Emergency Management and Commonly Encountered Outpatient Scenarios in Patients With Hyperkalemia

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Hyperkalemia is a common electrolyte disorder with potentially lethal consequences. Severe hyperkalemia can lead to life-threatening cardiac dysrhythmias, making a clear understanding of emergency management crucial. Recognition of patients at risk for cardiac arrhythmias should be followed by effective strategies for reduction in serum potassium levels. In the outpatient setting, diagnosis of hyperkalemia can be complicated by factitious elevations in serum potassium levels. True elevations in serum potassium levels are commonly due to medications used for cardiovascular disease in the setting of impaired glomerular filtration rate. The prevalence of chronic kidney disease is steadily increasing, likely leading to increases in risk of hyperkalemia. A systematic approach will aid in timely diagnosis and management of hyperkalemia.

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ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CHF = chronic heart failure; CKD = chronic kidney disease; ECG = electrocardiographic; GFR = glomerular filtration rate; NSAID = nonsteroidal anti-inflammatory drugs; RALES = Randomized Aldactone Evaluation Study

Hyperkalemia is a common metabolic disturbance with potentially life-threatening consequences. It is often silent, could occur suddenly, and leads to cardiac arrhythmias and potentially to death. In the general outpatient population, the incidence is relatively low and not well reported. In hospitalized patients, incidence ranges from 1% to 10%, with a mortality rate of 1 per 1000 patients.[1,2] The most common causes are potassium shift from the intracellular to the extracellular space, impaired excretion due to renal failure, or medications, with most patients having multiple etiologies.

The average North American consumes 40 to 80 mEq/L (to convert to mmol, multiply by 1) of potassium daily. Most (80%-90%) is excreted by the kidney, with the remainder excreted by the gastrointestinal tract. In the body, 98% of potassium is intracellular with tight regulatory control on the remaining 2% in the extracellular compartment.

LIFE-THREATENING HYPERKALEMIA

Because hyperkalemia can lead to life-threatening cardiac arrhythmias, prompt recognition and diagnosis are crucial. Patients with severe hyperkalemia could present with generalized weakness, paralysis, arrhythmias, or sudden cardiac arrest.

The generation of a resting membrane potential is crucial for cardiac myocyte contraction. Movement of potassium into the intracellular space via the sodium-potassium adenosine triphosphatase pump is responsible for the –90-mV (to convert to V, multiply by 1000) resting membrane potential. As the extracellular potassium concentration increases, the concentration gradient across the myocyte cell membrane decreases, eventually leading to a slowing of myocardial functioning.[3]

Electrocardiographic (ECG) findings could provide the first evidence of hyperkalemia (Figure 1).[4,5] In general, a correlation can be observed between increasing abnormality of ECG patterns and increasing serum potassium concentrations. However, patient-to-patient variability is high. Unfortunately, ECG changes might be subtle or even absent, further complicating the diagnosis. In a retrospective review, ECG changes were seen in 43% of patients with potassium values ranging from 6.0 to less than 6.8 mEq/L and in only 55% of patients with values of 6.8 mEq/L or greater.[1] Thus, ECG findings might not be sensitive in detecting mild and moderate hyperkalemia. Many case reports in the literature describe patients with severe hyperkalemia who present with a normal ECG result.[6] Therefore, any ECG change should be viewed as an emergency and empiric treatment initiated (Figure 2). Few clinical trials have evaluated the efficacy of treatment of hyperkalemia, but it is benign under most circumstances. No evidence exists indicating at which serum potassium value life-saving therapies should be administered.

CARDIAC STABLIZATION

CALCIUM SALTS

Calcium infusion, the first step in emergency management, stabilizes cardiac myocyte membranes. The usual dose is 500 to 1000 mg (5-10 mL of a 10% solution) given intrave-

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Serum potassium	Typical ECG appearance	Possible ECG abnormalities
Mild (5.5-6.5 mEq/L)		Peaked T waves Prolonged PR segment
Moderate (6.5-8.0 mEq/L)		Loss of P wave Prolonged QRS complex 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

FIGURE 1. Electrocardiographic (ECG) manifestations of hyperkalemia. Data from references 4 and 5.

nously over 2 to 3 minutes with cardiac monitoring. It has a rapid onset of action (3-5 minutes) and lasts for upwards of 1 hour. It has no effect on serum potassium level and is effective even when the patient is normocalcemic. Because of the unpredictable nature of cardiac arrhythmias, calcium infusion should be administered if any ECG change suggests hyperkalemia. Patients without ECG changes but who are at high risk for developing arrhythmias (eg, those with rapidly increasing potassium levels or coexisting electrolyte disorders) might benefit from prophylactic administration of calcium. If ECG changes are present, administration of intravenous calcium should normalize the ECG patterns. If it does not, a second dose can be administered.

Two formulations are available: calcium chloride and calcium gluconate. More calcium is contained in 10 mL of a 10% solution of calcium chloride (27.2 mg/dL [to convert to mmol, multiply by 0.25] than in 10 mL of a 10% solution of calcium gluconate (8.8 mg/dL). Calcium gluconate requires metabolism by the liver; in patients in a state of shock and with poor hepatic perfusion, conversion to the biologically active form may be impaired.[7] Calcium chloride can lead to venous irritation and tissue injury with extravasation.

The use of calcium infusion in patients with concurrent digitalis toxicity is of concern because the sudden influx of calcium into cardiac myocytes could worsen bradyarrhythmia and potentially cause arrest. Some authors recommend slow infusion of calcium gluconate if ECG changes due to hyperkalemia, such as loss of P waves or QRS complex widening, are present. In this situation, calcium should be diluted in 250 mL of 5% dextrose in water and given over 30 minutes.[3] Alternatively, cases have been reported in which cardiac arrhythmia improved only after administration of digoxinlike Fab fragments.[8] Last, hemodialysis might be required for rapid removal of the potassium in cases of digoxin toxicity, with concurrent administration of Fab fragments if other measures have failed.

No clinical trials on the efficacy of calcium infusion in patients with hyperkalemia have been conducted. Nevertheless, it has been used in the management of hyperkalemia for more than 100 years and should be the first step in management.

INSULIN

Insulin is a well-established therapy that rapidly decreases serum potassium concentrations by inducing intracellular shift. Intravenous administrations of insulin or continuous infusion with glucose have been shown to be effective.[9] Serum potassium levels decrease within 15 minutes, with the effect peaking at approximately 60 minutes and lasting for 4 to 6 hours. The magnitude of the decrease ranges from 0.5 to 1.0 mEq/L and is dose dependent, with a greater shift occurring after administration of 20 vs 10 U of regular insulin.[10] In the presence of hyperglycemia (blood glucose >360 mg/dL [to convert to mmol/L, multiply by 0.0555), insulin alone should be given, as additional glucose leads

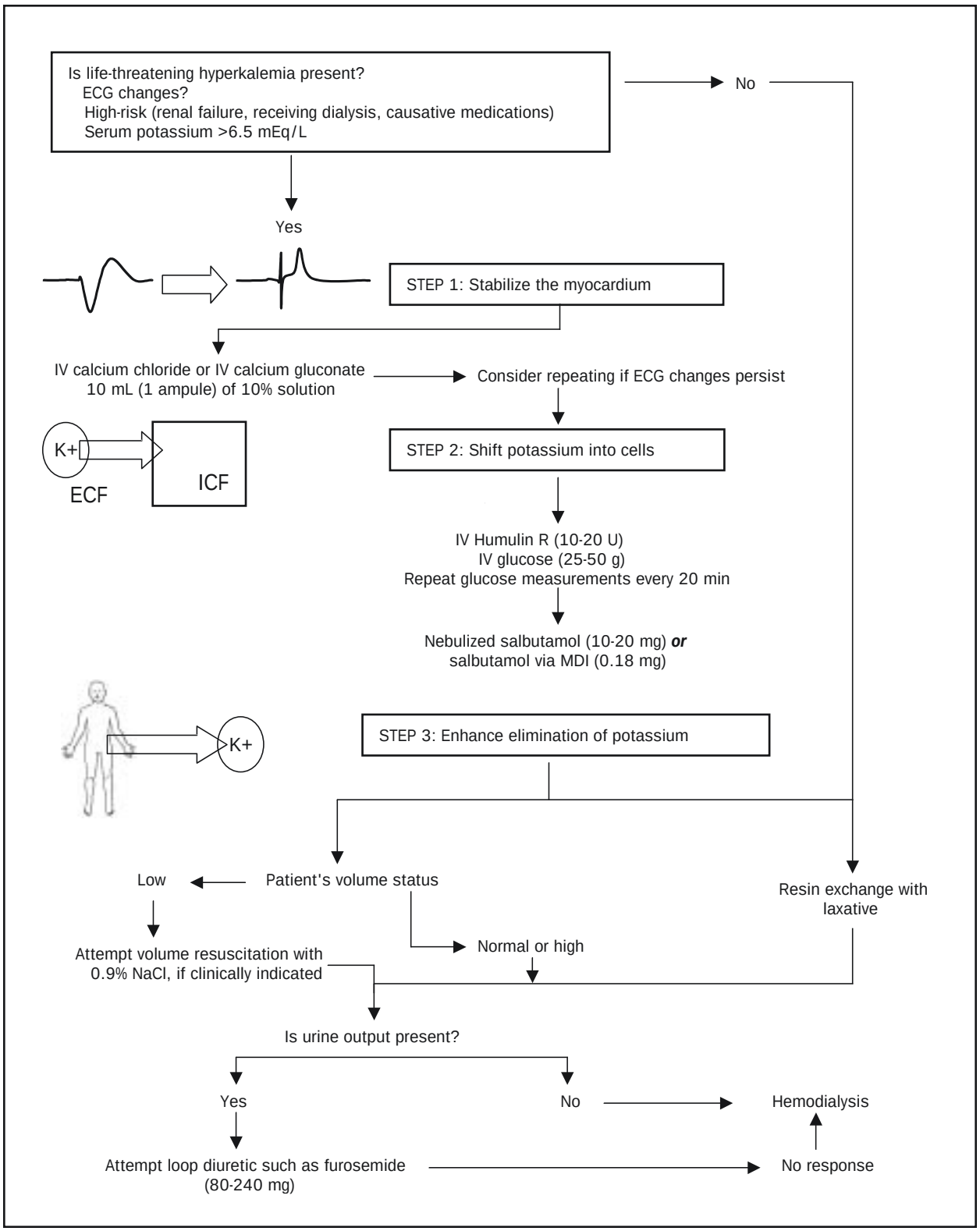

FIGURE 2. Algorithmic management of hyperkalemia. ECF = extracellular fluid; ECG = electrocardiographic; ICF = intracellular fluid; IV = intravenous; K = potassium; MDI = metered-dose inhaler; NaCl = sodium chloride.

to hypertonicity that can aggravate hyperkalemia. Hypoglycemia, the major adverse reaction, can be avoided by careful monitoring and administration of 25 to 50 g of glucose (1-2 ampules of 50% dextrose). In children, glucose administration alone is often used to increase endogenous insulin secretion.[11] Little evidence supports this approach in adults; paradoxically, osmolality could exacerbate the hyperkalemia.[12]

β-Agonists

When administered intravenously, or by a nebulizer or metered-dose inhaler, β-agonists decrease plasma potassium levels. Albuterol can be administered via a nebulizer (10-20 mg in 4 mL of saline) or via intravenous infusion (0.5 mg). A decrease in serum potassium levels occurs within 1 to 2 minutes and peaks at 40 to 80 minutes.[13] The effect lasts up to 4 to 6 hours, after which the level steadily increases to the original plasma potassium value. The reduction, which ranges from 0.4 to 1.5 mEq/L, is dose dependent.[9] In experimental settings, maximal decreases of 0.62 and 0.98 mEq/L have been reported after administration of 10 mg and 20 mg, respectively, of nebulized albuterol.[14]

Dosages of β-agonists administered in this setting are relatively high, ranging from 4 to 8 times that recommended for treatment of an acute asthma exacerbation.[15] The major adverse effects are tremor, tachycardia, anxiety, and flushing. Up to one-third of patients showed no response to β-agonists; no factors could be identified in these patients that would have predicted treatment failure. Further, caution must be advised with the use of β-agonists in patients prone to arrhythmias or with coronary artery disease. The effect of concomitant nonselective β-blocker use on potassium shift is unknown.

Bicarbonate

Bicarbonate therapy traditionally has been administered as either a continuous infusion or a bolus dose of 1 ampule (50 mEq) of sodium bicarbonate. Administration of large amounts may lead to alkalosis, volume overload, and hypernatremia. Unfortunately, bicarbonate therapy has failed to show significant, predictable reductions in serum potassium levels under experimental conditions.[16] In small studies of patients receiving hemodialysis,[16,17] bicarbonate has shown variable benefit in the reduction of serum potassium levels. This benefit was seen only in the presence of substantial metabolic acidosis (bicarbonate <22 mEq/L), and it is unclear whether this finding can be extrapolated to the general population.

Cation Exchange Resins and Laxatives

Cation exchange resins bind potassium in the gastrointestinal tract and enhance fecal elimination. Two major types are available: sodium polystyrene (exchanges sodium for potassium) and calcium resonium (exchanges calcium for potassium). Exchange resins can be administered orally or rectally, but the former is more effective because of its longer transit time. The usual oral dose is 15 to 30 g in 50 to 100 mL of 20% sorbitol. Conflicting data have been reported regarding the effectiveness of exchange resins in lowering serum potassium levels. The onset of action is slow (2 hours) with peak effects after 4 to 6 hours.[18] The major complication is intestinal necrosis and bowel perforation, with reported rates of 0.27% to 1.8%.[19]

Stool excretion of potassium is low but increases up to 3-fold in patients with chronic renal failure and end-stage renal disease.[20] In healthy people, as much as 4 mEq/L of gastrointestinal potassium can be excreted daily. Thus, under optimal conditions, up to 12 mEq/L of potassium can be removed by the colon daily; however, this rate is limited substantially by stool volume.[15]

Exchange resins are frequently administered with osmotic laxatives (eg, lactulose, sorbitol), and so it is unclear which agent is responsible for decreases in serum potassium levels. The potential of osmotic laxatives to induce hypokalemia became well known after a series of case reports illustrating electrolyte abnormalities with laxative abuse.[21] They are thought to increase stool potassium secretion and induce volume contraction, stimulating aldosterone release. Osmotic laxatives that are used for bowel cleansing before colonoscopy (eg, sodium phosphate and polyethylene glycol–electrolyte lavage solution) lead to colonic potassium loss. In an observational cohort study conducted to determine serum electrolyte levels after sodium phosphate administration in 100 patients who underwent outpatient colonoscopy, a 26% rate of hypokalemia and a reduction of mean serum potassium levels of 0.54 mEq/L were observed.[22] Thus, it remains unclear whether most of the colonic potassium loss was due to the osmotic laxatives alone or whether it was triggered by the addition of exchange resin. Nevertheless, exchange resins with or without laxative agents should not be used exclusively to treat acute hyperkalemia because of their slow onset of action.

Hemodialysis

Hemodialysis can rapidly remove large amounts of potassium and is the treatment of choice for patients with life-threatening hyperkalemia that is refractory to medical management. Under ideal conditions, the serum potassium level can decrease by 1.0 to 1.5 mEq/L for each hour of dialysis.[10] Superior potassium clearance can be achieved by decreasing the dialysate potassium concentration and increasing the blood pump speed.

Renal Excretion

More than 90% of absorbed potassium is excreted in the urine. Under normal conditions, 40 to 80 mEq of potassium is excreted in the urine daily; this rate greatly increases with increasing potassium load. If a patient's urine output is good, renal excretion is an excellent method to eliminate excess potassium. Urinary potassium elimination can also be increased by administration of loop diuretics (furosemide) with or without volume expansion with 0.9% sodium chloride.

The transtubular potassium gradient is a useful calculation for determining whether the renal response to hyperkalemia is appropriate. When potassium levels are high, renal excretion of potassium should also be high, when corrected for osmolality. A low transtubular potassium gradient is suggestive of a renal cause of hyperkalemia, whereas a high value suggests intracellular shift or intake.

COMMON CAUSES OF OUTPATIENT HYPERKALEMIA

After stabilization of the patient and emergency management, focus should shift to the underlying etiology of the hyperkalemia. Common etiologies of hyperkalemia are listed in Table 1[23] and discussed below, and a diagnostic approach is outlined in Figure 3.

Factitious Hyperkalemia

Factitious hyperkalemia (part of the differential diagnosis) occurs when the laboratory potassium value is higher than the actual plasma potassium value. The most common cause is lysis of red blood cells due to specimen handling or collection errors.[24] Elevations in potassium levels can be caused by fist clenching during collection, venipuncture downstream from intravenous infusions containing potassium, and forcible expression of blood. Prolonged storage and extremes in temperature also falsely elevate potassium values. Laboratories that continually report high rates of factitious results (often reported as a hemolyzed sample) should review their collection policies and sample-handling procedures. Hematological abnormalities, such as leukocytosis, thrombocytosis, and polycythemia, can also cause factitious hyperkalemia by increasing cell fragility.

When faced with an elevated potassium value of uncertain significance, the physician should consider the patient's risk factors for hyperkalemia. A history of renal disease, obstructive uropathy, clinical features of weakness or myopathy, and use of medications that increase potassium (eg, angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], aldosterone antagonists, nonsteroidal anti-inflammatory drugs [NSAIDs], potassium supplements, trimethoprim) should prompt concern. To help differentiate a factitious from a true value, the potassium level should be retested, with care taken to ensure minimal trauma, optimal storage conditions, and rapid analysis. If the patient is at considerable risk for hyperkalemia, an ECG test is warranted. To assess factitious hyperkalemia due to increased cell fragility, additional samples of serum and plasma potassium should be taken using a heparinized tube. A discrepancy of more than 0.3 mEq/L will secure the diagnosis.[25]

TABLE 1. **Causes of Hyperkalemia***

Factitious hyperkalemia
Increased intake
Potassium supplements
Penicillin G potassium
Nutritional supplements
Increased shift from intracellular space
Cell destruction
Massive hemolysis
Tumor lysis syndrome
Rhabdomyolysis
Burns
Trauma
Normal anion gap acidosis
Lack of insulin
Diabetic ketoacidosis
Starvation
Somatostatin
Hyperosmolality
Hyperkalemic periodic paralysis
Succinyl choline
β-Blockers
Digoxin intoxication
Dried toad skin (Chan Su/Senso)
Intravenous amino acids
Impaired renal excretion
Decreased distal flow
Decreased effective circulating volume
Chronic or acute renal failure
Nonsteroidal anti-inflammatory drugs
Hypoaldosteronism
Primary adrenal insufficiency
Medications and herbals
Spironolactone
Triamterene
Amiloride
ACE inhibitors/ARBs
Trimethoprim/pentamidine
Cyclosporine/tacrolimus
Heparin
Primary renin insufficiency
Pseudohypoaldosteronism
Distal renal tubular acidosis
Congenital adrenal hyperplasia
Interstitial renal disease
Unknown mechanism
Alfalfa
Dandelion
Noni juice

*ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker.
Data from reference 23.

Medication-Induced Hyperkalemia

Multiple medications are known to contribute to hyperkalemia. We will focus on the medications that are most

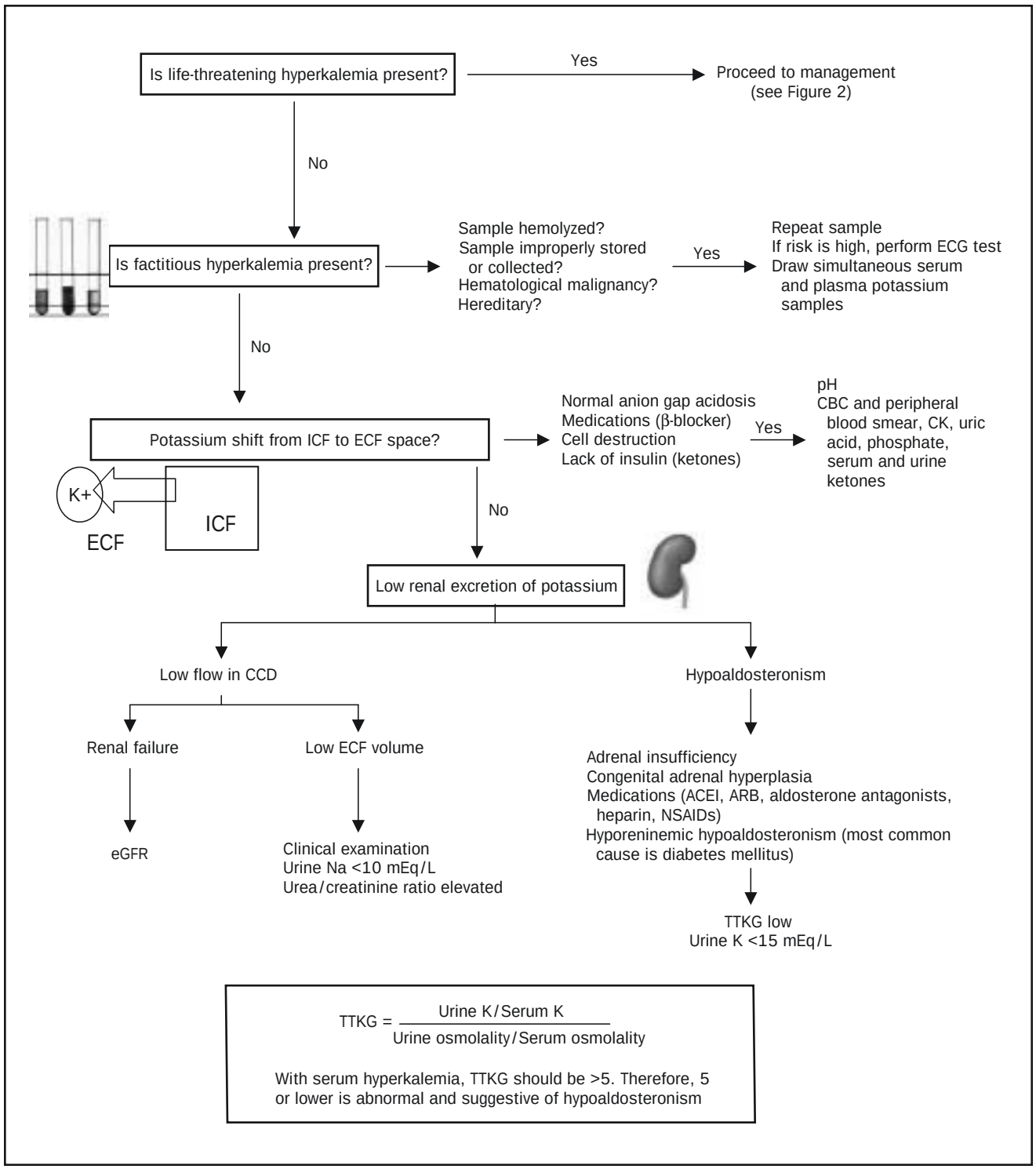

FIGURE 3. Algorithmic approach to the diagnosis of hyperkalemia. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CBC = complete blood cell count; CCD = cortical collecting duct; CK = creatine kinase; ECF = extracellular fluid; ECG = electrocardiographic; eGFR = estimated glomerular filtration rate; ICF = intracellular fluid; K = potassium; Na = sodium; NSAID = nonsteroidal anti-inflammatory drug; TTKG = transtubular potassium gradient.
SI values: To convert urine sodium and potassium values to mmol/L, multiply by 1.

commonly prescribed or causative, ie, ACE inhibitors, ARBs, aldosterone antagonists, β-blockers, NSAIDs, and heparin.

ACE Inhibitors and ARBs

ACE inhibitors act by blocking the enzyme that converts angiotensin I to angiotensin II, eventually leading to decreased aldosterone secretion and, in certain situations, a reduced glomerular filtration rate (GFR). ACE inhibitors decrease potassium excretion by causing hypoaldosteronism; whereas ARBs antagonize at the level of the angiotensin receptor. Large randomized controlled trials have examined the use of ACE inhibitors and ARBs in various populations; however, most have excluded patients with renal disease or have failed to report the rates of hyperkalemia. Because no difference has been observed between the 2 classes of agents in the rate and severity of hyperkalemia, their risks should be considered equivalent. In low-risk patients, the reported rates of hyperkalemia due to ACE inhibitors and ARBs are 1.3% and 1.5%, respectively.[25] This risk increases substantially with dose escalation, use of concurrent hyperkalemia-inducing medications, and use in patients with diabetes mellitus, chronic kidney disease (CKD), and chronic heart failure (CHF). Prevention and management strategies include careful monitoring, minimization of dosages, elimination of NSAIDs, and use of potassium-sparing diuretics. Thiazide diuretics (if creatinine clearance >30 mL/min) or loop diuretics can be administered to increase renal potassium clearance.

Aldosterone Antagonists

Aldosterone antagonists (also known as potassium-sparing diuretics) are commonly prescribed for the treatment of patients with CHF. Significant mortality benefit was observed in the Randomized Aldactone Evaluation Study (RALES) with the addition of spironolactone to standard CHF treatment.[26] Notably, patients were excluded if their creatinine level was more than 2.5 mg/dL (to convert to μmol/L, multiply by 88.4) or their serum potassium level was more than 5 mEq/L. This population had an average age of 65, and more than 90% were taking ACE inhibitors; the maximum dosage of spironolactone used was 50 mg/d. Juurlink et al[27] analyzed the effect of the RALES trial on patient prescriptions and hospitalization rates due to hyperkalemia. They found an increase in the rate of hospitalization due to hyperkalemia (from 2.4 to 11.0 per 1000 patients) and in mortality attributed to hyperkalemia (from 0.3 to 2.0 per 1000 patients). Juurlink et al thought these increases could be due to use of inappropriately high doses of spironolactone, use in patients with low GFR, and poor monitoring. Many other investigators have reported rates of hyperkalemia in the post-RALES era, with the highest being 36% in elderly (mean age, 73) patients with CHF who concurrently used ACE inhibitors and had a serum creatinine level greater than 1.7 mg/dL.[28] It is of particular concern that the rate of serious hyperkalemia (>6.0 mEq/L of potassium) ranged from 6% to 12%.[29,30] To reduce the number of adverse events with spironolactone, we recommend its use in appropriate patients (those with a serum creatinine level of <2.5 mg/dL or with CHF and an ejection fraction of grade 3 or 4) and serial monitoring of the serum potassium level up to 2 months after initiation, starting with the lowest available dosage and titrating upward with caution, taking care never to exceed 50 mg/d.

β-Blockers

Nonselective β-blockers can induce hyperkalemia by reducing renin secretion and by decreasing intracellular shift of potassium. Despite the wide use of β-blockers in the general population, there is little evidence that they consistently increase potassium levels. In some studies, patients often had other possible explanations for hyperkalemia, including other medications, recent operations, and coexistent renal disease.[31-34] Nevertheless, the reported incidence has been as high as 17% in some studies. At this time, the effect of β-blockers on the development of hyperkalemia remains unclear.

Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs induce hyperkalemia by impairing renin secretion and by decreasing GFR by afferent arteriolar constriction. Nonsteroidal anti-inflammatory drugs are a well-established cause of hyperkalemia; rates of up to 47% are reported with the use of high-dose indomethacin in a high-risk population.[35] The hyperkalemia often occurs in the setting of concomitant acute renal failure. Peak potassium levels occur 3 days to 3 weeks after initiation. The newer class of PTGS2 inhibitors are also implicated. Risk factors for NSAID-induced hyperkalemia include older age, mild to moderate renal insufficiency, and concurrent ACE inhibitor use.

Heparin

Heparin leads to hypoaldosteronism by inhibiting aldosterone production by the adrenal glands. Both unfractionated and low-molecular-weight heparins have been reported to lead to hyperkalemia. However, occurrences are uncommon, with reported rates of 7% to 8%,[36] and appear to be dependent on dose. The low dosages used for deep vein thrombosis prophylaxis (5000 U of subcutaneous heparin, 2-3 times daily) have also led to hyperkalemia even upon withdrawal and rechallenge.[37] Treatment of heparin-induced hyperkalemia is withdrawal of heparin;

however, Sherman et al[38] have reported successfully treating it using oral fludrocortisone (0.1 mg/d).

Chronic Kidney Disease

With gradual decreases in renal function, the kidney compensates and increases potassium excretion. In patients with CKD, increased aldosterone levels enhance potassium excretion in the cortical collecting duct. A 2-fold to 4-fold increase in colonic excretion is also observed. Eventually, as GFR decreases below 10 mL/min, hyperkalemia could develop as compensation mechanisms are overwhelmed. Due to the dependence on increased aldosterone for potassium secretion, medications that inhibit or interfere with aldosterone (ACE inhibitors, ARBs, NSAIDs, aldosterone antagonists) can lead to hyperkalemia in patients with CKD. Those with a GFR of less than 30 mL/min are generally susceptible.[39] Unfortunately, many hyperkalemia-inducing medications such as ACE inhibitors and ARBs also halt the progression of renal disease. Thus, a balance should be achieved between the need to continue these medications and the risks of hyperkalemia. Susceptible patients should be placed on a low-potassium diet and begin taking diuretics. Patients with metabolic acidosis should begin taking sodium bicarbonate. When ACE inhibitors and/or ARBs are initiated in patients with an estimated GFR of less than 60 mL/min, serum potassium levels should be checked within 1 week.

CONCLUSION

Hyperkalemia is a common electrolyte disorder with potentially lethal consequences. Recognition of and prompt treatment in hyperkalemic emergencies can prevent life-threatening cardiac arrhythmias. Identifying true hyperkalemia among outpatients can be challenging. The appropriate management of medications in patients who are susceptible is vital. The prevalence of CKD is steadily increasing, likely leading to a steady increase in risk of hyperkalemia.

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Questions About Hyperkalemia

1. Which *one* of the following statements regarding ECG findings in acute hyperkalemia is *false*?
   a. The classic findings are tall T waves, loss of P waves, and a widened QRS complex
   b. It is 100% sensitive for detecting hyperkalemia
   c. If ECG changes are present, should prompt immediate treatment
   d. They should normalize with the administration of intravenous calcium therapy
   e. They can include arrhythmias, such as heart block and junctional rhythms

2. Which *one* of the following is *not* an acceptable therapy for life-threatening hyperkalemia?
   a. Intravenous calcium chloride or calcium gluconate
   b. Hemodialysis
   c. Nebulized albuterol
   d. Subcutaneous insulin
   e. 4 to 8 puffs of albuterol via metered-dose inhaler

3. Which *one* of the following statements regarding factitious hyperkalemia is *false*?
   a. The major cause is error in collection and specimen handling
   b. It may be due to hematological abnormalities, such as leukocytosis
   c. It can never occur concurrently with life-threatening hyperkalemia
   d. If it occurs frequently, it should prompt review of collection, handling, and laboratory procedures
   e. It should prompt consideration of a patient's risk factors for true hyperkalemia

4. Which *one* of the following statements regarding medication-induced hyperkalemia is *true*?
   a. Hyperkalemia is more frequent and severe with use of ACE inhibitors than of ARBs
   b. The risk of hyperkalemia is high when ACE inhibitors and ARBs are used in low-risk patients
   c. The concurrent use of ACE inhibitors and aldosterone antagonists does not lead to further increases in serum potassium level vs administration of each agent individually
   d. Aldosterone antagonists are safe at doses of 50 mg/d and greater in patients with chronic renal failure
   e. Furosemide can offset the increase in serum potassium level seen with the use of ACE inhibitors and ARBs

5. Which *one* of the following is a *risk factor* for medication-induced hyperkalemia?
   a. Estimated creatinine clearance greater than 70 mL/min
   b. Female sex
   c. Presence of diabetes mellitus
   d. Use of analgesics, such as acetaminophen
   e. Age less than 45 years

Correct answers:
1. *b*, 2. *d*, 3. *c*, 4. *e*, 5. *c*

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