

Hypokalemia and Hyperkalemia

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Faculty Disclosure

Contributing faculty, Carol Whelan, APRN, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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Division Planner/Director Disclosure

The division planner and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for nurses and allied staff caring for patients who may present with hypokalemia or hyperkalemia.

Accreditations & Approvals



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Course Objective

The purpose of this course is to provide healthcare professionals with the information necessary to identify hypokalemia or hyperkalemia early and intervene to prevent long-term adverse effects.

Learning Objectives

Upon completion of this course, you should be able to:

1. Define hypo- and hyperkalemia.
2. Analyze the pathophysiology of hypo- and hyperkalemia.
3. Accurately diagnose patients with potassium imbalances using the appropriate laboratory testing.
4. Describe the management and referral of patients with hypo- or hyperkalemia.
5. Evaluate special topics related to a presentation with potassium abnormalities, including Addison disease, renal tubular acidosis, and hyperaldosteronism.



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PRACTICE
RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

The prevention of clinically significant hypokalemia and hyperkalemia is essential to avoiding serious and possibly fatal effects. However, hypokalemia and hyperkalemia can be caused by a variety of disorders. Hypokalemia is usually related to one or both of the following: extracellular-to-intracellular potassium shift or renal and extrarenal potassium losses. Inadequate potassium intake is a relatively uncommon cause of hypokalemia. Hyperkalemia is related to inadequate potassium excretion, excessive potassium intake, or an intracellular shift of potassium from tissue to serum.

Because potassium imbalance can appear in a wide range of patients, the information provided in this course will be helpful for the majority of healthcare professionals. First, the terms and clinical criteria for each condition will be thoroughly reviewed. Next, a clear overview of the clinical presentation, diagnosis, and useful tests to determine etiology will be given. Finally, the course will end with a discussion of treatment options and management techniques, including patient education points.

DEFINITION AND EPIDEMIOLOGY

The amount of potassium present in the average human body is approximately 50 mEq/kg. Of this, 90% is found in intracellular fluid, 8% in skin and bones, and 2% in extracellular fluid [1; 2; 3; 4; 5]. The maintenance of this relatively small amount of extracellular potassium is critical; small changes can cause serious clinical consequences.

The definitions of hypokalemia and hyperkalemia are stated in terms of extracellular (or serum) potassium. Normal values for serum potassium depend on individual laboratories, but the usual range for normal values is approximately 3.5–5.2 mEq/L [6]. Potassium imbalances can be defined as acute or chronic and can be further defined by the degree of severity.

Chronic hypokalemia and hyperkalemia develop in a minimum of weeks to months, and acute hypokalemia and hyperkalemia occur over hours to days. Mild hypokalemia occurs at serum levels of less than 3.5 mEq/L, but greater than 3 mEq/L; moderate hypokalemia at 2.5–3 mEq/L; and levels less than 2.5 mEq/L are considered severe [7; 8]. Mild-to-moderate hyperkalemia is defined as a serum level of 5.5–6.9 mEq/L, and severe hyperkalemia is a serum level of 7 mEq/L or greater [9]. Physician consultation is indicated for serum potassium levels less than 3 mEq/L or greater than 6 mEq/L.

Levels of potassium in the intracellular and extracellular fluids do not always correlate, as seen in diabetic ketoacidosis. Severe depletion of intracellular potassium (termed potassium deficiency) as a result of osmotic diuresis (which leads to increased renal loss of potassium), despite normal or even elevated extracellular (serum) levels of potassium, is caused by insulin deficiency [7]. In these cases, clinical hypokalemia may develop rapidly when exogenous insulin is administered [7].

In the vast majority of cases, hypokalemia is drug induced; approximately 20% to 50% of all patients who are treated with non-potassium-sparing diuretics develop low serum potassium levels [7; 9]. Other populations with a high incidence of hypokalemia include individuals who have undergone bariatric surgery and those with eating disorders, acquired immune deficiency syndrome (AIDS), and/or alcohol use disorder [10]. The incidence of hyperkalemia in the pediatric population is unknown, though it can exceed 50% in extremely low birth weight premature infants [9]. Most cases of chronic hyperkalemia are caused by renal failure; however, the increased use of spironolactone after the publication of the Randomized Aldactone Evaluation Study has resulted in a marked increase in morbidity and mortality from hyperkalemia, with an estimated 50 excess hospital admissions per 1,000 additional prescriptions for spironolactone [11; 12]. Careful surveillance of potassium and creatinine may improve survival in patients with severe heart failure being treated with spironolactone [13; 14].

PATHOPHYSIOLOGY

Potassium balance is affected by intake, excretion, and internal potassium regulation [1; 2; 3]. The minimum daily requirement for potassium intake in the healthy adult is approximately 40 to 50 mEq [1; 2; 3]. Excretion occurs primarily in the kidneys and gastrointestinal tract, with a small amount excreted in perspiration. Internal potassium regulation depends on acid-base balance, plasma insulin levels, plasma catecholamine levels, and aldosterone activity [3]. Excretion and conservation of potassium by the kidneys is accomplished via both active and passive mechanisms. Potassium is filtered via the glomerulus and then almost completely recovered in the proximal tubule and the loop of Henle. The proximal tubule is the site of the majority of reabsorption with 60% to 75% of filtered potassium reabsorbed at the proximal tubule via diffusion and solvent drag, with excretion occurring in the cortical collecting duct [1; 3]. Another 15% to 20% of filtered potassium is reabsorbed in the ascending limb of the loop of Henle. This reabsorption is inhibited by loop diuretics. The distal tubule is also involved in potassium recovery, and this process is inhibited by thiazide diuretics. Aldosterone is a key component in the regulation of potassium homeostasis at the cortical collecting duct. Aldosterone increases sodium and water reabsorption and potassium excretion (via the urine). Insulin is also integral to maintaining potassium regulation. Insulin causes increased liver and muscle potassium uptake, and high extracellular fluid potassium levels cause increased secretion of insulin.

HYPOKALEMIA

Because the kidneys are normally able to conserve potassium efficiently, hypokalemia is rarely a result of inadequate intake. The main causes of hypokalemia are increased renal loss from exogenous drug administration; primary or secondary hyper-

POSSIBLE CAUSES OF HYPOKALEMIA

Non-potassium-sparing diuretics
Certain antibiotics
Alcoholism
Osmotic diuresis
Primary hyperaldosteronism
Secondary hyperaldosteronism
Glucocorticoid-induced hypertension
Malignant hypertension
Renovascular hypertension
Renin-secreting tumor
Liddle syndrome
11 β -hydroxysteroid dehydrogenase deficiency
Excessive licorice ingestion
Congenital adrenal hyperplasia
Type 1 renal tubular acidosis
Type 2 renal tubular acidosis
Bartter syndrome
Gitelman syndrome
Hypomagnesemia
Exogenous insulin administration
Catecholamine excess
Familial periodic hypokalemic paralysis
Thyrotoxic hypokalemic paralysis
Leukemia
Beta-adrenergic agonists
Trauma

Source: Compiled by Author

Table 1

aldosteronism; and internal shifting of potassium from the extracellular to the intracellular space, which can occur with insulin administration or catecholamine excess (**Table 1**). Although vomiting may cause hypokalemia, this is not due to a loss of potassium from the gastrointestinal tract, but rather the result of secondary hyperaldosteronism related to volume depletion or, more rarely, metabolic alkalosis from loss of gastric secretions [5; 15]. Patients who eat true licorice (more popular in Europe) in large amounts may also decrease their potassium level significantly [16].

POSSIBLE CAUSES OF HYPERKALEMIA
Renal failure
Hypoaldosteronism
Type 4 renal tubular acidosis
Adrenal insufficiency (Addison disease)
Sickle cell anemia
Systemic lupus erythematosus
Insulin deficiency
Certain medications
Acidosis
Familial hyperkalemic periodic paralysis
Rhabdomyolysis
Tumor lysis syndrome
Traumatic venipuncture (pseudohyperkalemia)
Severe leukocytosis (pseudohyperkalemia)
Source: Compiled by Author

Table 2

HYPERKALEMIA

As noted, hyperkalemia is caused by excessive intake, impaired elimination, or increased shift of potassium from intracellular to extracellular space (**Table 2**). Excessive intake of potassium causing hyperkalemia is rarely seen in patients with normal renal function. Nonetheless, patients taking large doses of over-the-counter potassium supplements (often labeled “for heart health”) may indeed present with clinically significant hyperkalemia. Usually, ingestion of potassium only causes significant elevation in patients with low glomerular filtration rates (GFRs).

Impaired elimination of potassium can occur with acute or chronic renal injury, especially in the presence of decreased urinary flow rates. Often, patients with chronic kidney disease require large amounts of furosemide (Lasix), and this may increase potassium excretion. Care should be taken when holding diuretics in these patients, as they may experience a sudden increase in potassium.

Another possible cause of hyperkalemia is the use of medications that impair the elimination of potassium (**Table 3**). Potassium-sparing diuretics,

MEDICATIONS THAT MAY INDUCE HYPERKALEMIA
Angiotensin-converting enzyme (ACE) inhibitors
Potassium-sparing diuretics (e.g., spironolactone, amiloride)
Nonsteroidal anti-inflammatory drugs (NSAIDs)
Trimethoprim-sulfamethoxazole
Heparin
Cyclosporine
Tacrolimus
Trimethoprim
Pentamidine
Angiotensin receptor blockers (ARBs)
Direct renin inhibitors
Beta blockers
Calcium channel blockers
Succinylcholine
Digoxin
Mannitol
Potassium tablets
Source: [17; 19; 20]

Table 3

especially spironolactone, are a major cause of this type of hyperkalemia. As noted, due to the increased recognition of the importance of spironolactone in treating heart failure, hospital admissions for hyperkalemia have risen significantly [11]. Other medications that can cause impaired elimination include nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs). The use of any two of these medications together (especially a potassium-sparing diuretic and an ACE inhibitor or an ARB) should be closely monitored [17; 18]. If the medications are truly necessary (e.g., a patient with heart failure requiring spironolactone and an ACE inhibitor), the clinician can consider adding a small dose of a loop diuretic (e.g., furosemide) to aid in potassium excretion. The use of sodium polystyrene in sorbitol should probably be avoided in such a situation, both because of the possibility of sodium overload as well as safety concerns regarding the chronic use of sodium polystyrene.



According to the Department of Veteran Affairs, the mineralocorticoid receptor antagonists, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and direct renin inhibitors have all been associated with an increase in serum

potassium and/or risk for hyperkalemia. When multiple renin-angiotensin-aldosterone system blockers are used, the risk for hyperkalemia is further increased. For patients at risk for elevated serum potassium, increased diligence is recommended to monitor for hyperkalemia and acute kidney injury, which can also place additional burden and risk on the patient. Frequency of monitoring should take into account baseline serum potassium and renal function, adherence to low potassium diet, use of concomitant medications that may increase the risk for hyperkalemia, or conditions that may contribute to volume depletion.

(<https://www.healthquality.va.gov/guidelines/cd/ckd/index.asp>. Last accessed May 17, 2021.)

Level of Evidence: Expert Opinion/Consensus Statement

A third cause of impaired elimination is hypoaldosteronism, which may be as a result of Addison disease or renal injury. This will result in hyponatremia (via urinary excretion), volume depletion (due to loss of sodium), and hypotension. Pseudohypoaldosteronism is a group of disorders that include hyperkalemia, metabolic acidosis, and normal renal function. Generally, these disorders have some mineralocorticoid dysfunction as their basis [17; 20]. Another lesser cause of hyperkalemia due to impaired elimination is constipation, which may be seen in patients with myelodysplasia [17].

Increased shift of potassium from the intracellular space to the extracellular space can occur in many situations, including diabetes with decreased insulin levels, acidosis, increased osmolality (as occurs in hyperglycemia), and tissue damage like that seen in rhabdomyolysis or hemolysis [9]. Certain drugs can induce this shift, most notably digoxin. Hyperkalemic periodic paralysis can also cause this shift, so much so that people inheriting this condition will experience episodes of paralysis and hyperkalemia [17].

One cause of elevated potassium laboratory results is pseudohyperkalemia. This occurs when hemolysis is present in the blood sample from the patient. This can be the result of using a small needle for blood drawing, trauma during venipuncture, or the use of excessive alcohol on the skin (especially in capillary point-of-care test samples) [9; 17].

CLINICAL PRESENTATION

The prevention of clinically significant potassium imbalance is essential. In the absence of early detection and treatment, hypokalemia can cause serious complications and even death. The major symptoms are associated with skeletal muscle [2; 4]. Hypokalemia causes hyperpolarization, which decreases impulse conduction and muscular contraction [2; 8]. Flaccid paralysis, beginning in the extremities and moving centrally, can eventually lead to respiratory paralysis. Possible cardiac complications include ventricular arrhythmias. Typical electrocardiogram (ECG) findings include ST-segment depression, flattening and inversion of the T wave, and a prominent U wave [2; 4; 8]. The appearance and severity of these ECG abnormalities do not correspond to the degree of hypokalemia and should not be used as a substitute for monitoring serum levels [4].

Clinical manifestations of hyperkalemia are chiefly cardiac, although neuromuscular complications can also occur [2; 9]. ECG changes associated with hyperkalemia include peaked T waves (often the first ECG finding), ST-segment depression, widening of the QRS and PR intervals, and loss of the P wave [2]. A late ECG sign is the appearance of a sine-wave pattern, which usually indicates impending ventricular fibrillation and asystole [2; 4].

Although cardiac manifestations are obviously the most dangerous sequelae of hyperkalemia, neuromuscular complications, including paresthesias and fasciculations in the extremities, may be seen. Peripheral paralysis can occur, but paralysis of the respiratory muscles is rare [2].

COMPLICATIONS

Potassium abnormalities are potentially life-threatening. Cardiac conduction defects, arrhythmias, ileus, paralysis, muscle weakness, increased blood pressure, and renal injury are consequences of hypokalemia. Hyperkalemia causes cardiac arrhythmias, heart block, ventricular fibrillation, muscle weakness, and paralysis.

DIAGNOSIS

PHYSICAL EXAMINATION

A thorough history is the most important part of the physical examination. Any history of diuretic use, laxative use, vomiting, diarrhea, abnormal urinary output, diabetes, or hypertension, as well as a thorough diet and medication history, should be elicited. The physical examination should include a full assessment of vital signs (including orthostatic blood pressures), assessment of volume status, and examination of the neuromuscular system, including assessment of muscular strength and reflexes [5].

DIAGNOSTIC TESTS

Diagnostics should assess the degree of the potassium imbalance as well as the cause. Serum electrolytes, blood urea nitrogen (BUN), serum creatinine, serum glucose, a 12-lead ECG, and urinary electrolytes should be obtained [8].

Hypokalemia

Persons whose hypokalemia is not iatrogenic (i.e., drug induced) or the result of vomiting, diarrhea, alcoholism, or excessive licorice ingestion should be evaluated to determine the underlying cause of the hypokalemia. To effectively organize the diagnostic evaluation, those with hypokalemia may be subdivided into three groups: those with increased renal potassium excretion (>20 mEq/L) and hypertension, those with increased renal potassium excretion but without hypertension, and those with normal or decreased renal potassium excretion.

With concomitant hypertension, plasma renin activity (PRA) and plasma aldosterone levels should be measured, but only after the hypokalemia has been

corrected. Primary hyperaldosteronism is suggested if the PRA is suppressed and the plasma aldosterone levels are elevated. Secondary hyperaldosteronism will result in both a high PRA and a high plasma aldosterone level. Liddle syndrome will also cause hypokalemia and hypertension, but both PRA and plasma aldosterone levels will be suppressed [3; 9].

When blood pressure is normal, measurement of serum bicarbonate helps further the differential diagnosis [5; 9]. Low serum bicarbonate levels are consistent with diabetic ketoacidosis, metabolic acidosis, or renal tubular acidosis (RTA) [5; 21; 22]. Hypokalemia associated with hyperchloremic metabolic acidosis is suggestive of type 1 RTA; a morning urinary pH should be checked. A pH level greater than 6 is consistent with type 1 RTA [3; 22].

High serum bicarbonate levels in normotensive patients are consistent with Bartter syndrome [5; 23]. Bartter syndrome will also result in high PRA and plasma aldosterone levels, but this is quite rare and is usually seen only in children or young adults. In addition to the abnormal laboratory findings, patients with Bartter syndrome typically are of short stature, have muscle weakness, and are normotensive [3; 23].

Hypokalemia and normal serum bicarbonate levels in normotensive patients may also be caused by magnesium deficiency [3]. Individuals undergoing chemotherapy and those with a history of alcoholism and malabsorption syndrome are at risk for developing magnesium deficiency [3].

Occasionally, hypokalemia is not due to increased renal loss; these patients will have low urinary potassium (<20 mEq/L) [5]. The differential diagnosis is fairly limited and generally involves some sort of gastrointestinal loss, through laxative abuse, villous adenoma, or severe diarrhea [5]. Patients previously treated with non-potassium-sparing diuretics who are potassium depleted will also have low urinary potassium [5]. Catecholamine excess, whether endogenous (as seen in acute myocardial infarction) or exogenous (as in beta-adrenergic agonist administration), may also cause transient hypokalemia because of an increased cellular uptake of potassium [5].

If the cause of the hypokalemia is still unknown after thorough investigation of past medical history, medication profile, and evaluation, referral to an endocrinologist is indicated.

Hyperkalemia

Typical conditions leading to hyperkalemia include kidney injury (acute or chronic), hypoaldosteronism, and rhabdomyolysis [9].

In cases of hyperkalemia, renal status should be determined. Initial screening should be by evaluation of BUN, serum creatinine, serum sodium, and serum potassium. Individuals with chronic renal failure who previously had normal potassium levels should have a 24-hour urine collection to assess for creatinine clearance and should be questioned thoroughly regarding any diet changes, infection, trauma, and use of NSAIDs, spironolactone, and other medications [9]. Numerous cases of trimethoprim-sulfamethoxazole-induced hyperkalemia have been reported [24]. Individuals appearing to be most at risk include those with pre-existing renal impairment or disturbances in potassium excretion, those with human immunodeficiency virus (HIV) infection, and those treated with ACE inhibitors, ARBs, and/or spironolactone [9].

Persons with hyperkalemia but without renal failure should be assessed for adrenocortical insufficiency (Addison disease), which almost always results in hyponatremia, hypotension, hypovolemia, and renal insufficiency [9]. An adrenocorticotrophic hormone (ACTH or cosyntropin) stimulation test (with referral to an endocrinologist) should be performed if Addison disease is suspected.

Hyperkalemia may also result from hypoaldosteronism and is twice as common in patients with diabetes [3; 9]. PRA and plasma aldosterone levels are diagnostic. Secondary hypoaldosteronism can result from the prolonged use of heparin, but in general, the hyperkalemia in these patients is mild [3]. ACE inhibitors and ARBs also decrease aldosterone levels and can cause hyperkalemia [25; 26]. Tubular unresponsiveness to aldosterone may cause hyperkalemia and may be seen in sickle cell disease, systemic lupus erythematosus, and amyloidosis [3].

MANAGEMENT

The management of hypokalemia and hyperkalemia begins with identification of the underlying cause. Except for patients who are surreptitiously inducing vomiting or using large amounts of diuretics or laxatives, the cause of the potassium imbalance is usually readily apparent [5; 9]. Most cases are a result of either diuretic use or renal failure. In patients presenting with hyperkalemia, pseudohyperkalemia, generally caused by traumatic venipuncture or rarely leukocytosis in the setting of leukemia, should be considered [5].

All at-risk patients should be frequently screened using laboratory analysis. When diuretics are prescribed, the patient's serum potassium concentration should be checked before initiation of treatment and then one and four weeks after the initiation of therapy [5].

In persons with chronic hyperkalemia, any use of ACE inhibitors, ARBs, NSAIDs, potassium-sparing diuretics, or salt substitutes containing potassium chloride should be reassessed and most likely discontinued [9].

ACUTE HYPOKALEMIA

The treatment of acute hypokalemia involves the administration of oral or IV potassium supplements. If life-threatening arrhythmias or neuromuscular symptoms are present, IV potassium supplementation should be initiated [3]. IV potassium concentration should not exceed 40 mEq/L [18]. IV potassium is usually infused at a rate of less than 10 mEq/hr. Patients should receive no more than 20 mEq/h IV to avoid potential negative effects on the cardiac conduction system [18]. Cardiac monitoring and frequent serum potassium assessment (every two to four hours) are essential. After all cardiac arrhythmias or neuromuscular symptoms have resolved, the patient may be switched to oral replacement. The normal dosage for oral potassium is 20–40 mEq two times per day [18].

CHRONIC HYPOKALEMIA

The primary goal of treatment of chronic hypokalemia is identification of the underlying cause. In cases of drug-induced hypokalemia, the medication should be changed, if possible. If the clinical status prohibits this, treatment depends on the degree of hypokalemia. Some controversy exists as to whether individuals with mild hypokalemia (3.5–4 mEq/L) should be aggressively treated; however, they can certainly benefit from dietary teaching [3; 5]. In patients with potassium levels less than 3.5 mEq/L, oral supplementation should be given, with normal daily dosages ranging between 20 mEq and 80 mEq. Persons with hyperaldosteronism should be referred to an endocrinologist and may be successfully managed with spironolactone or eplerenone [10]. Eplerenone has been associated with fewer side effects because of its low affinity for sex hormone receptors [27; 28]. It is less likely to induce gynecomastia in men, which can be physically and psychologically painful and unacceptable. If an aldosterone-secreting tumor is identified, surgical removal may be preferred.

ACUTE HYPERKALEMIA

Treatment of hyperkalemia involves the following principles and practice, many of which occur parallel to each other. First, the patient should have an ECG to evaluate for toxicity and should be placed on a monitor, if warranted [9]. If the patient does have ECG changes, consider hospitalization if still in the outpatient setting. Next, identify sources of potassium intake and eliminate if possible. Consider whether to initiate a plan to shift potassium from the extracellular to the intracellular. Lastly, increase potassium excretion if needed for either short-term or long-term management [17].

Treatment of acute hyperkalemia with life-threatening symptoms (generally seen with potassium levels ≥ 7 mEq/L) is accomplished by the administration of IV calcium [2; 3; 4]. The usual recommended dose is 10 mL of a 10% calcium solution, such as calcium chloride [9; 18]. The ECG should be monitored while calcium is administered, and calcium should be administered only when ECG changes, such as a widening QRS, have occurred [3; 4]. Calcium does not correct the underlying hyperkalemia; it

only counters the adverse neuromuscular effects [4]. Calcium infusion should always be followed by specific therapy aimed at lowering the plasma potassium level (e.g., insulin and glucose infusion) [9].

The administration of IV glucose and insulin is the quickest way to treat acute hyperkalemia that has not yet resulted in life-threatening sequelae [3; 4; 9]. This results in a shift of extracellular potassium into the cell [4]. Care should be taken in patients with diabetes and hyperkalemia, as glucose infusion that is not accompanied by a matching infusion of insulin can result in increased hyperkalemia due to extracellular hyperosmolarity [2].

When the individual is able to safely take medication orally and life-threatening sequelae have not developed, treatment with sodium polystyrene sulfate (Kayexalate) in sorbitol solution may be used [18]. This may be the treatment of choice in outpatients who are stable but have potassium levels in the 5.5–6.9 mEq/L range. In patients unable to tolerate oral administration, polystyrene sulfate may be given rectally [3; 18]. Studies have raised the possibility of colonic complications from administration of polystyrene sulfate in sorbitol suspension, and there are no controlled studies of safety and efficacy for this use [29]. Due to this concern, concomitant use of sorbitol is no longer recommended [18]. Another strategy to avoid the use of polystyrene sulfate and associated adverse gastrointestinal events (e.g., ischemic colitis, bleeding, perforation, necrosis) would be the use of a loop diuretic or a thiazide diuretic [19].

Use of beta-adrenergic agonists may also be considered for temporary correction of serum potassium levels [18]. This is accomplished with the administration of albuterol or isoproterenol via nebulization [30]. The dosage required to obtain clinically significant reductions in potassium is quite high, with 10–20 mg of nebulized albuterol being the recommended dosage [9; 30]. This high of a dose is likely to produce tachycardia and should only be administered with appropriate monitoring of the patient [18]. Sodium bicarbonate is occasionally used in the treatment of hyperkalemia, both to address the accompanying acidosis and to correct

the hyperkalemia itself by causing a pH-dependent shift of potassium from the extracellular to the intracellular space [4; 9]. Sodium bicarbonate should be used with caution, and care should be taken not to cause sodium overload or metabolic alkalosis [3].

In 2015, the U.S. Food and Drug Administration approved patiomer for oral suspension (Veltassa) for the treatment of hyperkalemia [31]. In clinical trials, this drug effectively lowered potassium levels in patients with hyperkalemia and chronic kidney disease who were taking at least one drug that inhibited the renin-angiotensin-aldosterone system [32; 33; 34; 35; 36; 37]. Treatment effects on clinical outcomes (e.g., cardiac arrhythmias, major GI symptoms) have not been adequately studied [38]. Patiomer is a polymer-based, nonsystemic oral agent that exchanges cations through the GI tract. It binds potassium in the colon and increases its fecal excretion [18; 19]. Initial oral dosing is 8.4 g once daily. Dosing should be adjusted as needed in one-week intervals in increments of 8.4 g; the maximum daily dose is 25.2 g [18]. The most common adverse reactions are constipation, hypomagnesemia, diarrhea, nausea, abdominal discomfort, and flatulence [18].

In 2018, the FDA approved sodium zirconium cyclosilicate (SZC) (Lokelma) for the treatment of hyperkalemia [39; 40; 41]. The FDA considered data from three double-blind, placebo-controlled trials and two open-label trials [41]. SZC is a potassium binder that preferentially exchanges potassium for hydrogen and sodium. Potassium binding reduces the concentration of free potassium in the GI lumen, lowering serum potassium levels [18]. Initial oral dosing is 10 g three times daily for up to 48 hours. Dosing should be adjusted by 5 g daily at one-week intervals as needed based on serum potassium. The maximum daily dose is 15 g [18]. The most common adverse reactions are edema and hypokalemia [18].

CHRONIC HYPERKALEMIA

The most common cause of chronic hyperkalemia is renal failure; therefore, the most common management of chronic hyperkalemia is dialysis [9].

POTASSIUM CONTENT IN COMMON FOODS	
Food	Potassium Content
French fries (5 ounces)	17.7 mEq
Potato chips (1.5 ounces)	10.2 mEq
Banana (small)	8.6 mEq
White mushrooms (2.5 ounces)	8.1 mEq
Orange juice (7 ounces)	7.9 mEq
Whole milk (7 ounces)	7.7 mEq
Cooked broccoli (2.5 ounces)	5.8 mEq
Blueberries (3.5 ounces)	1.9 mEq
White chocolate (0.75 ounce)	1.8 mEq
Cooked onions (2.5 ounces)	1.5 mEq
Cola (14 ounces)	0.2 mEq
Source: [17] Table 4	

However, before resorting to dialysis, a combination of medications may be used to increase excretion of potassium, including sodium polystyrene sulfonate, furosemide, and/or intravenous calcium [42].

It is rare for intake alone to account for hyperkalemia because renal excretion increases with increased intake in patients with normal renal function [9]. However, diet modification is essential in persons with renal failure and chronic hyperkalemia. Because identification and replacement of potassium-rich foods can be complex, the help of a dietician is essential. Patients may have to give up foods such as potatoes and bananas, and replace them with cooked onions and blueberries (**Table 4**). Milk should be used sparingly, but cola can be used as a treat for dietary compliance. A comprehensive list of foods high in potassium that should be avoided, as well as a list of low-potassium foods that can be consumed in either limited or unlimited amounts, can be obtained from a dietician. Make sure the patient has access to information from a reliable source; keeping printed patient education materials regarding diet restrictions for patients with chronic hyperkalemia on hand to distribute is good practice.

It is important to remember, however, that patients with chronic hyperkalemia often have an underlying chronic illness causing their hyperkalemia, such as end-stage renal disease, which may have been caused by diabetes, hypertension, or both. Often, their diets may be so restricted that they feel unable to follow it and give up. A reasonable, palatable, nutritious diet must be agreed upon by all members of the healthcare team, not just the dietician or primary care provider. Compromise can often lead to even greater compliance and to an improved bond between patient and practitioner.

The treatment of chronic hyperkalemia caused by hypoaldosteronism may be accomplished with oral polystyrene sulfate or furosemide, but the preferred treatment is fludrocortisone acetate [18; 43]. If Addison disease is diagnosed, treatment with replacement hydrocortisone should correct the hyperkalemia.

INDICATIONS FOR REFERRAL OR HOSPITALIZATION

Any patients found to have an underlying metabolic disorder as a cause of hypokalemia or hyperkalemia and patients in whom the cause of the hypokalemia or hyperkalemia is unknown should be referred to an endocrinologist. Individuals with hyperkalemia and renal disease should always be referred to a renal specialist. All persons with life-threatening symptoms of hypokalemia or hyperkalemia should be evaluated for possible hospitalization. Those with hyperkalemia and acute renal failure should be urgently hospitalized.

PATIENT AND FAMILY EDUCATION

Patient education for hypokalemia or hyperkalemia should center on diet education and awareness of the importance of continued chronic supplementation therapy and laboratory monitoring [9]. Education regarding potential drug and diet effects on hypokalemia or hyperkalemia is also important. Chronic laxative use should be avoided, because this has been associated with potassium loss [3].

Individuals with chronic hypokalemia should be advised to avoid large amounts of licorice, which have also been associated with hypokalemia. Those taking potassium supplements should be instructed to swallow the tablet with a large glass of fluid. If untoward effects of supplementation occur, the patient should be advised to call or see a healthcare provider.

Because hyperkalemia is usually secondary to renal failure and hypokalemia is usually the result of diuretic use, health promotion should focus on the prevention of renal failure and hypertension. When prevention is no longer possible, patient education regarding the need for monitoring and prevention of complications is paramount.

SPECIAL TOPICS

ADDISON DISEASE

Addison disease, first identified by the British physician Dr. Thomas Addison in 1855, occurs when the adrenal glands do not produce enough steroid hormones, particularly mineralocorticoid and glucocorticoid steroid hormones [44].

Clinical Presentation

Addison disease generally presents with fatigue, weight loss, orthostatic hypotension, hyperpigmentation of the skin, hyperkalemia, hyponatremia, and hypercalcemia. Severe Addisonian crisis is a life-threatening syndrome that usually occurs in patients who have had chronic Addison disease and is usually precipitated by insults to homeostasis, such as sepsis or trauma. But, Addisonian crisis can also result from acute trauma to the adrenal gland in patients without a history of Addison disease. In addition to the chronic signs of Addison disease, acute Addisonian crisis may also present with acute vomiting, diarrhea, psychosis, lethargy, convulsions, and seizures [44].

Treatment of Addison disease focuses on the replacement of the hormones cortisol and aldosterone. Although hydrocortisone can function as replacement for both of these hormones, replacement

with fludrocortisone is often necessary [44]. Patients may also require either a diet high in salt or sodium replacement therapy.

Referral to an endocrinologist is necessary for the treatment and long-term management of Addison disease. Additional workup and long-term treatment will be supervised by the endocrinologist [44].

Patient Education

Patient education is an essential component of the treatment of Addison disease. Patients will require education to promote a diet low in potassium that also contains adequate amounts of salt. Also important is education regarding stress situations that can lead to adrenal crisis and appropriate interventions for “stress days.” Adrenal crisis occurs when the body experiences a stressful event that would normally result in an increase in hormone production by the adrenal glands, such as trauma, sepsis, childbirth, or even the death of a loved one. Patients should have a plan developed with their endocrinologist that outlines when to take an increased dose of steroids and when to contact their physician for management of the crisis. In addition, patients should be advised to wear an emergency identification bracelet or other identification that alerts emergency medical personnel of their condition [44].

RENAL TUBULAR ACIDOSIS

RTA is actually a group of three syndromes that occur when the kidneys fail to properly acidify the urine, leading to an accumulation of acid in the bloodstream. Modern classifications of RTA include types 1, 2, and 4. Type 3 is generally no longer recognized [30; 45].

In normally functioning kidneys, urine is filtered in the tubules, where the exchange of salts, acid equivalents, and other solutes occurs. In RTA syndromes, this exchange can be impaired either in the distal tubule (type 1 RTA), the proximal tubule (type 2 RTA), or in the proximal tubule but due to adrenal causes (type 4 RTA) [30; 45]. Type 3 RTA was previously viewed as an extremely rare pediatric disease of mixed proximal-distal cause.

Type 1 RTA is caused by a failure of the distal tubule to secrete acid into the urine, leading to acidosis and hypokalemia. Diagnostic workup will reveal alkalotic urine and possibly metabolic acidosis. (Renal excretion of uric acid and bicarbonate is the primary homeostatic mechanism of the body for maintaining normal pH within a very limited pH range.) Renal and bladder calculi may be seen due to high urine pH, and osteopenia or osteoporosis may develop due to urinary loss of calcium.

Type 2 RTA is the result of a lack of resorption of bicarbonate ion in the proximal tubule. As previously stated, the control of elimination of acid and bicarbonate is the main mechanism of pH control. Without the ability of the kidney to control overall pH of the blood, the body is forced to resort to respiratory mechanisms to maintain normal pH. This may lead to acidotic patients hyperventilating to “blow off” CO₂ to correct acidosis. Type 2 RTA is generally milder than type 1 RTA and has fewer symptoms. The only signs may be phosphate wasting and osteoporosis. Type 2 RTA may cause hypokalemia, but many patients have normal potassium levels.

Type 4 RTA is associated with hyperkalemia. It is actually not a primary renal disease, but rather a disease of the adrenals associated with abnormally low aldosterone levels leading to clinical hypoaldosteronism, which in turn causes reduced ammonium excretion. This decrease in ammonium (an alkaline) causes a decrease in the urine’s ability to absorb acid ions causing a decrease in urine buffering capacity, causing metabolic acidosis.

Although type 3 RTA is no longer clinically relevant, it does have an interesting place in medical history. Although most type 3 cases were simply distal RTA with some proximal involvement, there are case reports of a genetic mixed proximal-distal inherited type 3 RTA. True type 3 RTA was actually an inherited defect in the production of carbonic anhydrase II. It has been diagnosed primarily in populations in North Africa and the Middle East among close knit tribal regions and may be a result of high rates of consanguinity [46].

HYPERALDOSTERONISM

Primary hyperaldosteronism is a condition of increased aldosterone production. Its chief symptoms are hypertension and either overt or easily provoked hypokalemia (e.g., severe hypokalemia from very small doses of diuretics). Symptoms can also include fatigue, headache, hypernatremia (the opposite of Addison disease), muscular weakness or even paralysis, muscle spasms, metabolic alkalosis, and possible polydipsia and polyuria [47].

The diagnosis of hyperaldosteronism is made by testing the patient's blood for the aldosterone-renin ratio [47]. This level will be increased in primary hyperaldosteronism. Care must be taken when ordering this test, as the patient may need to stop taking ACE inhibitors, beta blockers, diuretics, NSAIDs, and steroids to achieve an accurate result [47]. Patients may also require modification of their intake of salt. Close consultation with the clinician ordering the test is important. The decision to investigate a possible diagnosis of hyperaldosteronism is often made after the patient is taking three or more antihypertensive drugs, and stopping these medications (even temporarily) may require consultation and close observation.

CASE STUDIES

CASE STUDY 1

Patient C is a woman, 32 years of age, with a history of hypertension and asthma. Her current medications include albuterol (as needed via inhaler), atenolol 25 mg twice daily, and 25 mg hydrochlorothiazide. She is admitted to the hospital with a diagnosis of exacerbation of asthma secondary to bronchitis. She is treated with albuterol treatments every three hours, a cephalosporin antibiotic, and a prednisone taper. Her atenolol is stopped due to fears it is exacerbating her asthma. After 24 hours, Patient C complains of severe muscle cramps despite the fact that her admission potassium level was 3.9 mEq/L, within normal limits. A basic metabolic profile (Chem-7) is requested, which reveals normal renal function and a potassium level of 2.9 mEq/L.

She is given 40 mEq of potassium immediately, and prescribed 40 mEq twice daily with close monitoring of her level.

Comments and rationale: Often, patients may be taking more than one medication that increases the elimination of potassium. Patient C was taking an obvious source and a less obvious source. The obvious source of potassium excretion was her thiazide diuretic. Its actual effect on potassium loss may have been mitigated by her use of a beta blocker. Once in the hospital, the beta blocker was stopped, but a number of medications with potential for increasing potassium elimination were started. First, she was given increased doses of albuterol, which is a beta-adrenergic agonist. Also, prednisone and antibiotics can all cause increased potassium loss. Given that this patient was on a thiazide diuretic, it might have been prudent (given her low normal potassium level) to start her on a low-dose potassium supplement and monitor her level closely.

CASE STUDY 2

Patient R is a man, 56 years of age, with diabetes and hypertension. He is currently being treated with metformin 1 g twice per day, lisinopril 40 mg/day, and amlodipine 10 mg/day. His blood pressure is 146/83 mm Hg, and lab work reveals the following abnormalities: BUN 83 mg/dL, serum creatinine 4.1 mg/dL, and potassium 7.3 mEq/L. He is rushed urgently via emergency medical services to the local hospital, where an ECG is obtained immediately. Blood gases are sent to rule out lactic acidosis due to use of metformin in acute renal failure. The ECG shows widening of the QRS wave, and Patient R is showing signs of muscle weakness. He is treated emergently with calcium gluconate 10% 10 mL infusion while his ECG is monitored. An infusion of 10% dextrose and insulin is started, and potassium levels are sent every 15 minutes.

Comments and rationale: Initial treatment of hyperkalemia should focus on evaluation of ECG monitoring and treatment of potentially life-threatening toxicity. Calcium does not correct the underlying hyperkalemia; it only counters the adverse neuromuscular effects of hyperkalemia. Calcium infusion should always be followed by specific therapy aimed at lowering the plasma potassium level (i.e., insulin and glucose infusion).

A repeat potassium level after infusion of dextrose and insulin reveals a level of 5.3 mEq/L. Upon questioning, the patient discloses that he has recently been taking large doses of NSAIDs for back pain. He is admitted to the intensive care unit and the metformin, lisinopril, and NSAIDs are stopped. He is placed on a low-potassium diet, and his renal function is monitored.

Comments and rationale: *Early identification of patients with risk factors for kidney disease, as well as identification of patients with early mild kidney disease, can help clinicians educate patients regarding medications that can cause renal injury, such as NSAIDs. Close monitoring of high-risk patients can also help identify patients with early-onset renal disease, so late disease complications, such as severe hyperkalemia, may be avoided.*

CASE STUDY 3

Patient K is a woman, 32 years of age, with a history of severe asthma who has had a fairly uneventful 40-week pregnancy. Although she had an asthma exacerbation treated with steroids in week 12 of her pregnancy, she has been otherwise stable and is looking forward to delivery. She spontaneously goes into labor at week 40 and is delivered without event. A few hours after delivery, however, she becomes lethargic with acute vomiting and suffers a convulsion. Initially, medical personnel consider a diagnosis of eclampsia, but Patient K is hypotensive (as opposed to hypertensive) and has had no proteinuria, despite frequent monitoring. Laboratory studies reveal hyponatremia, hyperkalemia, and a serum cortisol level of 3 mcg/dL. Questioning of her family reveals that she has been treated three to four times per year on average with prednisone for her asthma and takes a steroid inhaler for maintenance therapy. Patient K is diagnosed with acute Addisonian crisis.

Comments and rationale: *Patients who do not exhibit signs of Addison disease but may be at risk due to a history of steroid use can develop acute Addisonian crisis in times of stress. Chronic use of steroid creams or inhaled steroids, as well as intermittent use of oral or parenteral steroids, may predispose a patient to Addisonian crisis.*

CONCLUSION

In the vast majority of cases, hypokalemia is drug induced; approximately 30% of all patients who are treated with non-potassium-sparing diuretics develop low serum potassium levels. Most cases of chronic hyperkalemia are caused by renal failure; however, the increased use of spironolactone has resulted in a marked increase in morbidity and mortality from hyperkalemia.

In the absence of early detection and treatment, hypokalemia can cause serious complications and even death. Although cardiac manifestations are obviously the most dangerous sequelae of hyperkalemia, neuromuscular complications, including paresthesias and fasciculations in the extremities, may be seen. The prevention of clinically significant hypokalemia and hyperkalemia is essential.

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

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