at 48 hours (P<0.0001), 14 hours after the last dose. The SZC therapy appeared to be well tolerated across all doses and the incidence of adverse events was similar to placebo. Importantly, the GI adverse event rate was 3.5% in patients receiving SZC compared with 5.1% for those receiving placebo, with diarrhea being the most common event in both groups. There were no cases reported where there appeared to be over-correction or the development of hypokalemia. In addition, SZC does not lower calcium or magnesium levels.[20] The effect of SZC on heart failure patients from the HARMONIZE trial showed that all three doses of SZC were effective in lowering and maintaining normal potassium levels with similar safety profiles to that seen overall.[21,22]

Patiromer and SZC appear to be safe and efficacious for the treatment of hyperkalemia. Control of hyperkalemia in the setting of heart failure may lead to expanded use with improved medication adherence and persistence to these therapies, reduce the hazards of hyperkalemic events, and improve clinical outcomes. However, there are currently no data that reduction in serum potassium levels provides mortality benefit. Until there are more data on outcomes, these oral potassium-lowering agents are much less likely to be incorporated into heart failure treatment guidelines.

MANAGEMENT OF THE PATIENT WITH HYPERKALEMIA

Typical Etiologies and Presentations of Hyperkalemia

Hyperkalemia can be simplistically framed as being caused by increases in potassium release from cells or by impaired urinary potassium excretion. Often, it is a consequence of both processes occurring simultaneously.

Increased Potassium Release

Pseudohyperkalemia refers to those situations in which measured serum potassium is elevated due to the technique of specimen collection. Mechanical trauma during venipuncture, overly aggressive tourniquet application, and repeated fist clenching are the most common causes of pseudohyperkalemia and mandate specimen recollection. Point-of-care testing, in particular, may be associated with spuriously high potassium levels. Uncommon causes of pseudohyperkalemia include thrombocytosis, certain forms of leukemia and lymphoma, and rare red blood cell conditions such as stomatocytosis and xerocytosis.

Potassium is an intracellular anion. Any condition that forces a shift of potassium from the intracellular compartment to the serum will result in hyperkalemia. In metabolic acidosis conditions not related to lactic acidosis or ketoacidosis, there is a transcellular shift of potassium from the intracellular to the extracellular compartment to buffer hydrogen ions. This shift is less pronounced in respiratory causes of acidosis. Examples of emergency presentations that may involve hyperkalemia include insulin deficiency, hyperglycemia and hyperosmolarity, and the use of beta blockers, which all indirectly lead to increased intracellular potassium release by various mechanisms. Increased tissue breakdown with subsequent intracellular potassium release is seen in trauma, tumor lysis syndrome, hypothermia/rewarming injury, and exercise.

Reduced Urinary Potassium Excretion

As previously discussed, impaired potassium excretion is most often caused by acute or chronic renal disease, but may also be caused by drugs that affect the RAAS. Many drugs and diseases can negatively affect renal function, leading to CKD and impaired potassium excretion. Chronic Kidney Disease guidelines were introduced by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) in 2002.[23,24] The guidelines define CKD as a GFR less than 60 ml/min/1.73 m^2 for three months or more, irrespective of cause. Renal disease severity is classified into five stages according to the level of GFR (Table 3).

TABLE 03 Stages of Chronic Kidney Disease

Stage	Description	eGFR (mL/min)
1	Kidney damage with normal or ↑GFR	≥ 90
2	Kidney damage with mild or ↓ GFR	60-89
3	Moderate ↓ GFR	30-59
4	Severe ↓ GFR	15-29
5	Kidney failure	<15 or dialysis

Clinical Manifestations

Although many patients with mild hyperkalemia are asymptomatic, some may have mild nausea and vomiting. However, the most clinically relevant manifestations of hyperkalemia are muscle weakness leading to paralysis, cardiac conduction abnormalities, and dysrhythmias. Perhaps more importantly, a myriad of clinical presentations can be associated with the diseases that cause the CKD. For instance, polyuria and polydipsia can be secondary to uncontrolled diabetes mellitus, and joint and skin conditions may be related to autoimmune illnesses like systemic lupus erythematosus. Severe muscle weakness due to hyperkalemia often begins in the legs and progresses centrally to the trunk and arms ending in flaccid paralysis that can mimic acute inflammatory demyelinating polyradiculoneuropathy (AIDP), commonly known as Gillian-Barré Syndrome.[25] Rarely is weakness due to hyperkalemia associated with respiratory muscle failure, cranial nerve involvement or loss of sphincter tone as seen in spinal cord lesions.[26] Although most causes of hyperkalemia are acquired conditions, a rare autosomal dominant genetic disorder of the skeletal muscle sodium channel results in the condition hyperkalemic periodic paralysis. These patients develop profound myopathic weakness after heavy

exercise, stress, fasting or exogenous potassium loads in food. Their potassium levels are often elevated but may not be sufficiently high to be alarming. The levels are often normal in between episodes, which may occur daily.[27]

Cardiac Manifestations

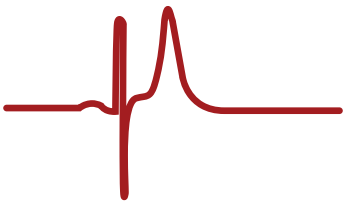
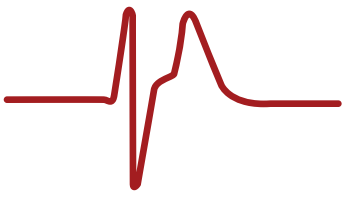
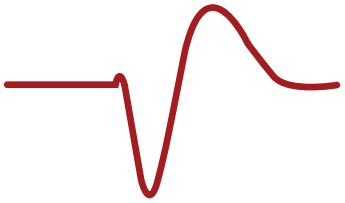
Electrocardiographic (ECG) changes in the setting of hyperkalemia commonly begin with peaked T waves and a shortened QT interval. Lengthening of the PR interval and widening of the QRS complex follows. Loss of P waves may occur as the QRS widens further to the characteristic "sine wave" morphology. In the setting of a patient at risk for profound hyperkalemia, the presence of the typical ECG changes can prompt emergency therapy prior to receiving the result of the serum assay. The probability of ECG abnormalities increases with rapidly rising serum potassium, but the absence of such changes is not sensitive enough to rule out a diagnosis of hyperkalemia.[28] Additionally, patients with CKD and ESRD on hemodialysis can have markedly elevated potassium levels without ECG changes, a phenomenon thought to be related to fluctuations in serum calcium.[29] Less common ECG manifestations include conduction disturbances such as bundle branch blocks and high-grade atrioventricular blocks. A myriad of dysrhythmias have been reported, including sinus bradycardia, slow idioventricular rhythm, sinus arrest, ventricular tachycardia, ventricular fibrillation and asystole (Table 4).[30]

Prehospital Management of the Patient with Suspected Hyperkalemia

Severe hyperkalemia represents a time-dependent life-threatening emergency, regardless of the patient's location. Unlike standard medical environments, the prehospital setting presents unique challenges in the diagnosis and treatment of hyperkalemia. Standard 911 emergency medical response, critical care interfacility transport, and care in disaster zones require special consideration.

In general, diagnosis and treatment of hyperkalemia are restricted to paramedics, since emergency medical

TABLE 04 ECG Changes Associated with Hyperkalemia

Serum potassium	Typical ECG appearance	Possible ECG abnormalities
Mild (5.5 - 6.5 mEq/L)		Peaked T waves Shortened QT interval Prolonged PR segment
Moderate (6.5 - 8.0 mEq/L)		Loss of P wave Prolonged QRS segment ST-segment elevation Ectopic beats and escape rhythms
Severe (>8.0 mEq/L)		Progressive widening of QRS complex Sine wave Ventricular fibrillation Asystole Axis deviations Bundle branch blocks Fascicular blocks

technicians are not able to interpret cardiac rhythms or 12-lead ECGs and have very limited ability to administer medications. Hyperkalemia is most commonly considered when evaluating the "H's and T's" of reversible causes of cardiac arrest, although less than 10% of cases of pulseless electrical activity are due to elevated potassium.[31] Point-of-care testing of electrolytes is uncommon in 911 services, leaving clinical suspicion and cardiac monitoring as the only diagnostic choices. Electrocardiography is neither sensitive nor specific for hyperkalemia,[32] and most paramedic training is narrowly focused on detection of ST-segment elevation myocardial infarction or cardiac conduction blocks. Highlighting the difficulty in hyperkalemia detection, anecdotal cases of hyperkalemia have been interpreted as stable ventricular tachycardia (wide complex tachycardia with a pulse) and treated with cardioversion and/or amiodarone.

When considered, treatment for hyperkalemia focuses on shifting of serum potassium to the intracellular space, since there are no commonly available prehospital treatments to eliminate potassium from the body. Continuous albuterol and intravenous sodium bicarbonate are the most widely available treatment options. Calcium is occasionally available, and insulin is not common in traditional emergency medical services (EMS). The use of furosemide in the prehospital setting is controversial,[33] and many EMS agencies no longer carry the medication.

Critical care transport differs from traditional EMS in important ways. Diagnoses, including electrolyte abnormalities, are usually known, and diagnostic and treatment options are expanded. Many services may have CLIA-waived point of care testing devices to monitor serum potassium levels, and insulin and calcium are more commonly stocked. However, treatment of hyperkalemia remains focused on intracellular shifting.

Two special scenarios require additional preparation for emergent treatment of hyperkalemia: reperfusion after crush injury and the care of ESRD patients in a disaster zone.

Crush injury with reperfusion syndrome is a much-feared complication after prolonged entrapment during structural collapse. The syndrome was first described during the London Blitz in World War II,[34] where survivors pulled from the rubble of collapsed buildings quickly succumbed for unknown reasons. The potassium released from injured myocytes does not enter the circulation until perfusion is restored. If not rapidly fatal, kidney injury from massive myoglobin release contributes to overt renal failure and the need for dialysis. Kidney injury and hyperkalemia remain significant contributors to morbidity and mortality after earthquakes,[35,36] and Urban Search and Rescue teams have protocols in place to prepare for acute hyperkalemia the moment a victim is freed. Similar to traditional EMS treatments, the focus is on shifting potassium into the intracellular space.

Any disaster that affects the operations of medical infrastructure, including earthquakes and hurricanes, poses unique challenges to those with chronic medical conditions. Care of dialysis-dependent patients in a disaster zone is complicated. After Hurricane Michael in 2018, all dialysis centers in a large county in the Florida panhandle closed for several days. Hospital-based dialysis was not an option, since both county hospitals were damaged by the storm and had to be evacuated. Many patients were not able to resume routine dialysis for more than a week (personal communication). Potassium shifting is not a viable temporizing strategy in such situations, and alternate methods of hyperkalemia treatment and prevention must be available.

Oral binding agents, such as sodium polystyrene sulfonate (SPS), patiromer, and SZC, may offer benefit. As in all disasters, preparedness and planning are essential, and operational aspects of medication acquisition and distribution must be tailored to each community. During Hurricane Michael, SPS was on national back order and generally unavailable; local pharmacies did not stock patiromer and a limited supply of samples was made available through pharmaceutical sales representatives. Many nephrologists had to prioritize distribution to higher-risk patients. Governmental and private disaster relief agencies and pharmaceutical companies should consider establishing strategic stockpiles of oral potassium-binding agents to mitigate risk to dialysis-dependent patients affected by care disruptions after disasters.

Emergency Department Management of Patients with Hyperkalemia

Current Pharmacologic Therapy for Hyperkalemia in the Emergency Department

The current pharmacologic approach to hyperkalemia management in the ED involves a combination of medications that primarily temporize adverse effects by altering membrane action potentials and shifting excess potassium from the extracellular to the intracellular space. Although other available therapeutics can promote potassium removal, they rely primarily on binding of potassium within the GI tract, resulting in inconsistent benefit. For patients who still produce urine, promotion of renal elimination can also be considered. Newer agents such as SZC and patiromer offer potential to dramatically improve upon existing treatment, but further testing is needed.

Cardiac Stabilization

Principal amongst the targets of initial therapy is the heart, where hyperkalemia alters the ionic milieu to shorten action potential duration, increasing the propensity for conduction defects and dysrhythmias. Although the severity of cardiac manifestations varies depending on the potassium concentration, initial treatment is typically directed towards cardiomyocyte membrane stabilization using intravenous calcium, which antagonizes the effect of hyperkalemia on a cellular level, resetting the threshold potential and reversing the impact on impulse propagation. Calcium therapy is often reserved for patients with ECG manifestations of hyperkalemia, but there is little harm associated with it and liberal use when hyperkalemia is present or suspected should be considered. Perhaps the only exception to this is for patients on digitalis, since this medication increases intracellular calcium concentration by blocking Na^+-K^+-ATPase, leading to theoretical concern for relative calcium excess and "stone heart." Although evidence supporting this concern is lacking, risks and benefits of calcium therapy in patients on digitalis should nonetheless be weighed prior to administration. Calcium is most often administered as a single 10 mL bolus of 10% calcium gluconate and its effects are rapid, producing resolution of ECG changes within minutes and providing time for other concurrent therapies to work. Repeat dosing should be administered in 3-5 minutes if the initial ECG findings do not resolve, and as needed thereafter based on clinical status or recurrent conduction abnormalities identified through continuous telemetric or ECG monitoring. Calcium chloride, which has a threefold greater calcium concentration in a 10% solution (27.2 mg/ml vs. 8.9 mg/ml) can also be used, though this is frequently reserved for those with cardiac arrest or other severe consequences of hyperkalemia. Due to the risk of tissue injury from extravasation of calcium chloride, ideally it should be administered through a central line or a large bore, secure peripheral line.

Intracellular Shift of Potassium

Therapeutic intervention to further mitigate the effects of potassium by shifting it from the extracellular to the intracellular compartment should be delivered concurrently with calcium.[37] Insulin and glucose are effective for inducing rapid potassium shifts, promoting hepatic and skeletal muscle uptake in a dose-dependent manner. Typically given as a combination of regular insulin (10 units) and a single ampule of D50 (50 ml of 50% dextrose solution), such therapy results in a rapid shift that peaks 20-30 minutes post-administration, reducing potassium concentration by approximately 1 mEq/L. Serum potassium reductions that are of a similar magnitude but more sustained can be achieved using an infusion of regular insulin (20 units administered over one hour), but doing so can lead to delayed onset of peak effect and greater risk of hypoglycemia. As a result, neither bolus nor infusion alone is optimal and a combined approach with a loading bolus (6 units of regular insulin) followed by a one-hour infusion of regular insulin (20 units/hour) plus dextrose (60 g) may be preferred.[37] However, such an approach has not been rigorously studied and the comparative effectiveness (as well as safety) has yet to be confirmed. Beta-2 agonists such as albuterol are also generally effective for shifting potassium, decreasing potassium by 0.3 to 0.6 mEq/L within 30 minutes of administration.[37] Delivered most often by nebulizer, albuterol is quick and easy to administer, though it should be noted that not all patients respond to such treatment and tachycardia can be a complication. Sodium bicarbonate has historically been used to induce potassium shifts as well, but its true effect on hyperkalemia is uncertain. Some studies suggest a direct, proportional relationship with a 2 mEq/L decrease in potassium for each 10 mEq/L

rise in bicarbonate while others have found no clear effect. For patients with adequate renal function, sodium bicarbonate can enhance urinary potassium excretion and its use should be considered primarily in such individuals.

Definitive Potassium Removal

Ultimately, definitive treatment to remove potassium from the body is needed to effectively manage hyperkalemia. For patients with ESRD or those with severe hyperkalemia in the setting of AKI, dialysis is by far the most effective mechanism to eliminate potassium. However, due to cost and the equipment and personnel needed to perform dialysis, it is largely inaccessible as an emergent treatment, making the availability of effective pharmacotherapeutics essential. As noted, sodium bicarbonate can facilitate kaliuresis (excretion of potassium in the urine) with intact or modestly compromised renal function, as can loop diuretics. Although there is no standardized dosing of the latter for purposes of promoting renal potassium elimination, bolus intravenous furosemide at 40-80 mg repeated every 8 to 12 hours is reasonable.

Aside from dialysis or renal elimination, the only other way to remove potassium is through the GI tract. Sodium polystyrene sulfate, which was approved in 1958 based on small, case-based data, has for decades been the only pharmacologic agent available for elimination of potassium through the gut. SPS can be administered orally or rectally, with or without sorbitol, at doses ranging from 15-45 g and repeated as needed based on serum potassium concentrations. It is a cation exchange resin that non-selectively binds potassium, magnesium and calcium, then exchanges sodium for potassium in the colon,[38] with the greatest effect occurring in the rectum where potassium concentrations are highest. Because the potassium exchange occurs in the colon, the onset of action of SPS is delayed and variable (between 2 and 6 hours) and its duration of action is unpredictable (between 6 and 24 hours). Despite many years of use for acute hyperkalemia and routine inclusion in management protocols, no randomized, controlled trials have ever demonstrated that SPS is effective at inducing fecal potassium losses. Moreover, there are questions about its safety due to its well-documented risk for hypomagnesemia and hypocalcemia, and numerous reports of serious GI complications including colonic necrosis.[39] The latter may be more closely related to combined use with sorbitol, prompting the U.S. Food and Drug Administration to issue a black box warning related to co-administration.

Given such concerns, there exists an unmet need for agents that can safely and reliably lower potassium in the setting of hyperkalemia. Patiromer, a novel binding resin that was approved for clinical use in 2015, works in a similar fashion to SPS with a mechanism of action that is based on gradient-dependent exchange, but supplants calcium rather than sodium for potassium. It offers some advantages over SPS, including a better safety profile, no evidence of necrosis and reduced sodium load. Definitive trials in the setting of outpatient hyperkalemia management show that patiromer is effective at lowering chronically elevated potassium in a dose-dependent manner. A single oral dose of 8.4 g has been shown to lower potassium by 0.23 mEq/L within 7 hours of administration,[18] but its use in acute care settings has never been tested and its potential role in the management of emergent hyperkalemia remains uncertain. Patiromer also binds to many orally administered medications and decreases their bioavailability, which is a caveat that may further preclude its future use in acute care settings.

Sodium zirconium cyclosilicate, which was approved by the FDA in 2018 for treatment of hyperkalemia, offers particular promise for acute care. It is an inorganic cation exchanger that has been engineered to have a highly selective, high-capacity crystalline lattice structure.[10,19] The structure allows SZC to preferentially entrap monovalent cations (e.g., potassium ions) over divalent cations (e.g., calcium and magnesium).[19] This agent is available in a tasteless, odorless powder and requires no special handling, refrigeration, or special preparation.[19] Operating as a novel ion trap rather than an exchange resin, it overcomes many of the limitations of SPS and patiromer, selectively binding potassium throughout the GI tract rather than primarily in the distal colon, thereby allowing a more rapid and sustained reduction.[40] It has more than nine times the binding capacity for potassium and is more selective for potassium than SPS, resulting in a more reliable excretion of potassium.[38] Post-hoc analysis of 45 patients from two completed trials who had serum potassium concentrations > 6.0 mEq/L (mean 6.3 mEq/L with a range of 6.1-7.2 mEq/L) showed substantial signal of acute benefit with reductions of 0.4 mEq/L at 1 hour, 0.6 mEq/L at 2 hours,

and 0.7 mEq/L at 4 hours (P < 0.001) after administration of a single 10 g dose.[41] Based on this, an ED-based phase II randomized trial called ENERGIZE (A Study to Evaluate a Potassium Normalization Treatment Regimen Including Sodium Zirconium Cyclosilicate (ZS) Among Patients with S-K ≥5.8), was designed (NCT03337477). Currently recruiting subjects, ENERGIZE will enroll a total of 132 patients, providing critical data on the efficacy of SZC for acute potassium reduction, and the first-ever prospective intervention trial evidence related to ED management of hyperkalemia.

An algorithm for the acute management of patients with hyperkalemia is presented in Figure 1.

Indications for Hemodialysis for Patients with Hyperkalemia in the Emergency Department

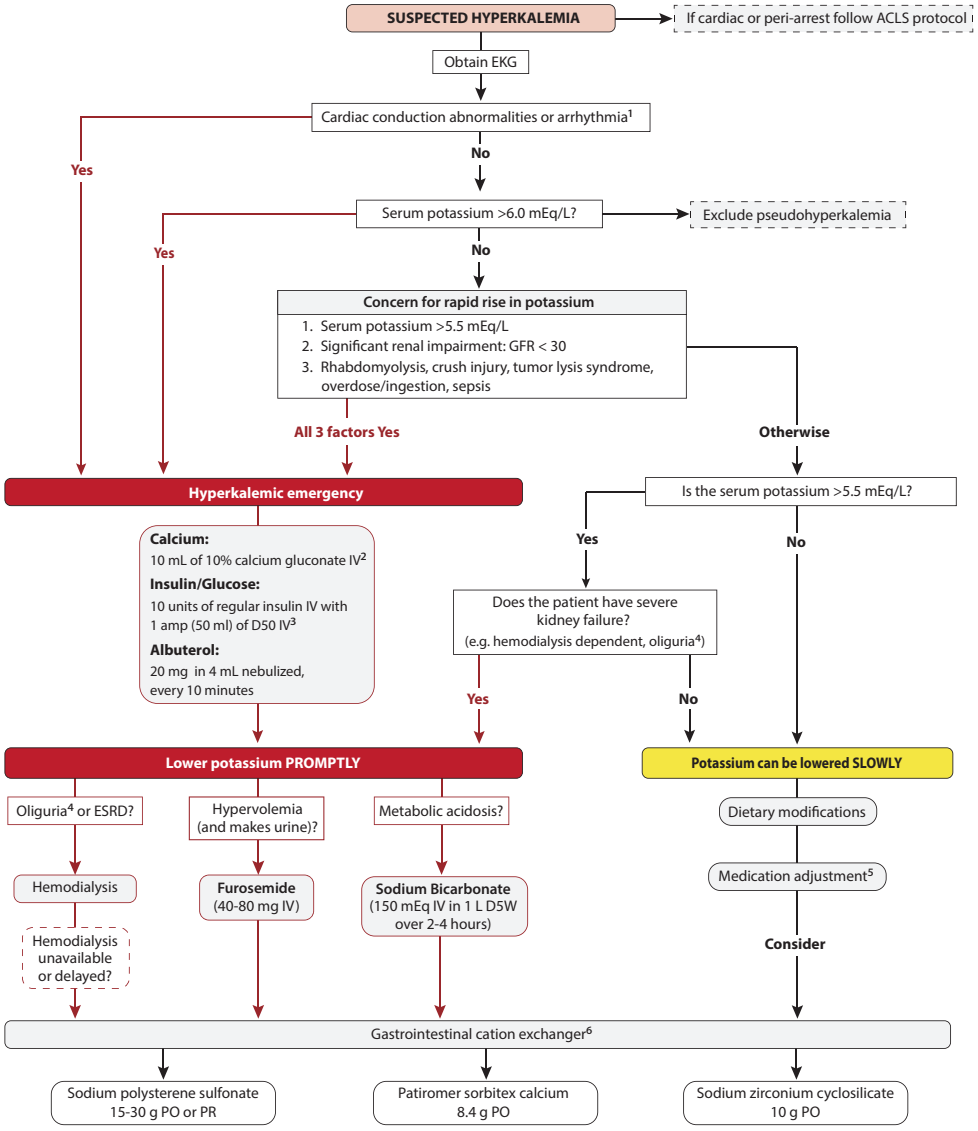
For extreme hyperkalemia, the ultimate therapeutic modality is dialysis. Hyperkalemia is the second most common reason for patients receiving emergent hemodialysis, with fluid overload being the most common.[42] Emergent hemodialysis should be considered in patients with hyperkalemia who demonstrate an inadequate response to standard medical therapies. One commonly cited indication is persistent ECG changes despite maximal medical therapy. Because ECG changes are incompletely sensitive for hyperkalemia, and elevated serum potassium has been shown to correlate with mortality, other authors have proposed particular serum potassium levels as an indication for dialysis after the employment of medical therapy.[32] The emergency physician faced with a patient whose serum potassium level is greater than 6.0 mEq/L despite treatment should strongly consider moving toward emergent hemodialysis. In addition, patients with hyperkalemia who suffer a cardiac arrest, evolving critical illness, acute myocardial infarction or signs and symptoms of neuromuscular weakness are candidates for emergent hemodialysis.[43] Notably, although there is often some delay from decision to employ hemodialysis to actual initiation, the onset of action of lowering the serum potassium is extremely rapid once dialysis is initiated.[44] The physician managing the dialysis can also increase the rapidity of potassium removal by modulating the gradient across the hemodialysis membrane.[45] Special considerations when caring for these complicated patients include vascular access, anticoagulation, and special situations associated with hemodialysis.

Vascular access is critical for hemodialysis. This may not be an issue for patients on chronic dialysis. However, patients who have not yet had dialysis initiated or who have had acute decompensation may require de novo access. The typical first choice for the required large double lumen catheter is the internal jugular vein. The right internal jugular vein is generally preferred over the left, since the more direct route decreases mechanical issues leading to clotting in the line. When possible, the subclavian vein should be avoided. There is a high incidence of subsequent venous stenosis, which may significantly complicate venous access if chronic hemodialysis is required. If the femoral route is required, a longer catheter (19-25 cm) is preferred since this will reduce the incidence of venous to arterial port recirculation that can occur in up to 23% of shorter (13.5 cm) catheters.[46] It should be noted that if a patient with a hemodialysis catheter in place needs lifesaving therapy and other intravenous access cannot be obtained, the hemodialysis catheter can be used for intravenous fluid and medication administration.

Patients requiring emergent hemodialysis may have many complicating medical conditions. Patients who undergo dialysis often receive anticoagulation, most commonly with unfractionated heparin. This may be unwanted in the emergency patient. In that setting, careful discussions with the physician managing the dialysis should be held. Alternatives, such as brief hemodialysis without anticoagulation, regional anticoagulation of the actual circuit with pre-filter use of heparin and post-filter use of protamine, or the use of citrate anticoagulation, may be desired.[46] Complications in the setting of emergent hemodialysis may include dialysis disequilibrium syndrome (discussed in the neurocritical care section of this monograph), air embolism, allergic reaction, and vascular access hemorrhage.

Finally, one special consideration for patients that may present with hyperkalemia is the ever-increasing number of undocumented immigrants with ESRD who have variable access to regular dialysis. This group may present recurrently or episodically to the ED seeking care. They are at markedly increased risk for mortality and may present with very high serum potassium levels and must be aggressively managed in the ED.[47]

FIGURE 01 **Hyperkalemia Treatment Algorithm**



FOOTNOTES:

1: Tall peaked T waves, widening of the QRS interval, "sine waves," ventricular arrhythmias.
2: May repeat dosing at 5 minutes if ECG abnormalities persist.
3: Close glucose monitoring is required. Can be repeated every 15-30 minutes as needed based on ECG findings or clinical instability. Alternative administration of insulin as a combination bolus of 6 units followed by an infusion at 20 units/hour with continuous D5W at a maintenance rate can be considered.
4: Oliguria defined by <400 mL per day.
5 Discontinuing NSAIDs, adjusting drugs that inhibit RAAS, adding oral diuretics, initiating oral bicarbonate therapy (if metabolic acidosis present).
6: Refer to Table. None of these agents have been FDA approved for hyperkalemia in the acute care setting.

TABLE: GASTROINTESTINAL CATION EXCHANGER CHARACTERISTICS

	Sodium Polysterene Sulfonate	Patiromer	Sodium Zirconium Cyclosilicate
Mechanism of action	· Na^+ - K^+ exchange resin/polymer · Non-selectively binds K^+, Ca^{++}, Mg^{++} · Commonly given with sorbitol	· Organic exchange resin/polymer · Nonspecific binding of cations	· 3 dimensional crystalline lattice · Selectively traps K^+
Binding site	Colon	Colon	Proximal and distal GI tract
Time of onset (hrs)	Variable (2-6)	7	1
Median time to K^+ normalization (hrs)	Variable	>48	2.2
Side effects	· Variable efficacy · Acute bowel necrosis · Hypernatremia · Volume overload · Drug-drug interactions	· GI discomfort (diarrhea, constipation, nausea) · Hypomagnesemia · Drug-drug interactions- requires timed separation of oral drug administration	· Edema · Reduction in BUN · Rise in HCO_3 (may be favorable) · May affect absorption of drugs with pH dependent solubility

Algorithm available online at https://www.emcreg.org/algorithms

The Emergency Department Challenge of Delays in Definitive Care

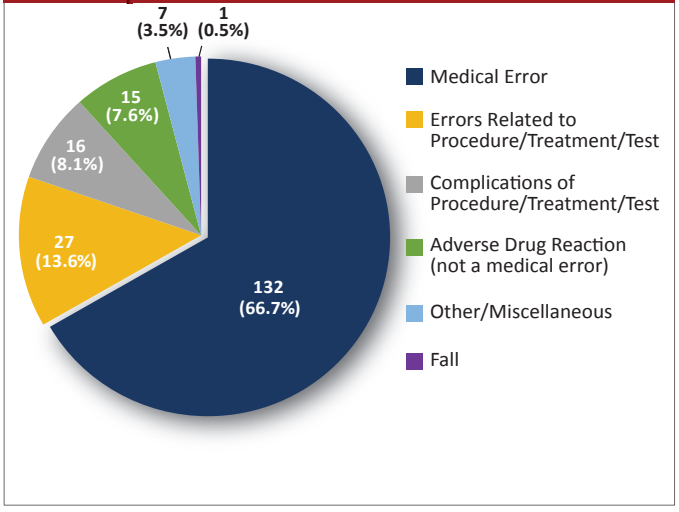
Hyperkalemia has a poorly defined standard of care in the ED setting.[48] It has been shown that nearly half of ED visits by patients with ESRD result in hospital admission, that they present 6 times more frequently to the ED than the general population, and that the hospital admission rate from the ED is 4 times higher than the mean national rate.[49] Characteristics of patients with ESRD in the United States include high ED usage and frequent co-morbid conditions such as heart failure, chest pain, hyperkalemia, and fluid overload.[49]

A major challenge for the emergency physician, hospitalist, and critical care physician is the management of life-threatening hyperkalemia at times of ED overcrowding, boarding of patients and delayed definitive care/dialysis. Emergency Department crowding, which is a prevalent health delivery problem and has been described by the Institute of Medicine as a public health crisis, may adversely affect the outcomes of those patients requiring admission to an inpatient setting.[50] It has been shown that in periods of high ED crowding and boarding, inpatient mortality rates are increased, as are lengths of stay and costs for admitted patients.[51,52] In addition, many hospitals do not provide emergent dialysis services and there are often delays in treatment in those that do. Emergency Departments without dialysis capabilities routinely have to treat chronic dialysis patients who have missed their dialysis appointments until transportation can be arranged. Long transportation times and limited supplies of emergency potassium-lowering medications carried by ambulance services and aeromedical services are further concerns in the treatment of hyperkalemic patients. If left untreated, hyperkalemia can lead to life-threatening cardiac dysrhythmias with a resultant increased mortality risk.

The management of potentially life-threatening hyperkalemia over a prolonged time period is not well described in the ED setting. The medications used for acute management of hyperkalemia have short half-lives and the resulting decreases in serum potassium are short-lived.[53] For example, calcium has an almost immediate onset of action but its duration is only a few minutes and it frequently needs re-dosing. Insulin has a 15-minute onset of action with a 60-minute peak duration. Rebound hyperkalemia is a potential life threat for the patient.[54] Because of this, continued monitoring of potassium levels is indicated and this becomes a challenge at times of ED overcrowding and boarding.

When patients cannot receive dialysis in a timely manner and/or ED patient boarding is occurring, these short-acting medications must be frequently re-administered due to the temporary redistribution of potassium. In a busy ED, time-appropriate and dose-accurate administration of these medications is often challenging. Insulin and glucose medication errors for the treatment of hyperkalemia in the hospital setting have been reported (Figure 2), and the ED was the most frequent patient care area where the events occurred. The most common medication errors reported were dosing delays, wrong route, and wrong dose.[55] Beta-2 agonist side effects, such as tremors and tachycardia, are frequent occurrences, so these medications should be used with caution in patients with ischemic cardiac disease.[54] In addition, patient monitoring with cardiac telemetry is not sensitive in picking up the early, often subtle, ECG changes associated with hyperkalemia. T-wave changes, typically the earliest manifestations of hyperkalemia, often occur in other conditions and repeat ECGs for patients with hyperkalemia during overcrowding and boarding may get overlooked or not performed in a timely manner.

FIGURE 02 **Reported Event Types for Hyperkalemia Events Involving Errors with Insulin or Dextrose (N=198)**



In patients with severe hyperkalemia and/or hemodynamic instability, admission for cardiac monitoring and nephrology consultation for immediate dialysis is indicated. Currently, during times of ED overcrowding and boarding or while waiting for definitive care, the rapidly acting transient therapies must be continued until dialysis. Newer cation exchangers offer some hope for lowering serum potassium levels relatively quickly and providing a longer duration of effectiveness. It has yet to be established whether patiromer and/or SZC will have a role in acutely reducing serum potassium levels in patients with a hyperkalemic emergency. It is encouraging that a clinically significant treatment effect of SZC was observed within one hour after administration and the steepest decline in serum potassium occurred during the first four hours of therapy.[19] New cation exchange medications may have a significant role in the treatment of hyperkalemic patients especially in times of ED overcrowding, boarding and delayed definitive care.

Critical Care Management of Patients with Hyperkalemia

Hyperkalemia in the Medical Intensive Care Unit

Hyperkalemia is a common abnormality in the medical intensive care unit (MICU). Whereas initial management of hyperkalemia, specifically therapy aimed at cardiac stabilization and shifting potassium into cells, is widely known, interventions that aim to remove potassium from the body have been less consistently applied. With the emergence of a new pharmacologic agent that more reliably excretes potassium, the management of hyperkalemia in the MICU should be approached in a new light. Moreover, extracorporeal removal of potassium remains a mainstay of treatment for life-threatening hyperkalemia. Understanding the different modes of renal replacement therapy (RRT) and how each mode affects potassium removal can help the intensivist manage this condition more effectively.

Hyperkalemia and Outcomes

Alterations in serum potassium have a variety of clinical consequences that are particularly deleterious in the critically ill patient. The link between hyperkalemia and worse outcomes is strong in the critically ill population. In one retrospective trial of over 900 patients in Korea, cardiac dysrhythmias and cardiac arrest frequently occurred in patients with potassium levels greater than 6.5 mEq/L. Compared with survivors of hyperkalemia, the non-survivors had higher potassium levels prior to death.[56] In a large retrospective analysis of over 39,000 patients, hyperkalemia was found to be associated with mortality following initiation of critical care, and the risk of death persisted even after adjusting for potential confounders. It was also noted that resolution of the hyperkalemia within 48 hours was associated with a survival advantage.[57] Other data have demonstrated that not only the absolute degree of hyperkalemia, but also the acuity of onset and the duration of hyperkalemia, portend worse outcomes.[58] Aggressive treatment with interventions to modify hyperkalemia has been associated with a survival advantage.[56] Although it is not known whether correcting potassium levels is a direct cause of improved survival or merely an association, there is general agreement that severe hyperkalemia can be lethal, and that evidence-based treatment guidelines are needed.

Treatment of Hyperkalemia in the MICU- A Focus on Potassium Elimination

The general treatment modalities for severe hyperkalemia in a medical ICU include the following: stabilization of the cardiac membrane, redistribution of potassium into cells, elimination of potassium from the body, and lastly, addressing the underlying ailment that led to the hyperkalemia. It is important to recognize, however, that calcium infusion for cardiac membrane stabilization and shifting agents are short-term, temporary interventions, and in the case of sodium bicarbonate therapy, of uncertain efficacy.[59] Elimination of potassium from the body by the mechanisms described below provides a more salient and permanent strategy.

Urinary potassium excretion: Inducing kaliuresis with the use of loop-acting diuretics alone, or in combination with a thiazide diuretic, is one treatment option for potassium excretion. However, many patients in a MICU setting have either impaired renal function or are volume depleted, and therefore this therapy is either ineffective or worsens volume contraction. Moreover, patients with CKD often have a blunted effect and therefore require higher diuretic dosing.[60] Diuretic therapy, for purposes of achieving potassium elimination, is best reserved for patients with mild to moderate hyperkalemia who have preserved renal function and who are volume overloaded.

Gastrointestinal potassium excretion: Sodium polystyrene sulfonate was once commonly used for GI elimination of potassium, but no longer has a role in the treatment of hyperkalemia in the MICU setting for numerous reasons. Its onset of action is delayed, and both its onset and duration of action are unpredictable. It also has a high sodium content that is delivered to the body during the potassium exchange, thus making it potentially dangerous for patients with cardiac compromise. The risk of colonic necrosis is also of concern.[39] Patiromer has been shown to be of use in chronic hyperkalemia therapy only, since its principle onset of action within the colon is approximately 7 hours after administration and other oral medications cannot be given within 3 hours of its intake.[18] Although it remains a therapeutic option for long-standing management of hyperkalemia in the chronic outpatient setting, it does not play a role in the management of the MICU patient whose electrolyte and acid-base profile are unpredictable.

Sodium zirconium cyclosilicate, unlike SPS and patiromer, is a new therapeutic option for patients with acute hyperkalemia in the MICU. Its non-absorbing crystalline structure has a higher affinity for potassium and ammonium ions than other cations. There are numerous reasons why SZC is an ideal agent for potassium removal in the MICU hyperkalemic patient. It has no impact on calcium and magnesium, but rather decreases blood urea nitrogen (BUN) and increases serum bicarbonate due to its removal of ammonium, making it a more favorable electrolyte profile for a critically ill patient that is prone to dysrhythmias and acidosis. In clinical trials, the most pronounced effects of SZC were observed when hyperkalemia was severe.[19,21] More importantly, SZC binds potassium in the proximal as well as the distal GI tract, suggesting a more immediate effect and therefore an advantage in the acute care setting. Although the phase III trials of SZC were not specifically designed to examine its effect on acute hyperkalemia, data suggest that it is the optimal drug for this indication.[19,21] In the trials, the steepest decline was noted in the first four hours of therapy, with the median time to achieving a normal serum potassium level being 2.2 hours.[21] The median time for the serum potassium level to decrease to less than 6.0 mEq/L was 1.07 hours and by 4 hours, 90% of the patients had a serum level less than 6.0 mEq/L. The only noted side effects were non-clinically relevant prolongation of QTc and edema, which were more common in higher doses (10 and 15 g), albeit rates were still low.[21]

Sodium zirconium cyclosilicate, with its early and predictable onset of action, has great promise as an adjunctive agent for patients who present with, or develop, severe hyperkalemia in the MICU. In patients with life-threatening hyperkalemia, shifting agents provide a temporary safety mechanism to rapidly lower serum potassium until definitive removal of potassium can be accomplished. Definitive removal of potassium by diuretics is often not feasible, and removal by dialysis, as described below, is invasive, not always readily available, and may not be necessary in hyperkalemic patients who do not have persistent cellular excretion of potassium.

Renal replacement therapy: By far the most effective and efficient means of removing potassium from the body is by dialysis. When hyperkalemia is life-threatening, or when the underlying condition causes rapid and/or persistent release of potassium stores into circulation, dialysis is the mainstay of therapy. The overall goal of dialysis is to remove potassium to a range low enough to avoid increases from the underlying pathology. This requires coordination between the intensivist and the nephrologist to select the optimal mode of dialysis, to obtain adequate vascular access and flow, and to modify dialysate composition or replacement fluid, all while maintaining an appreciation for the natural course of the underlying disease process. Abrupt, extensive, and persistent release of potassium into circulation are most apparent in conditions of cell destruction and/or cell turnover as seen in tumor lysis syndrome, crush injury, rhabdomyolysis, and reperfusion injury. The acute care physician should have a very low threshold to initiate dialysis in patients with these conditions, especially when renal failure is also present, since it further disrupts potassium elimination.

The general modes of RRT include intermittent hemodialysis (IHD) or continuous venovenous hemofiltration (CVVH) or a combination of the two (Table 5). In IHD, solute is removed by diffusion; there is an electrochemical gradient across the membrane using a flow-past system with a dialysate solution. Blood flow rates in IHD are usually 300 to 400 ml/min and can remove 25 to 50 mEq of potas-

sium per hour. The rate of potassium removal depends on various parameters, including the initial serum potassium concentration, and therefore shifting agents should be discontinued prior to starting IHD.[11] Potassium removal also depends on flow rates, the concentration of the dialysate, and the underlying cause of the hyperkalemia.[61] Because blood flow rates are high in IHD, this mode is the most efficient means of reducing potassium and should be used first in life-threatening hyperkalemia. There are several forms of continuous renal replacement therapies, including CVVH, continuous venovenous hemodialysis (CVVHD), and continuous venovenous hemodiafiltration (CVVHDF). A detailed description of each type is beyond the scope of this review. Continuous modes of RRT, such as CVVH, remove solute by convection; there is a transmembrane, pressure driven solvent-drag where solute moves with the solvent across the membrane. The ultra-filtration is discarded and replacement fluid is given back to the patient. Blood flow rates are generally lower at 100 to 200 ml/min. Therefore, CVVH is best implemented for patients with hemodynamic instability, persistent acidemia, cerebral edema (to avoid large shifts in osmolarity) and when ongoing fluid removal is necessary. Because the initial potassium load in severe hyperkalemia may exceed the capacity of CVVH, a reasonable approach would be to start with IHD in these patients, then subsequently switch to a continuous mode of RRT in order to maintain ongoing safe serum potassium levels, or consider a hybrid approach. This is especially advantageous for patients with persistent potassium loads or when rebound hyperkalemia occurs. Post-dialysis rebound occurs when the potassium that is removed from serum creates a gradient, resulting in subsequent efflux of potassium from the cells into the extracellular fluid.[62] Rebound effect may be exacerbated by previously administered shifting agents or by ongoing cellular turnover, and can be detected about 4 to 6 hours after dialysis is complete. Frequent monitoring of serum potassium levels is therefore necessary.[62] Continuous RRT or multiple sessions of IHD, even in the same day, may be necessary in some circumstances. In general, the "best" mode of RRT remains controversial and requires regular consultation with a nephrologist.

In addition to the mode of dialysis, the potassium concentration of the dialysate or replacement fluid also influences the rate of potassium removal. Most dialysate solutions contain 2.0 mEq/L of potassium to safely remove potassium from circulation. Utilizing lower potassium dialysate concentrations can be employed for severe hyperkalemia in a monitored ICU setting. However, the consequences of rapid reduction in extracellular potassium are not known and some data demonstrate increased dysrhythmias with potassium-free dialysate.[63]

In CKD patients who are not on dialysis and yet are prone to hyperkalemia in the ICU due to acidemia, the optimal timing to initiate dialysis is controversial. Some data suggest that these patients have "adapted" to higher levels of serum potassium.[56,64] However, these patients are also at high risk for cardiac dysrhythmias due to metabolic derangements, particularly when sick enough to require ICU admission. Therefore, it is prudent to initiate dialysis

TABLE 05 **Comparison of Intermittent vs. Continuous Renal Replacement Therapy for the Hyperkalemic ICU Patient**

Therapy	Clinical Indications	Advantages	Disadvantages
IHD (Diffusion)	• Hemodynamically stable • Extremely high K^+ levels	• Rapid removal of K^+ • Lower cost • Can utilize fistula, graft, or vascular access	• Induce hemodynamic instability • Rebound hyperkalemia after treatment • Technically more complex • Insufficient time for equilibration between compartments, can cause cerebral edema
CRRT (Convection ± Diffusion)	• Hemodynamically unstable • At risk for elevated ICP	• Continuous removal of K^+ • Hemodynamically stable • Easy control of fluid balance • User friendly machines	• Slower clearance of K^+ (often requires CVVHD) • Immobilization • Increased cost • Can only use vascular catheters for access

IHD, intermittent hemodialysis; CRRT, continuous renal replacement therapy; ICP, intracranial pressure; CVVHD, continuous veno-venous hemodialysis

when the potassium level rises to the level that would necessitate dialysis in a patient with normal renal function. The exact cutoff, however, remains unknown.

Finally, initiating dialysis is not without potential side effects, and requires careful consideration. Insertion of a central line for access places patients at risk for infection, trauma, and pain. Obtaining enough resources, including nursing support, can be a challenge. Despite its known efficiency at removing potassium from the body, RRT has not been shown to be associated with improved survival like other modalities such as insulin. It is unclear whether this is because dialysis is performed as a "last resort" intervention, because rapid reduction in potassium levels is deleterious, or because IHD/CVVH is associated with higher complication rates.

An algorithmic approach to the treatment of hyperkalemia in the ICU: Conditions commonly seen in the ICU setting, such as tissue necrosis, acidemia, and kidney injury, all increase the risk for hyperkalemia and further portend worse outcomes.[56] Despite decades of knowledge about this potentially life-threatening electrolyte, there are very few guidelines that stipulate exactly how hyperkalemia should be managed in critically ill patients. The approach below provides a logical way to characterize and treat hyperkalemia in the MICU setting.

Although definitions of "hyperkalemic emergency" vary, true "emergency" can be defined by those conditions that require rapid intervention, and not necessarily the absolute number. Most agree that potassium levels greater than 6.0 mEq/L in non-ESRD patients or greater than 6.5 mEq/L in ESRD patients constitute "emergent" electrolyte abnormalities.[43] However, the presence of symptoms, including neuromuscular weakness, dysrhythmias, and cardiac arrest, as they relate to elevated potassium levels regardless of the absolute level, also constitute hyperkalemic emergencies in MICU patients.[43] Conditions that predispose the patient to persistent release of potassium into the circulation or failure to eliminate potassium, such as concurrent tissue breakdown, severe acidemia, and renal injury, should be considered hyperkalemic emergencies since immediate therapy is indicated. Likewise, patients with an abrupt rise in serum potassium (e.g., 1.0 mEq/L above 4.5 mEq/L within 24 hours) should also be considered "emergent," since rapid changes in electrolytes are equally likely to result in cardiac toxicity in a critically ill patient.[43] The management of emergent hyperkalemia first requires cardiac stabilization and reliably shifting potassium into the intracellular space while preparations for elimination are prepared. In most cases of emergent hyperkalemia, dialysis will be necessary to appropriately prevent fatal dysrhythmias. As stated above, the mode of dialysis, whether IHD or CVVH or a combination of the two, can vary. In some circumstances in which the underlying condition can be ameliorated quickly (e.g., diabetic ketoacidosis), dialysis can be avoided.

In contrast to a hyperkalemic emergency, a "hyperkalemia urgency" can be defined by those conditions that require a more gradual lowering of potassium over approximately 2 to 6 hours and are not associated with cardiac or neuromuscular compromise.[43] These are patients who have hyperkalemia due to a multitude of factors in the MICU, including non-oligoanuric kidney injury, acidemia due to sepsis, medication side effects, or hypothermia. Potassium levels in hyperkalemic urgency are generally above 5.0-5.5 mEq/L in patients with normal kidney function, 5.5-6.0 mEq/L in patients with CKD, and 6.0-6.5 in patients with ESRD on HD. These patients do not require rapid cardiac stabilization or shifting agents, but rather the focus should be on potassium removal and treatment of the underlying cause. For patients with normal renal function and volume overload, such as a patient with heart failure, a diuretic challenge may be prescribed. For patients who are capable of tolerating oral medication administration, a 10 g dose of SZC can be considered to help facilitate excretion of potassium through the gut. Since SZC has only been used orally in clinical trials, its use in patients with nasal or oral gastric feeding tubes has not yet been evaluated. Dialysis is rarely required in hyperkalemic urgency, unless the patient is a regular dialysis patient and may need an additional or expedited dialysis treatment.

Lastly, the intensivist must be attentive to all potential causes for rapid increases in potassium among MICU patients. Blood product administration, sepsis, adrenal insufficiency, rewarming of a hypothermic patient, missed dialysis sessions due to surgeries, and use of succinylcholine or other medications can all result in hyperkalemia.[43] Failure to recognize the development of hyperkalemia and intervene appropriately could have fatal consequences.

Hyperkalemia in the Neurocritical Care Unit

Impact of Hyperkalemia in Patients with Neurologic Emergencies

Electrolyte disturbances in patients with neurologic emergencies, particularly hyperkalemia and sodium disturbances, have the potential to confound the neurologic exam, alter pharmacologic choices by clinicians, and impact long-term neurologic outcomes. There are several scenarios in which the management of hyperkalemia must be tailored specifically for patients with neurologic emergencies. These include the choice of drugs in rapid sequence intubation, special considerations for dialysis, potassium management in hypothermia, and the use of mannitol.

The incidence of hyperkalemia in neurologic emergencies is relatively low, but should not be overlooked in the workup of common neurologic emergencies, such as ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, traumatic brain injury, and status epilepticus. It is important to obtain electrolytes in any patient presenting with a neurologic emergency since hyperkalemia may confound the neurologic exam.[65] Hyperkalemia may worsen or mask other neurologic symptoms. It is a rare cause of ascending muscle weakness, which may mimic Guillain-Barré syndrome. Typically, weakness due to hyperkalemia is associated with areflexia, intact sensory function, and intact sphincter tone. Weakness that is secondary to hyperkalemia typically resolves rapidly once potassium falls to a normal level.

One of the most serious complications of neuromuscular blockade during rapid sequence intubation is sudden hyperkalemic cardiac arrest after administration of succinylcholine. Succinylcholine is an attractive drug for rapid sequence intubation in the setting of neurologic emergencies because of its rapid onset and short half-life, which allow for a rapid neurologic exam within minutes.[66] Although the majority of patients with neurologic emergencies are likely safe to receive succinylcholine, patients with denervation disorders, such as motor neuron diseases and peripheral nerve disorders, and patients with certain other muscular disorders, such as immobilization and burn injury, are at risk for cardiac arrest secondary to sudden hyperkalemia related to succinylcholine. Denervation disorders cause upregulation of acetylcholine receptors at the neuromuscular junction, which leads to rapid efflux of potassium after succinylcholine administration.[67] Although patients with neuromuscular junction disorders would not be anticipated to develop hyperkalemia with succinylcholine administration, those with myasthenia gravis are more resistant to succinylcholine, and those with Lambert-Eaton myasthenic syndrome have increased sensitivity to succinylcholine. Succinylcholine is contraindicated for patients with spinal muscle atrophy, amyotrophic lateral sclerosis, Guillain-Barré syndrome, congenital muscular dystrophies, congenital myopathies, and glycogen storage disease.[68] Although succinylcholine is safe immediately after a traumatic spinal cord injury, it should be avoided after the immediate phase. Additionally, there are numerous conditions, including myopathies and other muscular diseases, that may result in rhabdomyolysis, myotonic contractures, and malignant hyperthermia with the administration of succinylcholine.

There is no ideal neuromuscular blocking agent for rapid sequence intubation for patients in the neurocritical care unit, and drugs must be tailored to specific circumstances. In patients for whom succinylcholine is contraindicated, rocuronium should be utilized, keeping in mind that sugammadex, a non-depolarizing agent for rocuronium reversal, may be administered if an immediate neurologic exam is necessary following intubation to guide treatment decisions. Sugammadex is more rapid than cholinesterase inhibitors for reversal and leads to fewer side effects.[69]

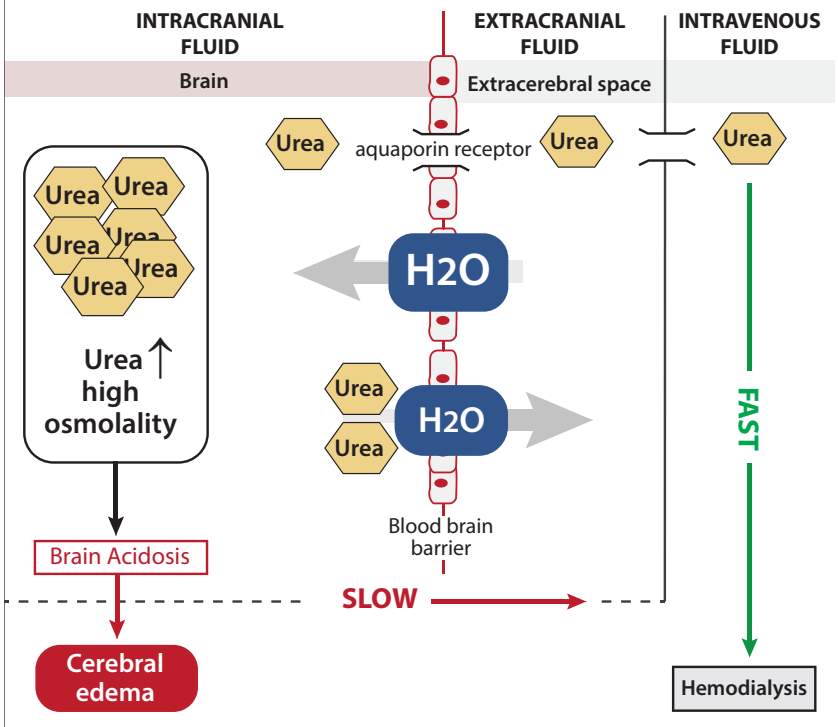
Certain patients with neurologic emergencies and concomitant renal failure leading to hyperkalemia require emergent dialysis. Dialysis decisions are more nuanced in patients for whom there is concern for space-occupying lesions or elevated intracranial pressure because of the risk of dialysis disequilibrium syndrome (DDS); see Figure 3. Dialysis transports solutes from the blood into the dialysate solution and removes water by ultrafiltration. During dialysis, urea and other osmoles that have accumulated in the brain do not clear as quickly as they do in the plasma. This leads to a gradient that favors water entering the brain. Aquaporin is also upregulated with the start of dialysis and leads to an increase of water movement into the brain. Additionally, paradoxical brain acidosis in the setting of CKD may contribute to abnormalities. These processes together

can increase brain water content and vasogenic edema, which may lead to DDS.[70] In patients without neurologic emergencies, the average increase in brain volume after dialysis is about 3% based on pre- and post-dialysis MRIs. For individuals with mass lesions, known cerebral edema, or decreased compliance, this increased brain volume may result in herniation.[71] Symptoms in patients without concomitant intracranial pathology are typically mild and may include headache or nausea. Severe DDS is typically seen in patients who are receiving dialysis for the first time and have a concomitant mass lesion, but may also be seen in patients who receive chronic dialysis and have developed an intracranial space occupying lesion.[72] Typically, the herniation event is irreversible and may lead to brain death, so prevention of DDS is imperative.

The risk of DDS is mitigated by providing continuous RRT, rather than IHD, since this decreases the speed of acute fluid shifts. The development of DDS is related to both the urea reduction ratio ([pre-dialysis BUN – post-dialysis BUN]/pre-dialysis BUN) and the speed of dialysis treatment.[73] Although continuous RRT has typically has been described as a safe alternative to IHD in the patient with risk of increased intracranial pressure, there has been one case of DDS in a patient receiving CRRT in whom the BUN decreased very rapidly.[74] Continuous RRT requires that a dialysis line be placed at the bedside, and is time and labor intensive for nursing staff in the ICU to setup and maintain. Thus, potassium may not be rapidly corrected even in the best circumstances.

Although cardiac arrest is not traditionally considered a neurologic emergency, neurointensivists are commonly consulted to manage hypothermia after cardiac arrest, or targeted temperature management (TTM). Hypothermia leads to significant potassium shifts, and electrolyte derangements are a recognized complication of TTM. Typically, hypokalemia occurs more commonly during TTM,

FIGURE 03 **Dialysis Disequilibrium Syndrome: Urea Leaves the Serum Quickly but the Brain Slowly**



In patients with renal insufficiency, urea and other solutes accumulate in the brain (left) and lead to elevated intracranial osmolality. Dialysis removes urea and other solutes quickly from the blood into the dialysate solution (right). Urea and other solutes are not pulled from the intracranial space as quickly due to the tight blood brain barrier (center). As urea is cleared from the blood during hemodialysis, the higher osmolality of the intracranial space favors a gradient that allows water to enter the brain, potentially leading to increased intracranial edema. Further, upregulation of aquaporin receptors and brain acidosis may contribute to increased intracranial water content.

Adapted from Tonsawan P (2013). ESRD, HD & death. [PowerPoint presentation]. Available at: http://slideplayer.com/slide/3451190/ (Accessed: October 1, 2018).

since hypothermia leads to both an intracellular shift of potassium and cold diuresis. However, hyperkalemia may be found in up to 32% of patients undergoing TTM, with an additional 10% developing hyperkalemia after rewarming. The prognostic significance of this is unknown, but in one study individuals with hypokalemia during TTM had lower odds of death and a statistically nonsignificant trend toward lower odds of poor neurologic outcome compared to those with normal potassium or hyperkalemia.[75]

Lastly, important pharmacologic interventions in patients with neurologic emergencies may lead to hyperkalemia. Mannitol, a drug rarely used outside the realm of neurologic emergencies, increases the serum potassium with a mean maximum increase of 1.5mEq/L from baseline when given in high doses (2 g/kg), and may lead to associated hyperkalemic ECG findings. Although the exact mechanisms for development of hyperkalemia after high dose mannitol administration are not clear, it is hypothesized that high doses of mannitol expand extracellular fluids, dilute bicarbonate leading to acidosis, lead to hemolysis of red blood cells, and create a solvent drag phenomena shifting intracellular potassium into the extracellular compartment.[76] In patients who receive mannitol either perioperatively or for treatment of elevated intracranial pressure, it is imperative to carefully monitor serum electrolytes and osmolarity.

Management of Acute Kidney Injury in the Neurocritical Care Unit

It is well known that AKI, and particularly AKI requiring RRT, is associated with increased morbidity and mortality among patients admitted to the ICU.[77,78] Due to reduced renal clearance, hyperkalemia frequently accompanies AKI and severe hyperkalemia may lead to cardiac dysfunction and sudden cardiac death.[79] Electrolyte homeostasis is a goal of ICU management and factors that contribute to nephrotoxicity and reduced renal clearance in ICU patients may worsen hyperkalemia. The incidence of AKI in general medical or surgical ICUs is well described. Depending on the definition of AKI used, up to 67% of ICU patients develop AKI.[78] Data on the frequency and complications of AKI in the neurological/neurosurgical ICU (neuro-ICU) are limited.[80]

There has been one single-center study of AKI in a mixed neurological/neurosurgical ICU, which included all 681 patients admitted to the unit from January 2005 to December 2011. Of the 681 patients, 57 (8.4%) had known CKD and 79 (11.6%) developed AKI. Of those with AKI, 36 (45.6%) required dialysis, and sepsis was the cause in 50% of cases. Antibiotics, nephrotoxic medications, CKD and cerebrovascular disease were independent risk factors for AKI. The need for dialysis was associated with increased mortality (hazard ratio, 2.8; CI, 1.3-6.3).[80]

Given these limited available data, the incidence, complications, treatments and impact on outcome of patients with AKI and hyperkalemia in the neuro-ICU are poorly described in the existing literature and only limited recommendations can be made. Nonetheless, AKI is clearly highly prevalent in the neuro-ICU with rates similar to those observed in medical and surgical ICUs.[78,81] The need for RRT among neuro-ICU patients (approximately 5% of all patients) is also similar to that observed in general ICU patients.[78] Consistent with data from the general ICU literature, sepsis, antibiotics and nephrotoxic medications are associated with AKI in the neuro-ICU, and the need for RRT is associated with increased mortality. Thus, infection prevention and avoidance of nephrotoxic drugs may help mitigate AKI and hyperkalemia in the neuro-ICU.

Impact of Hyperkalemia on the Surgical Patient and Critical Care Management

Hyperkalemia in the surgical patient is generally a reflection of acute changes in renal function, muscle ischemia or injury, or as a consequence of massive packed red blood cell (PRBC) component transfusion therapy. Since these events occur with a measurable, and in some circumstances, increasing frequency, evaluating evidence-based approaches to hyperkalemia management is important for reducing variations in care as one way of improving the quality and safety of care, as well as responsible economic stewardship.[82]

General Approach in Critically Ill Surgical Patients

Clinicians caring for surgical patients should remain vigilant for hyperkalemia in circumstances where acute changes in renal function may be anticipated, as well as in circumstances where therapy may be accompanied by unintended large volume potassium administration. Three specific circumstances are especially relevant:

1) Intra-operative care during procedures in which fluid administration is planned to be limited to decrease salt and water accumulation with its untoward impact on bowel wall edema and anastomotic integrity. Examples include enhanced recovery after surgery (ERAS) protocol colon resection, complex ventral hernia repair, and re-operative abdominal surgery.
2) Septic shock where AKI is common and may be progressive.
3) Hemostatic resuscitation after major injury where the transfusion of PRBCs, in particular units at the end of their storage life, may inadvertently infuse up to 60 mEq/L of potassium. Transfusion of more than seven units of PRBCs is strongly associated with hyperkalemia and appears to be associated with rapid infusion.[83]

Although a plethora of approaches to hyperkalemia management are currently utilized across ICUs, there are some commonalities that join the approaches.[84] They all focus on the three key elements: 1) support of myocardial conduction, 2) potassium displacement, and 3) potassium clearance. All patients may participate in the specific elements of 1) and 2) as previously discussed; however, the method of potassium clearance intimately depends upon both renal and GI function as well as plasma volume.

Potassium Clearance

The approach to potassium clearance may be conveniently grouped into two broad categories based on the ability to augment renal solute and water excretion in response to plasma volume expansion coupled with diuretic administration.

Preserved solute and water clearance: Expanding plasma volume with a solution that has a lower potassium concentration than the plasma reduces the overall potassium concentration. In this way, 0.9% normal saline solution (NSS), lactated Ringer's, Plasmalyte-B, and Normosol-R are all efficacious. Normal saline solution has traditionally been used in this setting since it is devoid of potassium. However, since patients with hyperkalemia are generally acidotic, the administration of "unbalanced" saline that may worsen acidosis via a hyperchloremia mechanism may be disadvantageous.[85] While acute plasma expansion is beginning to clear and dilute plasma potassium, accelerated clearance can be facilitated by administration of a loop diuretic to drive kaliuresis. Solutions that are hyperchloremic compared to plasma are generally acidifying whereas loop diuretics such as furosemide are generally alkalinizing. As a result, many are left with no change in their acid-base balance, which is ideal for normal individuals, but those with pre-existing acidosis may benefit from a more normal pH. In this regard, solutions other than 0.9% NSS may be ideal for "forced diuresis," as this approach is commonly known.

Impaired, ineffective or absent solute and water clearance: For those who are unable to respond to a diuretic challenge, one must determine whether they may safely receive plasma volume expansion. Bedside critical care ultrasound may be the optimal assessment tool for this purpose, but may be complemented by other measures to determine hypovolemia.[86] The determination of hypervolemia is less clearly defined outside of those with heart failure, or in whom plasma volume excess is evident on physical examination. Hypovolemic patients should be restored to euvolemia to improve systemic and microcirculation as well as to dilute the plasma potassium concentration. These patients can then be acutely rescued in the same manner as those who are unable to tolerate plasma volume expansion. A renal support technique, such as ultrafiltration, acute IHD, or continuous RRT, can be used depending on the need for metabolic clearance other than that related to hyperkalemia.

Patients who have impaired renal potassium excretion due to kidney disease are at further risk for hyperkalemia when their enteral potassium elimination is limited by GI transit pathology, such as in post-operative surgical patients. The GI mucosa is an electrolyte exchange membrane, and it is physiologically reasonable to use it as a means of augmenting potassium clearance. Cation exchange resins such as SPS have been used in that fashion. A key feature of such an agent is the ability to osmotically direct electrolyte rich fluid into the GI lumen, which has driven the preparation of SPS in a sorbitol base. Therefore, three conditions must be satisfied prior to use of a cation exchange resin such as SPS: 1) the patient is not hypovolemic, 2) there is access to the GI tract since SPS is poorly tolerated orally, and 3) there is preserved GI motility. The first and the third are of prime importance, since patients with hypovo-

lemia cannot move fluid into the GI lumen to participate in the exchange, and those with impaired motility are at increased risk of bowel wall ischemia under the influence of an immobile hypertonic therapeutic agent. Intestinal necrosis and perforation have been robustly described in this circumstance and have led to emergency laparotomy as well as a high fatality rate.[39] Therefore, the use of such resins should be strictly avoided in those patients with hypovolemia and/or ileus, and are absolutely contraindicated in patients with intestinal obstruction since the ultimate effect of resin administration is diarrhea. If all of the above prerequisites are not met, SPS management may be ineffective and prove harmful.

The Hospitalist Perspective on Care of Patients with Hyperkalemia

Criteria for Admitting Patients with Hyperkalemia

Based on 2011 data, approximately 67,000 patients with hyperkalemia presented to the ED in the United States and, of these, 50% were hospitalized. The average length of stay in the hospital for hyperkalemic patients was 3.2 days, at a mean cost of approximately $24,000 per stay. Overall, estimated hospital charges from Medicare admissions with a primary diagnosis of hyperkalemia were approximately $700 million per year.[87]

Age and comorbidities are important factors in determining the need for admission. The risk of hyperkalemia-associated mortality is highest in older patients who have comorbid illnesses.[87] Physicians should have a lower threshold for admission for patients who are older and/or have conditions such as heart failure, CKD, and diabetes than for patients who are younger and healthier. Another key factor in determining hospital admission is serum potassium concentration. As serum potassium levels rise above the normal range, there is an increase in hyperkalemia-associated mortality.[57] There is some controversy regarding the appropriate serum potassium concentration to use to determine which patients require hospital admission. A conservative approach would be to admit asymptomatic patients between 5.0 and 5.5 mEq/L, but a cut-off concentration of greater than 5.5 mEq/L may be more appropriate for some individuals. All patients with ECG changes, dysrhythmias, or muscle weakness associated with hyperkalemia should be admitted.

Criteria for Discharging Patients with Hyperkalemia

Three criteria need to be met before considering hospital discharge for a patient with hyperkalemia. First, the serum potassium levels should be normal. Second, symptoms, if they were present, should have abated. Third, the underlying cause should be identified and addressed. In patients with heart disease and CKD being treated with a RAAS inhibitor, the risk of hyperkalemia is a lifelong problem that requires finding a balance between effectively using RAAS inhibitor therapy and minimizing the risk of hyperkalemia over the long term. Before the novel potassium binders became available, physicians were faced with a very difficult choice to either reduce RAAS inhibitor therapy and increase the risk of morbidity, hospitalization, and mortality due to the progression of heart failure and CKD, or continue to administer RAAS inhibitor therapy and risk potentially life-threatening hyperkalemia. The novel potassium-binding agents may allow most patients with heart failure to receive the full benefits of RAAS inhibitor therapy while greatly reducing the risk of hyperkalemia.

Continuum of Care for Patients with Hyperkalemia

For patients with hyperkalemia who have other comorbidities, complex drug regimens, and dietary restrictions, such as heart failure patients taking RAAS inhibitors, successful transition of care from inpatient to outpatient status is critically important. The physician must ensure that the latest updates in the patient's medical condition, laboratory test results, new medications, and procedures are communicated to all the members of the patient's health care team. Accurate communication and comprehensive coordination of care are essential to ensure effective follow-up and prevent polypharmacy errors. Ideally, while in the hospital setting, the multidisciplinary team that is involved in the patient's acute and long-term care should be brought together for discussion. The admitting physician not only manages the patient's inpatient care, but also coordinates care with various specialists, including non-physicians, who can enhance patient care and provide education. Anyone involved in the patient's care, including the patient, should be updated and educated on the patient's latest medical condition, drug regimens, and nutritional requirements. Properly managing hyperkalemia requires dedicated self-care while away from the watchful eyes of health care professionals, most notably concerning dietary restrictions

involving potassium-containing foods. The patient needs to be monitored regularly to make sure that their serum potassium concentration remains within the normal range. The importance of monitoring serum potassium concentration in hyperkalemic patients after discharge depends on the underlying cause of the hyperkalemia. If the underlying cause can be completely eliminated (e.g., an AKI), there is no need for further monitoring. Conversely, patients with heart failure and CKD who are being treated with RAAS inhibitors will always be at risk for hyperkalemia and therefore need regular outpatient monitoring.

CONCLUSION AND FUTURE DIRECTIONS

This monograph summarizes the recommendations of the EMCREG-International Multidisciplinary Hyperkalemia Consensus Panel regarding management of hyperkalemia, particularly in the acute care setting, based on currently available data. Management of severe hyperkalemia requires interventions that are timely, synergistic and evidence-based. Interventions include myocardial protection, shifting of potassium to the intracellular space, correction of metabolic acidosis, and elimination of potassium through kaliuresis or RRT.

The newer GI cation exchange agents, patiromer and SZC, offer promise for reliable reduction of potassium in the outpatient setting. They appear to be safe and efficacious for the treatment of hyperkalemia and are well positioned to be further studied as an adjunct to ACEI, ARB, and MRA therapies in patients with heart failure and other cardiovascular diseases. However, the surrogate outcome of lowering potassium will likely not be enough to change practice. Currently, there are no randomized controlled data using GI cation exchange agents to manage hyperkalemia that demonstrate more effective titration of heart failure medication doses or improved outcomes.

Sodium zirconium cyclosilicate holds promise for rapid reduction of potassium in the ED and critical care settings, although it has not yet been studied for acute care. The upcoming ENERGIZE trial will investigate the efficacy of SZC for acute potassium reduction in the ED. The role of SZC in lowering and maintaining normal potassium levels in the critical care setting has also not yet been studied and serves as an important environment for further study.

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1. **The normal body's responses that allow it to handle increased potassium intake include all of the following EXCEPT:**
   - A. A gastric kidney reflex that inhibits the Na^+-Cl^- co-transporter
   - B. Decreased production of aldosterone
   - C. Increased flow and sodium delivery to the distal nephron
   - D. Circadian rhythm in which potassium excretion increases during the day when intake is highest

2. **Which of the following statements regarding hyperkalemia is TRUE?**
   - A. Hyperkalemia is usually defined as a potassium level > 6.0mEq/L
   - B. The single most important factor in hyperkalemia is decreased renal excretion due to medications
   - C. Contemporary diets contain approximately four-fold greater potassium content than prehistoric diets
   - D. Acute kidney injury (AKI) is often associated with severe reductions in the GFR (<10 ml/min), which becomes rate limiting for potassium secretion

3. **Factors that cause hyperkalemia by causing potassium to redistribute to the extracellular space include all of the following EXCEPT:**
   - A. Beta blockers
   - B. Cell injury
   - C. Metabolic acidosis
   - D. Heparin

4. **Guideline-directed medical therapies for heart failure that increase a patient's risk for hyperkalemia include all of the following EXCEPT:**
   - A. Angiotensin-converting enzyme inhibitors (ACEIs)
   - B. Loop diuretics
   - C. Beta blockers
   - D. Angiotensin receptor blockers (ARBs)

5. **All of the following medications increase the risk for hyperkalemia EXCEPT:**
   - A. Non-steroidal anti-inflammatory medications (NSAIDs)
   - B. Trimethoprim
   - C. Clonidine
   - B. Ketoconazole

6. **Which of the following electrocardiographic changes has/have been described in patients with hyperkalemia?**
   - A. Peaked T waves
   - B. Loss of P waves
   - C. QRS widening
   - D. Ventricular tachycardia
   - E. All of the above

7. **Which of the following hyperkalemia management drugs is specifically used to prevent cardiotoxicity?**
   - A. Calcium gluconate
   - B. Insulin
   - C. Sodium zirconium cyclosilicate (SZC)
   - D. Patiromer

8. **Which of the following therapies is considered a "definitive" treatment for hyperkalemia?**
   - A. Insulin/glucose
   - B. Calcium gluconate
   - C. Furosemide
   - D. Albuterol

9. **All of the following statements regarding management of hyperkalemia are true EXCEPT:**
   - A. Sodium polystyrene sulfonate (SPS) has been proven effective for hyperkalemia management in multiple, large randomized, controlled trials
   - B. SZC is approved by the Food and Drug Administration for the treatment of adults with hyperkalemia
   - C. Calcium gluconate is considered first-line therapy for hyperkalemia
   - D. Optimal kalemic effects of insulin occur when administered as a bolus followed by an infusion

10. **Common prehospital interventions for hyperkalemia are:**
    - A. Albuterol and sodium bicarbonate
    - B. Albuterol, sodium bicarbonate, and insulin
    - C. Albuterol, sodium bicarbonate, insulin, and furosemide
    - D. Emergent hemodialysis

11. **Special consideration for hyperkalemia should be taken in the following scenario(s):**
    - A. Construction worker partially buried in a trench for 12 hours
    - B. Victim of an earthquake trapped in a collapsed building
    - C. Dialysis-dependent person rescued from their home six days after a hurricane
    - D. All of the above

12. **Which anatomical site(s) would be considered the most appropriate for placement of a dialysis catheter in a patient who needs emergent hemodialysis?**
    - A. The subclavian vein
    - B. The femoral artery
    - C. The internal jugular vein
    - D. The radial artery

13. Insulin and glucose medication errors during the treatment of hyperkalemia have been identified most frequently in which of the following patient care areas?

A. Medical intensive care unit

B. Emergency department

C. Medical/surgical unit

D. Telemetry unit

14. A patient is admitted to the medical intensive care unit (ICU) with rhabdomyolysis and has the following electrolyte abnormalities: a potassium of 7.8 mEq/L, bicarbonate of 18 mEq/L and creatinine of 3.1 mEq/L. The patient has no history of renal disease and is hemodynamically stable. Which of the following statements regarding the management of hyperkalemia in this patient is TRUE?

A. Shifting agents, including insulin and beta agonists, should be continued until and during dialysis in order to reduce serum potassium levels.

B. Continuous renal replacement therapy (CVVH) is the optimal initial choice of renal replacement therapy in this patient.

C. A low potassium dialysate concentration (zero K bath) should be used since it will quickly lower the patient's potassium levels without any potential side effects.

D. Data suggest that this patient may be at higher risk of complications from this level of hyperkalemia than a patient with chronic kidney disease.

15. A patient is admitted to the ICU with septic shock secondary to pneumonia. The patient is on a high flow nasal cannula, vasoactive infusions and has developed non-oliguric acute on chronic kidney injury. Labs are significant for a potassium of 5.9, bicarbonate of 18, BUN of 60 and creatinine of 4.0. The patient is still making urine, has no ECG changes and no weakness. An appropriate treatment strategy to lower serum potassium safely in this patient is:

A. This patient has hyperkalemic urgency. Treatment should focus on potassium excretion in a relatively gradual yet reliable manner with a 10 g dose of SZC.

B. This patient has hyperkalemic emergency. The patient should receive shifting agents emergently and then potassium levels should be closely monitored.

C. This patient has hyperkalemic emergency. The patient should receive shifting agents in preparation for starting renal replacement therapy (CVVH).

D. This patient has no clinical signs of hyperkalemia. Treatment should focus on underlying cause only.

16. Sodium zirconium cyclosilicate could be considered as an option to enhance potassium elimination in the medical ICU patient because of all of the following EXCEPT:

A. It binds potassium throughout the gastrointestinal tract, providing a more immediate and predictable onset of action.

B. Data suggest that the steepest decline in potassium after its administration occurs during the first four hours of therapy.

C. In patients who are unable to take oral medications, it can be administered either through a nasogastric tube or rectally.

D. During clinical trials, its side effects, including edema and QTc prolongation, were minimal and not clinically relevant.

17. Which of the following is a neurologic symptom of hyperkalemia?

A. Diffuse numbness

B. Bulbar muscle weakness

C. Paresthesias

D. Ascending muscle weakness

18. A patient with which of the following conditions would be at high risk for hyperkalemic cardiac arrest following the administration of succinylcholine?

A. Post-operative spinal cord injury

B. Lambert-Eaton syndrome

C. Congenital muscular dystrophy

D. Myasthenia gravis

19. All of the following statements regarding AKI in patients in the neuro-ICU are true EXCEPT:

A. <10% of patients with AKI in the neuro-ICU require dialysis

B. Sepsis is the most common etiology of the AKI

C. Nephrotoxic medications are an independent risk factor for AKI

D. Need for dialysis is associated with increased mortality

20. A patient with a history of Stage 3 chronic kidney disease and systolic congestive heart failure has hyperkalemia after a lower extremity revascularization procedure. Her potassium is 6.8 mEq/L with an increase in creatinine to 3.3 from her baseline of 2.4. Her urine output over 6 hours is 34 ml and her blood pressure is 102/72 mmHg. The most appropriate next step in managing her hyperkalemia is:

A. D50W by bolus plus insulin 10 units intravenously (IV)

B. 1-liter plasma volume expansion

C. Calcium gluconate by IV bolus

D. Immediate Nephrology consultation

(Answer sheet next page)

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Evaluation Questionnaire

On a scale of 1 to 5, with 1 being highly satisfied and 5 being highly dissatisfied, please rate this program with respect to:

Overall quality of material:	1	2	3	4	5
Content of monograph:	1	2	3	4	5
Other similar CME programs:	1	2	3	4	5
Course objectives were met:	1	2	3	4	5

1. **What topics would be of interest to you for future CME programs?**

   _____

2. **Was there commercial or promotional bias in this monograph?**

   ☐ **YES** ☐ **NO** **If YES, please explain:** _____

   _____

3. **How long did it take for you to complete this monograph?** _____

Name (Please Print Clearly): _____

Email (Required): _____

E-mail is required by CME office to generate CME certificates, create your identify in our system, and for CME Office support.

Degree: _____ Specialty: _____

Academic Affiliation (if applicable): _____

CME ANSWER SHEET

(circle correct answer)

1.	**a**	**b**	**c**	**d**	
2.	**a**	**b**	**c**	**d**	
3.	**a**	**b**	**c**	**d**	
4.	**a**	**b**	**c**	**d**	
5.	**a**	**b**	**c**	**d**	
6.	**a**	**b**	**c**	**d**	**e**
7.	**a**	**b**	**c**	**d**	
8.	**a**	**b**	**c**	**d**	
9.	**a**	**b**	**c**	**d**	
10.	**a**	**b**	**c**	**d**	
11.	**a**	**b**	**c**	**d**	
12.	**a**	**b**	**c**	**d**	
13.	**a**	**b**	**c**	**d**	
14.	**a**	**b**	**c**	**d**	
15.	**a**	**b**	**c**	**d**	
16.	**a**	**b**	**c**	**d**	
17.	**a**	**b**	**c**	**d**	
18.	**a**	**b**	**c**	**d**	
19.	**a**	**b**	**c**	**d**	
20.	**a**	**b**	**c**	**d**	

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