Chapter 70: Disorders of Potassium and Magnesium Homeostasis

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UPDATE SUMMARY

Update Summary

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The following sections were updated:

- Pharmacologic therapy for hypokalemia: Clarified regular monitoring of serum potassium concentrations throughout the treatment of hypokalemia to prevent overcorrection
- Alternative therapies for hypokalemia: Clarified spironolactone and eplerenone use
- Redistribution of potassium into the extracellular space: Clarified etiologies
- Pharmacologic therapy of hyperkalemia: Clarified role of concomitant glucose and insulin administration when managing hyperkalemia
- Pharmacologic therapy of hyperkalemia: Clarified mechanism of action of sodium zirconium cyclosilicate
- Self-assessment questions: Clarified questions 1-15

CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 77, Electrolyte Homeostasis.

KEY CONCEPTS

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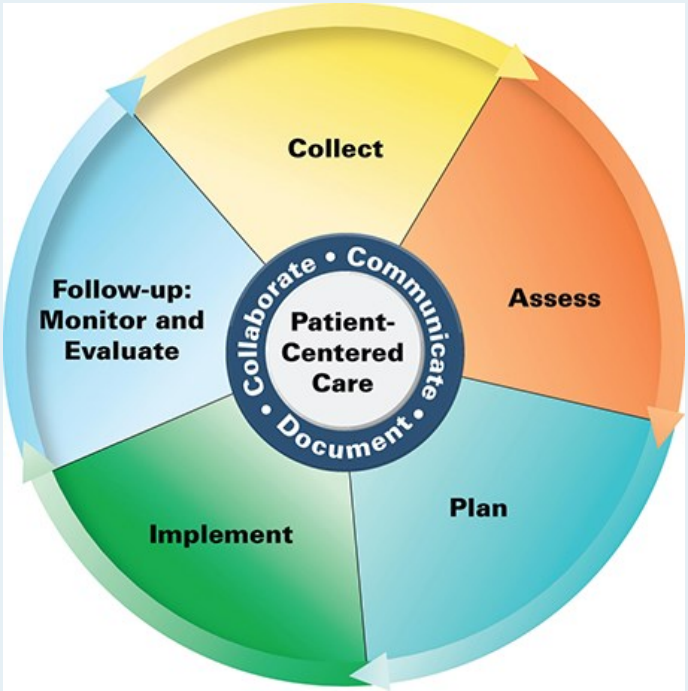
1. Potassium regulates many biochemical processes in the body and is a key cation for electrical action potentials across cellular membranes.
2. The kidney is the primary route of potassium elimination.
3. In patients with concomitant hypokalemia and hypomagnesemia, it is imperative to correct the hypomagnesemia before the hypokalemia.
4. Potassium chloride is the preferred potassium supplement for the most common causes of hypokalemia.
5. Hyperkalemia is a common occurrence in patients with acute kidney injury or chronic kidney disease.
6. Hypomagnesemia is commonly caused by excessive gastrointestinal or renal magnesium wasting.
7. Hypermagnesemia is predominantly observed in patients with acute or chronic kidney disease.
8. Severe hypermagnesemia may affect the neuromuscular and cardiovascular systems.

PATIENT CARE PROCESS

Patient Care Process* for the Management of Potassium and Magnesium Disorders



Collect

- Patient characteristics (eg, age, race, sex)
- Patient history (past medical, family, social–dietary habits)
- Current medications including over-the-counter medications, herbals, dietary supplements

- Subjective data
  - Musculoskeletal and neuromuscular review of systems
  - Intake (food and fluid) and output (urine and stool)
- Objective data
  - Blood pressure, heart rate, height, weight
  - Labs (eg, basic metabolic panel, calcium, magnesium, phosphorus)
  - Other diagnostic tests when indicated (eg, electrocardiogram [ECG], urinalysis, urine electrolytes)

Assess

- Presence of symptoms of an electrolyte disorder
- Presence of ECG changes (see Fig. 70-1)
- Severity of electrolyte disorder (eg, change from baseline value, timing of development of electrolyte disorder)
- Kidney function (eg, estimated glomerular filtration rate [GFR], creatinine clearance [CrCl], presence of chronic kidney disease [CKD])
- Current medications that may contribute to electrolyte disorder (see Tables 70-1, 70-6, and 70-8)
- Current diet that may contribute to electrolyte disorder (see Tables 70-2 and 70-9)

Plan*

- Identification of the most likely cause of the electrolyte disorder and discontinuation of offending medication or substance (if applicable)
- Dietary modifications (see Tables 70-2 and 70-9)
- Medication therapy regimen including specific medication, dose, route, frequency, and duration; specify the continuation and discontinuation of existing therapies (see Tables 70-4, 70-5, and 70-7)
- Monitoring parameters including efficacy (eg, potassium, magnesium, serum creatinine [SCr]), safety (medication-specific adverse medication reactions), and need for repeat or additional medication therapy
- Patient education (eg, purpose of treatment, dietary and lifestyle modification, medication therapy)
- Referrals to other providers when appropriate (eg, physician, dietitian)

Implement*

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up

Follow-up: Monitor and Evaluate

- Resolution of electrolyte disorder and prevention of further episodes
- Presence of adverse medication reactions

- Development/progression of kidney impairment
- Patient adherence to treatment plan using multiple sources of information

Collaborate with patient, caregivers, and other health professionals

BEYOND THE BOOK

BEYOND THE BOOK

Watch the video entitled "Hyperkalemia in Primary Care Practice" by the National Kidney Foundation. (https://www.kidney.org/content/hyperkalemia-primary-care-practice) This ~11-minute video provides a brief overview of the risks associated with hyperkalemia, the various causes of hyperkalemia, and prevention and treatment strategies. The video is useful to enhance student understanding of the COLLECT, ASSESS, and PLAN steps in the patient care process.

INTRODUCTION

Potassium and magnesium are electrolytes that are responsible for numerous metabolic activities. Disorders of these electrolytes are frequently seen in both the acute care and community ambulatory care settings. Therefore, clinicians need a firm understanding of the etiology, pathophysiology, symptoms, pharmacotherapy, and monitoring of these disorders. This chapter describes the homeostatic mechanisms that are responsible for the maintenance of normal potassium and magnesium serum concentrations. The clinical disorders responsible for the development of hyperkalemia, hypermagnesemia, hypokalemia, and hypomagnesemia are also reviewed.

POTASSIUM

Potassium is the most abundant cation in the body, with estimated total-body stores of 3,000 to 4,000 mEq (mmol).[1] Ninety-eight percent of this amount is contained within the intracellular compartment, and the remaining 2% is distributed within the extracellular compartment. The sodium-potassium adenosine triphosphatase (Na^+-K^+-ATPase) pump located in the cell membrane is responsible for the compartmentalization of potassium. This pump is an active transport system that maintains increased intracellular stores of potassium by transporting sodium out of the cell and potassium into the cell at a ratio of 3:2. Consequently, the pump maintains a higher concentration of potassium inside the cell.

The normal serum concentration range for potassium is 3.5 to 5 mEq/L (mmol/L), whereas the intracellular potassium concentration is approximately 150 mEq/L (mmol/L).[2] Approximately 75% of the intracellular potassium is located in skeletal muscle; the remaining 25% is located in the liver and red blood cells. Extracellular potassium is distributed throughout the serum and interstitial space. Potassium is dynamic in that it is constantly moving between the intracellular and extracellular compartments according to the body's needs. Thus, the serum potassium concentration alone does not accurately reflect the total-body potassium content.

1 Potassium has many physiologic functions within cells, including protein and glycogen synthesis and cellular metabolism and growth. It is also a determinant of the electrical action potential across the cell membrane.[1] The ratio of the intracellular-to-extracellular potassium concentration is the major determinant of the resting potential across the cell membrane. Serum potassium concentrations outside the normal range can have disastrous effects on neuromuscular activity, in particular cardiac conduction. Hypo- and hyperkalemia are both associated with potentially fatal cardiac arrhythmias, along with other neuromuscular disturbances. Finally, potassium is integral to maintaining blood pressure, prevention of stroke, and potentially other cardiovascular diseases.[3] Both the National High Blood Pressure Education Program and the Institute of Medicine recommend potassium supplementation as a strategy for preventing and treating hypertension.[4,5]

Control of Potassium Homeostasis

Potassium homeostasis, the maintenance of serum potassium within the normal range, is affected by dietary intake, gastrointestinal (GI) and urinary

excretion, hepatic and muscular sequestration, hormones, acid-base balance, body fluid tonicity, central and peripheral circadian clocks, and a highly integrated feedback mechanism.[6,7] Together, these mechanisms usually maintain total-body potassium content within a narrow window without appreciable changes in the serum potassium concentration.[6] Deviations in serum potassium concentrations outside the normal range are a result of nonhomeostatic processes that are not sensitive to changes in potassium balance.[6] The recommended adequate intake of dietary potassium in the United States is 2,600 mg/day for adult females and 3,400 mg/day for adult males.[8] Potassium is considered to be a nutrient of concern, because of its beneficial effects on blood pressure, reduction in the risk of kidney stones, and decrease of bone loss.[9] Potassium is abundant in fruits, vegetables, meats, whole grains, and milk products. Most dietary potassium is absorbed, with only 10 to 20 mEq/day (mmol/day) eliminated in feces. The amount eliminated in the feces increases, however, in patients with diarrhea and in those with chronic kidney disease (CKD).[7]

2 The kidney is the primary route of potassium elimination. Potassium is freely filtered, but almost all of it is reabsorbed passively in the proximal tubule and the thick ascending limb of the loop of Henle.[9] Although the amount of potassium filtered by the glomerulus approaches 700 mEq (mmol) per day, only approximately 10% to 20% is actually excreted in the urine.[9] Potassium excretion is regulated by its secretion into the distal tubule and collecting duct. Variations in potassium excretion are based on dietary intake, serum potassium concentration, and aldosterone activity. For example, more potassium is renally excreted in conditions that result in high aldosterone activity (eg, dehydration) when the body is attempting to conserve sodium or when there is an increase in dietary potassium intake. In addition, enteric solute sensors increase kaliuresis in response to high dietary potassium intake.[1]

Hormones such as insulin, catecholamines, and aldosterone dramatically affect potassium homeostasis. Aldosterone controls renal potassium excretion, which can take several hours to adjust serum potassium concentrations. Rapid buffering of serum potassium concentrations occurs through potassium cellular redistribution, of which insulin and catecholamines play a large role. Insulin is the most important hormonal mediator of potassium balance because it stimulates the cellular Na^+-K^+-ATPase pump to increase transport of potassium into liver, muscle, and adipose tissue.[6] There is a complex negative feedback loop in which insulin secretion tightly regulates serum potassium concentrations: an increase of only a few tenths of a milliequivalent of potassium stimulates pancreatic insulin secretion in an attempt to prevent hyperkalemia from developing.[1] If hyperkalemia does occur, glucagon is released from the liver to protect against insulin-induced hypoglycemia. Conversely, hypokalemia inhibits insulin secretion, a finding that explains why some patients receiving diuretics develop hyperglycemia.

An elevation in circulating catecholamines such as epinephrine usually results in the intracellular movement of potassium by two mechanisms.[9] Stimulation of the β-receptor, which directly activates the Na^+-K^+-ATPase pump and glycogenolysis, which raises blood glucose concentrations, thereby increasing insulin secretion. This dual mechanism is often used therapeutically in patients with hyperkalemia to normalize serum potassium concentrations.

Aldosterone, a mineralocorticoid that is secreted from the adrenal glands in response to high serum potassium concentrations, promotes urinary potassium excretion. Aldosterone acts on the distal tubule and collecting duct to promote the reabsorption of sodium and water in exchange for potassium. It also increases potassium permeability and transport across the luminal membrane of the nephron by stimulating the cellular Na^+-K^+-ATPase pump activity.[7] In patients with impaired kidney function, aldosterone increases potassium excretion in the distal colon.[10]

Changes in acid–base status can dramatically affect the serum potassium concentration. For example, the infusion of metabolic inorganic acids, such as hydrochloric acid, results in an increase in serum potassium. The body compensates for excessive hydrogen ions by moving them from the serum into the cell in exchange for intracellular potassium, to maintain electroneutrality. The processes by which this occurs are highly complex and involve cellular H^+-K^+-ATPase pumps and both $_{Na^+ - HCO_3^-}$Na+−HCO3− and $_{K^+ - HCO_3^-}$K+−HCO3− cotransporters.[11] The efflux of potassium into the serum can result in hyperkalemia. A commonly quoted approximation of the pH effect is that for every 0.1 unit decrease in pH, serum potassium concentration increases by 0.6 to 0.8 mEq/L (mmol/L) (with a wide range of 0.2-1.7).[12] This is often referred to as *false hyperkalemia* because there is not a true excess of total-body potassium. Metabolic acidosis associated with lactic acidosis and ketoacidosis typically does not lead to clinically significant hyperkalemia, because both cations and anions enter the cell, thus maintaining electroneutrality.[1] Respiratory acidosis also does not significantly affect the serum potassium concentration.

Conversely, metabolic alkalosis has been associated with hypokalemia. As a result of a net loss of hydrogen ion from the serum, intracellular hydrogen ions enter the serum to increase the acidity of the blood. To maintain electroneutrality, extracellular potassium ions are shifted intracellularly. This

creates a relative deficiency of potassium in the serum. Serum potassium decreases approximately 0.6 mEq/L (mmol/L) for each 0.1 unit increase in blood pH. This is frequently termed *false hypokalemia* because there is not a true deficiency in total-body potassium.

Finally, hyperosmolality can result in enhanced movement of potassium from the cell into the extracellular fluid. Water movement favors potassium efflux through solvent drag. As cells shrink, intracellular potassium concentrations increase, further promoting potassium efflux.[7] This is seen in conditions such as diabetic ketoacidosis. Conversely, hypoosmolality does not seem to affect potassium distribution.

HYPOKALEMIA

Epidemiology

Hypokalemia (defined as a serum potassium concentration less than 3.5 mEq/L [mmol/L]) is a commonly encountered electrolyte abnormality in clinical practice. Hypokalemia is often categorized as mild (serum potassium 3.1-3.4 mEq/L [mmol/L]), moderate (serum potassium 2.5-3 mEq/L [mmol/L]), or severe (less than 2.5 mEq/L [mmol/L]).[13] When hypokalemia is detected, the diagnostic workup should evaluate the patient's comorbid disease states and concomitant medications. Hypokalemia is virtually nonexistent in healthy adults. This is due in part to the potassium content in the typical Western diet as well as the body's effective potassium-sparing mechanisms, which tightly regulate the serum potassium concentration. However, as many as 20% of hospitalized patients and up to 40% of patients taking thiazide diuretics will develop hypokalemia.[14]

While transient hypokalemia may be thought of as merely a laboratory abnormality, there are serious potential consequences associated with persistent hypokalemia. Hypokalemia increases mortality in patients with heart failure, CKD, or diabetes mellitus, populations typically thought to be more sensitive to the effects of hyperkalemia.[15] Low dietary potassium intake is associated with worsening hypertension and higher risk of stroke.[3]

Etiology and Pathophysiology

Hypokalemia results when there is a total-body potassium deficit, or when serum potassium is shifted into the intracellular compartment. Total-body deficits occur in the setting of poor dietary intake of potassium, or when there are excessive renal and GI losses of potassium. Maintaining a consistent dietary intake of potassium is important because the body has no effective method for storing potassium. At steady state, potassium excretion matches potassium intake; approximately 90% of ingested potassium is renally excreted, whereas 10% is excreted in feces.[9] This underscores the importance of eating a well-balanced diet. Older adults with chronic diseases and those undergoing surgery are at increased risk for developing hypokalemia because of insufficient intake or losses resulting from surgery.

Many medications can cause hypokalemia by a variety of mechanisms including intracellular potassium shifting and increased renal or stool losses (Table 70-1). The most common cause of medication-induced hypokalemia is loop and thiazide diuretic administration as these agents inhibit sodium reabsorption in the kidney, which results in increased sodium delivery to the distal tubule. Consequently, hypokalemia develops because the distal tubule selectively reabsorbs sodium and excretes potassium. Second, because diuretics result in vascular volume contraction, aldosterone is secreted that further promotes the renal excretion of potassium. If concomitant potassium supplements are not provided to patients receiving loop and thiazide diuretics, mild-to-moderate hypokalemia is inevitable.

TABLE 70-1

Mechanism of Medication-Induced Hypokalemia

Transcellular Shift	Enhanced Renal Excretion	Enhanced Fecal Elimination
β_2-Receptor agonists Epinephrine Albuterol Terbutaline Fomoterol Salmeterol Isoproterenol Ephedrine Pseudoephedrine Theophylline Levothyroxine Decongestants Caffeine Insulin overdose Verapamil overdose Barium overdose	Diuretics Acetazolamide Thiazides Indapamide Metolazone Furosemide Torsemide Bumetanide Ethacrynic acid High-dose penicillins Nafcillin Ampicillin Penicillin Mineralocorticoids Miscellaneous Aminoglycosides Amphotericin B Cisplatin	Laxatives Sodium polystyrene sulfonate Sorbitol Patiromer Sodium zirconium cyclosilicate

The second most common etiology of hypokalemia is excessive loss of potassium-rich GI fluid as a result of diarrhea and/or vomiting. The typical potassium loss in feces is approximately 10 mEq (mmol) per day.[7] In diarrheal states, this amount increases proportionally with the volume of stool output. Fecal potassium losses may be as high as 130 to 170 mEq/L (mmol/L).[16] Vomiting also accounts for substantial potassium losses, which have been estimated to be as high as 30 to 50 mEq (mmol) per liter of vomitus.[17] Metabolic alkalosis which often develops in those with severe diarrhea and vomiting as a result of loss of these bicarbonate-rich fluids causes an intracellular shift of potassium, thereby lowering the serum concentration of potassium even further. Prolonged diarrhea and vomiting tend to affect children and older adults profoundly because their kidneys are unable to effectively maintain adequate fluid status.

3 Hypomagnesemia, which is present in more than 50% of patients with clinically significant hypokalemia, contributes to the development of hypokalemia because it reduces the intracellular potassium concentration and promotes renal potassium wasting.[18] While the precise mechanism of the accelerated renal loss is unknown, many believe that the intracellular potassium concentration may decrease because hypomagnesemia impairs the function of the Na^+-K^+-ATPase pump thereby promoting potassium wasting. Alternatively, the combination of increased sodium delivery to the distal tubule, elevated aldosterone concentrations, and hypomagnesemia may cause the kidney outer medullary potassium channels to excrete more potassium.[18] What is clear is that hypokalemia and hypomagnesemia often coexist as a result of medications (diuretic administration) or disease states (diarrhea). When concomitant hypokalemia and hypomagnesemia occur, the magnesium deficiency should be corrected first; otherwise, full repletion of the potassium deficit is difficult.

Treatment

Desired Outcomes

The goals of hypokalemia management are to prevent and/or treat serious life-threatening complications, normalize the serum potassium

concentration, identify and correct the underlying cause of hypokalemia, and finally prevent overcorrection of the serum potassium concentration.

General Approach to Therapy

The general approach to therapy depends on the degree and rapidity with which hypokalemia developed and the presence of signs and symptoms. Serum potassium concentrations between 3.5 and 4 mEq/L (mmol/L) are a sign of early potassium depletion. No pharmacologic therapy is recommended; however, patients should be encouraged to increase their dietary intake of potassium-rich foods. When the serum potassium concentration is between 3 and 3.4 mEq/L (mmol/L), the patient's concomitant conditions and medications will largely determine whether pharmacologic therapy should be initiated. Most patients will not have signs or symptoms if serum potassium concentrations remain greater than 3 mEq/L (mmol/L). The presence of signs or symptoms with mild hypokalemia warrants the initiation of potassium supplementation. Oral potassium supplementation should be initiated in patients with underlying cardiac conditions that predispose them to cardiac arrhythmias. Patients with serum potassium concentrations less than 3 mEq/L (mmol/L) should always be treated to achieve values between 4 and 4.5 mEq/L (mmol/L). In asymptomatic patients, oral therapy is the preferred route of administration. Intravenous (IV) potassium may be necessary in symptomatic patients with severe depletion, or in patients who are intolerant to oral supplementation. In patients with concomitant moderate to severe hypomagnesemia, the magnesium deficit should be corrected before potassium supplementation is started.[9,14]

CLINICAL PRESENTATION: Hypokalemia

General

- The signs and symptoms of hypokalemia are usually nonspecific and highly variable between patients.

Symptoms

- Symptoms are dependent on the degree of hypokalemia and its rapidity of onset.
- Mild hypokalemia is often asymptomatic.
- Moderate hypokalemia is associated with cramping, weakness, malaise, and myalgias.

Signs

- Cardiovascular: In severe hypokalemia, ECG changes often include ST-segment depression or flattening, T-wave inversion, and U-wave elevation. Clinical arrhythmias include heart block, atrial flutter, paroxysmal atrial tachycardia, ventricular fibrillation, and digitalis-induced arrhythmias.
- Musculoskeletal: Cramping and impaired muscle contraction.

Laboratory Tests

- Serum potassium concentration below 3.5 mEq/L (mmol/L) is diagnostic. Hypomagnesemia (serum magnesium concentration below 1.7 mg/dL [1.4 mEq/L; 0.70 mmol/L]) can also be present.

Nonpharmacologic Therapy

The best and most abundant sources of dietary potassium supplementation are fresh fruits and vegetables, fruit juices, and meats (Table 70-2). Increased dietary intake of foods with high potassium content, however, is not recommended long-term because it can add unwanted calories to the patient's diet. Moreover, dietary potassium is almost entirely coupled with phosphate, rather than chloride, so it is not as effective in correcting potassium loss associated with hypochloremic conditions such as vomiting, nasogastric suctioning, and diuretic therapy. Salt substitutes that contain potassium chloride are another effective, inexpensive source of potassium and because they provide chloride as well and are frequently recommended.

TABLE 70-2

Foods That Are High in Potassium

High content (>250 mg)	Very high content (>500 mg)
Kidney beans, cooked	Potato, baked, flesh and skin
Lentils, cooked	Sweet potato, baked in skin
Soybeans, green, cooked	Juice, canned
Lima beans, cooked	Prunes
Soybeans, mature, cooked	Carrot
Pinto beans, cooked	Tomato
Lentils, cooked	Tomato paste
Halibut, cooked	Tomato puree
Rockfish, Pacific, cooked	Beet greens, cooked
Cod, Pacific, cooked	White beans, canned
Tuna, yellowfin, cooked	Plain yogurt, nonfat or low-fat
Rainbow trout, cooked	Clams, canned
Evaporated milk, nonfat	
Low-fat (1%) or reduced fat (2%) chocolate milk	
Skim milk (nonfat)	
Low-fat milk or buttermilk (1%)	
Orange juice, fresh	
Bananas	
Peaches, dried, uncooked	
Prunes, stewed	
Apricots, dried, uncooked	
Plantains, cooked	
Tomato sauce	

Pork loin, center rib, lean, roasted	
Spinach, cooked	

Pharmacologic Therapy

Formal guidelines for potassium supplementation were last published by the National Council on Potassium in Clinical Practice in 2000 (Table 70-3).[19] While these guidelines are not from a major medical society, they do provide a comprehensive framework for potassium administration as a prophylactic and therapeutic replacement for many patient populations. When deciding how to design the optimal regimen, one must consider: (a) the patient's normal, that is, baseline potassium concentration; (b) underlying medical conditions that can affect potassium balance; (c) concomitant medications that can affect potassium balance; (d) the patient's dietary salt intake; and (e) the patient's ability to comply with the therapeutic regimen.[19]

TABLE 70-3

General Consensus Guidelines for Potassium Replacement

Guideline	Comment
Potassium replacement therapy should accompany dietary consumption of potassium-rich foods.	Potassium-rich foods often cannot completely replace potassium associated with chloride losses (vomiting, diuretics, or nasogastric suction) because it is almost entirely coupled to phosphate. Furthermore, increasing dietary intake of these foods can lead to unwanted weight gain.
Potassium replacement is recommended for sodium-sensitive and hypertensive patients.	A high-sodium diet often results in excessive urinary potassium excretion.
Potassium replacement is recommended in patients who are subject to vomiting, diarrhea, or diuretic/laxative misuse.	These conditions promote excessive renal and GI potassium loss.
Potassium supplementation is best administered orally in divided doses over several days to achieve full repletion.	
Laboratory measurement of serum potassium is convenient, but not always accurate.	Clinicians should be aware of the factors that result in transcellular potassium shifts. Monitoring 24-hour urinary potassium excretion can be necessary in high-risk patients.
Patient adherence to potassium replacement can be increased with compliance-enhancing regimens.	Microencapsulated products have no bitter smell or aftertaste and have much better GI tolerance. Regimens should be made as simple as possible to follow.
A potassium dosage of 20 mEq/day (mmol/day) is usually sufficient to prevent hypokalemia from occurring. Doses of 40-100 mEq (mmol) are usually sufficient to treat hypokalemia.	

A general rule for potassium replacement is that for every 1 mEq/L (mmol/L) decrease of serum potassium below 3.5 mEq/L (mmol/L), there is a corresponding total-body potassium deficit of 100 to 400 mEq (mmol). Because of the wide variance in projected deficits, each patient's therapy must

be individualized and adjustments made on the basis of the patient's signs, symptoms, and frequent measurements of serum potassium. In the acute care setting, the administration of 10 mEq (mmol) of IV or oral potassium should increase the serum potassium concentration by 0.1 mEq/L (mmol/L). This approximation is used as a basis for dose calculations, with frequent measurements of serum potassium to avoid overestimation. In patients receiving chronic loop or thiazide diuretic therapy, 40 to 100 mEq (mmol) of oral potassium supplementation can correct mild-to-moderate potassium deficits. Doses up to 120 mEq (mmol) can be required in more severe deficiencies. When providing oral potassium supplementation, the total daily dose should be divided into three to four doses to minimize the development of adverse medication reactions in the GI tract. Patients receiving diuretics can become chronically hypokalemic and can benefit from combination potassium-sparing diuretic therapy.

4 Whenever possible, potassium supplementation should be administered by mouth. Four salts are available for oral potassium supplementation: chloride, gluconate, phosphate, and bicarbonate. Potassium phosphate should be used when the patient is both hypokalemic and hypophosphatemic; potassium bicarbonate is most commonly used when potassium depletion occurs in the setting of metabolic acidosis. Potassium chloride, however, is the primary salt form used because it is the most effective treatment for the most common causes of potassium depletion (ie, diuretic and diarrhea-induced) as these conditions are associated with potassium and chloride losses.

Potassium chloride can be administered in either tablet or liquid formulations (Table 70-4). The liquid forms are generally less expensive; however, patient compliance can be low because of their strong, unpleasant taste. Liquid forms should be used when a rapid response to supplementation is desired. Two sustained-release solid dosage forms are currently available in the United States: a wax-matrix formulation, and a microencapsulated formulation. The microencapsulated tablet is generally preferred because it is associated with less GI irritation. IV potassium use should be limited to: (a) severe hypokalemia (serum concentration less than 2.5 mEq/L [mmol/L]); (b) patients exhibiting signs and symptoms such as ECG changes or muscle spasms; or (c) patients unable to tolerate oral therapy. IV supplementation requires more monitoring than oral therapy because it is more likely to result in hyperkalemia, phlebitis, and pain at the site of infusion.

TABLE 70-4

Differences Among Oral Potassium Supplements

Supplement	Comment
Controlled-release microencapsulated tablet	Disintegrates better in GI tract; fewer GI erosions as compared to wax-matrix tablets
Encapsulated controlled-release microencapsulated particles	Fewer erosions as compared to wax-matrix tablets
Potassium chloride elixir	Inexpensive, poor taste, poor compliance, immediate effect
Potassium chloride effervescent tablets for solution	More expensive than elixir, convenient
Wax-matrix extended-release tablets	Easier to swallow; more GI erosions as compared to other therapies

The vehicle in which IV potassium is administered is important. Whenever possible, potassium should be prepared in saline-containing solutions (eg, 0.9%-0.45% sodium chloride [NaCl]). Dextrose-containing solutions stimulate insulin secretion, which can cause intracellular shifting of potassium, worsening the patient's hypokalemia, and should be avoided whenever possible. Generally, 10 to 20 mEq (mmol) of potassium is diluted in 100 mL 0.9% NaCl for IV administration. These concentrations are safe when administered through a peripheral vein over an hour. When infusion rates exceed 10 mEq/h (mmol/h), ECG monitoring should be performed to detect cardiac changes. The serum potassium concentration should be evaluated regularly throughout treatment to prevent hyperkalemia and guide further dosing. For example, assess serum potassium concentrations following the infusion of each 20 to 40 mEq (mmol) to guide further potassium replacement administration. Multiple doses of potassium can be repeated as needed until the serum potassium concentration normalizes. To allow adequate time for the potassium to equilibrate between the intra- and extracellular spaces, one should wait at least 30 minutes from the end of each infusion and care should be taken to avoid sampling from the same line in which the potassium was infused, as this can result in a spuriously high potassium concentration.

In patients with severe potassium depletion, replacement with as much as 300 to 400 mEq/day (mmol/day) may be needed. In this instance, it is a

common practice to dilute 40 to 60 mEq (mmol) in 1,000 mL 0.45% NaCl and infuse at a rate not exceeding 40 mEq/h (mmol/h). The total 24-hour dose should not exceed 400 mEq (mmol). This should be performed in an intensive care unit (ICU) under continuous ECG monitoring. Because of the high potassium concentration and the risk for burning pain and peripheral venous sclerosis, the infusion should be through a central venous catheter into a large vein (eg, superior vena cava) but care must be taken not to place the tip of the catheter into the right atrium.[20] Directly delivering high potassium concentrations into the heart can result in cardiac arrhythmias. Given the volume required to infuse this dose of potassium, this infusion strategy might be impractical in certain clinical situations (eg, patients requiring fluid restriction). A reasonable approach is to split the potassium dose between the oral and IV routes. For example, if a symptomatic patient requires 120 mEq (mmol) of potassium, the clinician can give 60 mEq (mmol) as the immediate-release potassium liquid, and the other 60 mEq (mmol) can be given through the IV route (20 mEq/100 mL/h [mmol/100 mL/h] in three doses). When giving large potassium doses, serum monitoring should be performed frequently at convenient intervals (ie, after each 1-2 L of fluid containing potassium) to guide the need for additional potassium. This can also help avoid the development of hyperkalemia.

In the rare circumstances when cardiac arrest from hypokalemia is imminent, IV bolus dosing of potassium 10 mEq (mmol) over 5 minutes can be initiated and repeated once, if necessary.[20]

Alternative Therapies

Potassium-sparing diuretics are a viable alternative to chronic exogenous potassium supplementation, especially when patients are concomitantly receiving medications that are known to deplete potassium (eg, diuretics). Steroidal mineralocorticoid receptor antagonists, such as spironolactone and eplerenone, inhibits the effect of aldosterone in the distal convoluted tubule of the kidney, thereby decreasing potassium elimination in the urine. These medications are especially effective as a potassium-sparing agent in patients with primary or secondary hyperaldosteronism. Amiloride and triamterene are reasonable second-line agents that act by blocking tubular epithelial sodium channels, leading to decreased renal potassium excretion.

Spironolactone is available as 25-, 50-, and 100-mg tablets. The usual starting dose is 25 to 50 mg daily and can be titrated to a maximum dose of 400 mg/day. The potassium-retaining effects generally take 48 hours to be evident. Principal adverse medication reactions include hyperkalemia, gynecomastia, breast tenderness, and impotence in men. Eplerenone is available as 25 and 50 mg tablets. The usual starting dose is 25 to 50 mg daily and can be titrated to a maximum dose of 300 mg/day. Hyperkalemia is a dose-dependent adverse medication reaction of eplerenone. However, eplerenone has a lower risk of sex steroid-related adverse medication reactions compared to spironolactone. Triamterene is available as 50- and 100-mg capsules. The usual starting dose is 50 mg twice daily, which can be titrated to 100 mg twice daily. Triamterene is also available as a combination product with hydrochlorothiazide (37.5/25 mg, 50/25 mg, or 75/50 mg) and is commonly used for the treatment of hypertension. Common adverse medication reactions include hyperkalemia, sodium depletion, and metabolic acidosis. The usual starting dose of amiloride is 5 mg daily; however, 10 mg can be given in those with severe hypokalemia. This is also available as a combination product with hydrochlorothiazide 50 mg. The most common adverse medication reactions are hyperkalemia and metabolic acidosis.

Concomitant use of potassium supplementation with potassium-sparing diuretics is generally not necessary, but when used there is a risk of hyperkalemia, especially in patients with CKD or diabetes mellitus.

Evaluation of Therapeutic Outcomes

Serum potassium concentrations should be monitored regularly while the patient is receiving potassium supplementation. For ambulatory patients receiving prophylactic potassium supplementation during diuretic therapy, the serum potassium and magnesium concentrations, as well as kidney function should be monitored every 1 to 2 months. In hospitalized patients receiving oral therapy for mild hypokalemia, the potassium concentration should be monitored every 1 to 3 days. If it does not increase by at least 1 mEq/L (mmol/L) within 96 hours, the clinician should suspect concomitant magnesium depletion. Patients receiving IV potassium supplementation require close ECG monitoring if the infusion rate is greater than 20 mEq/h (mmol/h): doses greater than this should be administered only in the presence of continuous ECG monitoring. Additionally, the patient should have serum potassium concentrations obtained regularly during, and 30 minutes following completion of the total potassium dose to guide further potassium administration. Finally, the patient should be assessed for adverse medication reactions such as pain at the infusion site or phlebitis.

Clinical Bottom Line

Hypokalemia is a frequent medical condition caused by both biological processes as well as medication therapy. While mild hypokalemia is frequently

asymptomatic, severe hypokalemia can cause fatal cardiac dysrhythmias, particularly in patients with underlying cardiac disease. Patients receiving medications that cause potassium wasting (eg, thiazide or loop diuretics) should be closely followed for the development of hypokalemia and appropriate potassium supplementation should be started when necessary. Generally oral potassium is sufficient for the management of mild hypokalemia; IV potassium should be reserved for severe deficiency, and its use should be monitored closely.

HYPERKALEMIA

Hyperkalemia, defined as a serum potassium concentration greater than 5 mEq/L (mmol/L), can be further classified according to its severity: mild hyperkalemia (5.1-5.9 mEq/L [mmol/L]), moderate hyperkalemia (6-7 mEq/L [mmol/L]), and severe hyperkalemia (above 7 mEq/L [mmol/L]).[19]

Epidemiology

5 Hyperkalemia is much less common than hypokalemia. In fact, if all patients with AKI and CKD were excluded, the prevalence of hyperkalemia would be less than 1% in the rest of the population. The incidence of hyperkalemia in hospitalized patients is highly variable, ranging from 1% to 10%.[21] The incidence of hyperkalemia has increased over time likely from the aging of the population, increased prevalence of CKD and diabetes mellitus, and increased use of medications that inhibit the renin-angiotensin-aldosterone system.[22] Severe hyperkalemia occurs more commonly in older adults with impaired kidney function who have been receiving chronic oral potassium supplementation.

Etiology and Pathophysiology

Hyperkalemia develops when potassium intake exceeds excretion (true hyperkalemia) (ie, elevated total-body stores) or when the transcellular distribution of potassium is disturbed (ie, normal total-body stores). The four primary causes of hyperkalemia—(a) increased potassium intake, (b) decreased potassium excretion, (c) tubular unresponsiveness to aldosterone, and (d) redistribution of potassium into the extracellular space—are discussed further.

Hyperkalemia Associated with Increased Potassium Intake

Hyperkalemia in this setting is almost always associated with impaired kidney function. Patients with stage 4 or 5 CKD and dialysis patients who are noncompliant with dietary potassium restrictions often present with life-threatening hyperkalemia. Dietary potassium restrictions are difficult to adhere to since many foods that are considered part of a healthy diet contain potassium. Another common dietary source associated with the development of hyperkalemia is potassium chloride salt substitutes. Many dialysis patients are instructed to use salt substitutes to avoid excessive sodium intake in an attempt to control volume overload. These patients unwittingly become hyperkalemic because these products contain approximately 10 to 15 mEq (mmol) potassium per gram or 200 mEq (mmol) per tablespoon. Finally, some over-the-counter herbal and alternative medicine products may contain large amounts of potassium. It is thus essential for patients with CKD to receive education regarding dietary sources of potassium as well as information on the potassium content of herbal products when available.

Hyperkalemia Associated with Decreased Renal Potassium Excretion

Normally functioning kidneys excrete 90% of the daily potassium intake. Therefore, when the kidney is unable to excrete potassium appropriately, as in AKI and stage 4 to 5 CKD, potassium is retained and often results in hyperkalemia. Finally, because aldosterone is responsible for potassium excretion via the kidney cortical collecting duct, medications and diseases that inhibit this process contribute to hyperkalemia.[23]

Severe hyperkalemia is more common in AKI than in CKD because patients are often hypercatabolic and have underlying disorders, such as rhabdomyolysis or tumor lysis syndrome, which result in release of potassium from injured or lysed cells.[24] Severe hyperkalemia is rare in stable stage 1 to 4 CKD, perhaps because of enhanced GI and renal potassium excretion.[25] Additionally, hyperkalemia directly stimulates renal potassium excretion through an effect that is independent of, and additive to, that of aldosterone.[26] Renal excretion of potassium is also inhibited by various endocrine disorders, including adrenal insufficiency, Addison disease, and selective hypoaldosteronism. All of these disorders involve a decreased production of aldosterone, which results in the retention of potassium.

Several medications have profound effects on the kidney's ability to regulate potassium. These include five medication classes in particular:

angiotensin-converting enzyme inhibitors (ACEIs), angiotensin-II receptor blockers (ARBs), direct renin inhibitors, mineralocorticoid receptor antagonists (MRAs) and other potassium-sparing diuretics, and prostaglandin inhibitors such as nonsteroidal anti-inflammatory drugs (NSAIDs). Although hyperkalemia is typically dose-dependent, the rates of hyperkalemia may range from 2% to 10%.[27,28] Finerenone (Kerendia®), a non-steroidal MRA FDA-approved for use in patients with diabetic nephropathy, should not be initiated in patients with a serum potassium greater than 5 mEq/L (mmol/L) and should be withheld if the serum potassium rises above 5.5 mEq/L (mmol/L).[29] It has a novel mechanism of action compared to other medications in the class such as spironolactone and eplerenone but similar rates of hyperkalemia.[30] Other commonly used medications that can cause hyperkalemia are β-blockers, digoxin, cyclosporine, tacrolimus, trimethoprim–sulfamethoxazole, and heparin.

Tubular Unresponsiveness to Aldosterone

Sickle cell anemia, systemic lupus erythematosus, and amyloidosis can produce a defect in renal tubular potassium secretion, possibly as the result of an alteration in the aldosterone-binding site.

Redistribution of Potassium into the Extracellular Space

The efflux of potassium from within the cell into the extracellular space, which is associated with no change in total-body potassium stores, is often observed in the presence of metabolic acidosis (from inorganic acids), diabetes mellitus, or CKD. β-Blockers can also result in a transcellular potassium shift.

The serum potassium concentration can also be falsely elevated in some conditions and not reflect the actual in vivo potassium concentration, that is, pseudohyperkalemia. Pseudohyperkalemia occurs most commonly in the setting of extravascular hemolysis of red blood cells. When a blood specimen is not processed promptly and cellular destruction occurs, intracellular potassium is released into the serum. It can also occur in conditions of thrombocytosis or leukocytosis. If severe hyperkalemia is found in a patient who is asymptomatic with an otherwise normal laboratory report, the hyperkalemia is most likely pseudohyperkalemia, and a repeat blood sample should be collected. Truly elevated potassium concentrations are normally associated with other laboratory abnormalities such as low carbon dioxide (acidosis) or elevated blood urea nitrogen and creatinine concentrations (indicating impaired kidney function).

CLINICAL PRESENTATION: Hyperkalemia

General

- Related to the effects of excessive potassium on neuromuscular, cardiac, and smooth muscle cell function.

Symptoms

- Frequently asymptomatic.
- The patient might complain of heart palpitations or skipped heartbeats.

Signs

- ECG changes (Fig. 70-1)

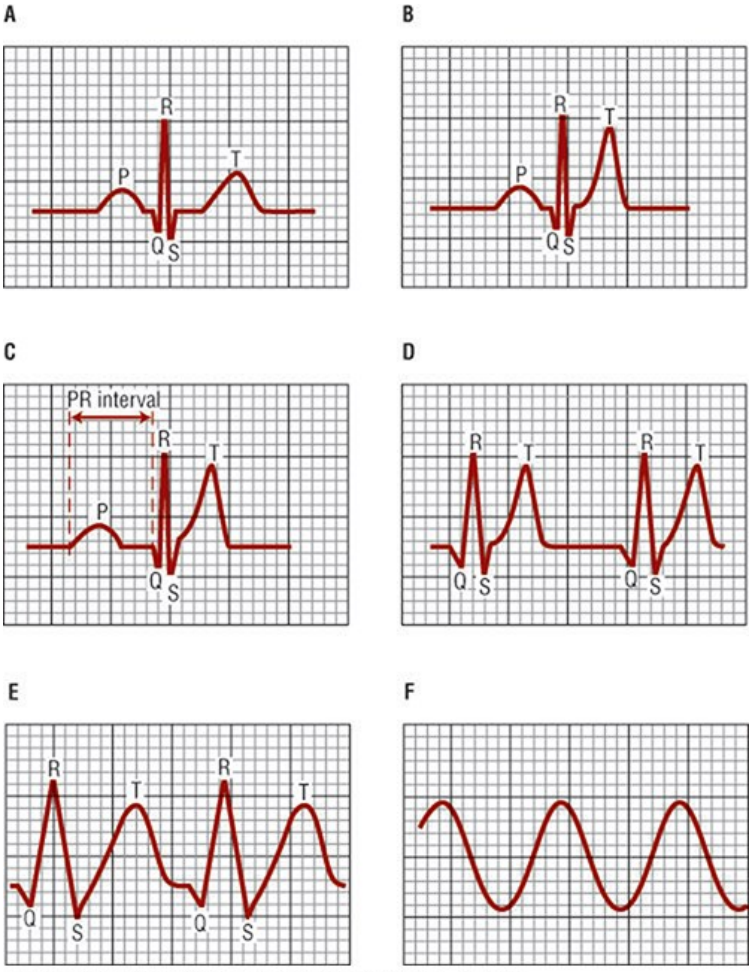
Laboratory Tests

- Serum potassium concentration above 5.0 mEq/L (mmol/L) is diagnostic.

FIGURE 70-1

The earliest electrocardiographic manifestation of hyperkalemia is an increase in the rate of ventricular repolarization, which results in a peaking of the T wave at serum potassium concentrations of ~5.5 to 6 mEq/L (mmol/L) (*B*), relative to the normal ECG presentation (*A*). Further increases in the

serum potassium concentration above 6 mEq/L (mmol/L) result in conduction delays through the His-Purkinje system, the atrial myocardium, and the ventricular myocardium. The ECG manifestations of these conduction delays and the sequence in which they occur are a widening of the PR interval (*C*), delay through the His-Purkinje system, a loss of the P wave (*D*), delay through the atrial myocardium, a widening of the QRS complex (*E*), and delay through the ventricular myocardium. Finally, there is a merging of the QRS complex with the T wave (*F*), which results in a sine-wave appearance.



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Treatment

Desired Outcomes

The goals of therapy for the treatment of hyperkalemia are to antagonize adverse cardiac effects, reverse signs and symptoms that are present, and return the serum and total-body stores of potassium to normal. The optimal treatment approach is dependent on the severity of hyperkalemia, the rapidity of its development, and the patient's clinical condition. Cardiac instability and arrhythmias, which can be life-threatening, may be present especially when serum potassium is above 6 mEq/L (mmol/L). Although ECG changes are directly proportional to the serum potassium concentration and its rate of increase, they may not be present in all patients. Asymptomatic patients with mild hyperkalemia usually require no specific therapy other than dietary education to control intake, and monitoring of serum potassium daily if an inpatient or weekly if an outpatient to assure resolution.

Severe hyperkalemia (above 7 mEq/L [mmol/L]) or moderate hyperkalemia (6-6.9 mEq/L [mmol/L]), when associated with clinical symptoms or ECG changes, requires immediate treatment. Initial treatment should be focused on antagonism of the cardiac membrane actions of hyperkalemia (eg, administration of calcium). Secondarily, one should attempt to decrease extracellular potassium concentration by promoting its intracellular movement (eg, with insulin, β_2-receptor agonists, or sodium bicarbonate) or enhance its removal from the body by hemodialysis: the oral

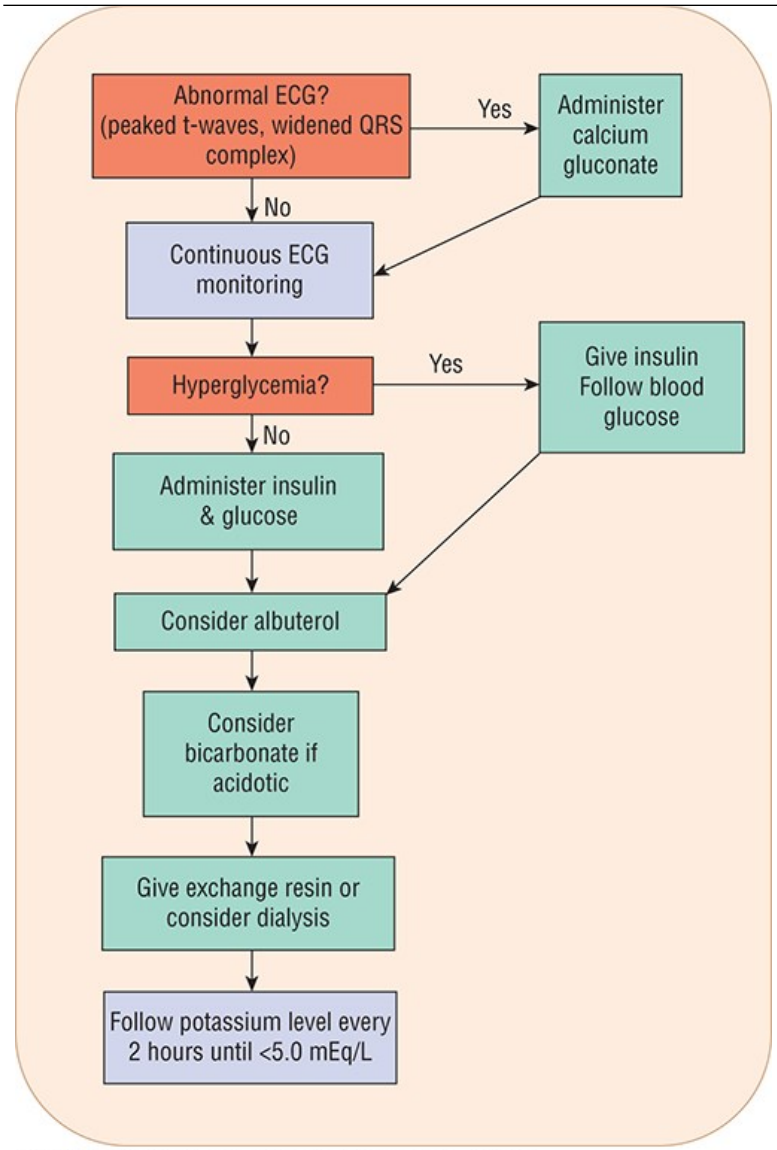
administration of cation-exchange resins, and/or the use of loop diuretics may also be considered in some patients. In any case, the underlying cause of hyperkalemia should be identified and reversed, and exogenous potassium must be withheld.

General Approach to Treatment

A treatment approach for patients with hyperkalemia is outlined in Fig. 70-2. In patients who have acute ECG changes, IV calcium should be administered to raise the threshold potential and stabilize the myocardium.[31] At the same time, the serum potassium concentration should be rapidly decreased to below 5 mEq/L (mmol/L) within minutes by administering medications that cause an intracellular shift of potassium, followed by the initiation of those that increase the elimination of potassium from the body.[31] If the patient is asymptomatic, rapid correction may not be necessary and will likely depend on the clinical context associated with the rise in serum potassium concentration. If one anticipates the need to reduce total-body potassium stores, an ion exchange resin that results in removal of potassium from the body over several hours to days may be initiated shortly after the emergent care has been instituted. An IV loop diuretic can be used to facilitate potassium removal through diuresis in patients who are hypervolemic and have preserved kidney function.[31]

FIGURE 70-2

Treatment approach for hyperkalemia. (Serum potassium of 5.0 mEq/L is equivalent to 5.0 mmol/L.)



Nonpharmacologic Therapy

Hemodialysis patients who ingest foods supplemented with glycyrrhetinic acid, the active ingredient in licorice, may be better able to maintain serum potassium concentrations within the normal range.[32,33] Glycyrrhetinic acid inhibits the enzyme 11β-hydroxy-steroid dehydrogenase II, thereby increasing cortisol availability in the colon. The net result is enhanced potassium elimination in the feces. Other nonpharmacologic therapies, specifically available for dialysis-dependent patients are the tailoring of their intermittent dialysis or hemofiltration therapy to include a low potassium dialysate to enhance the removal of potassium (see Chapter 64). Emergency dialysis can be considered in patients with acute kidney injury who have persistent ECG changes or insufficient response to therapies that cause intracellular potassium shifts, although the optimal time to initiate dialysis is not known.[34]

Pharmacologic Therapy

There are several medication therapy options to lower the serum potassium concentration. The optimal regimen for a given patient is dependent on the rapidity and degree of lowering that is necessary. Table 70-5 provides an overview of the available therapies and their respective onset and

duration of action.

TABLE 70-5

Therapeutic Alternatives for the Management of Hyperkalemia

Medication	Dose	Route of Administration	Onset/Duration of Action	Acuity	Mechanism of Action	Expected Result
Calcium gluconate or chloride	1 g	IV over 5-10 minutes	1-2 min/10-30 min	Acute	Raises cardiac threshold potential	Reverses electrocardiographic effects
Furosemide	20-40 mg	IV	5-15 min/4-6 h	Acute	Inhibits renal Na^+ reabsorption	Increased urinary K^+ loss
Regular insulin	5-10 units	IV or subcut	30 min/2-6 h	Acute	Stimulates intracellular K^+ uptake	Intracellular K^+ redistribution
Dextrose 10%	1,000 mL (100 g)	IV over 1-2 hours	30 min/2-6 h	Acute	Stimulates insulin release	Intracellular K^+ redistribution
Dextrose 50%	50 mL (25 g)	IV over 5 minutes	30 min/2-6 h	Acute	Stimulates insulin release	Intracellular K^+ redistribution
Sodium bicarbonate	50-100 mEq (50-100 mmol)	IV over 2-5 minutes	30 min/2-6 h	Acute	Raises serum pH	Intracellular K^+ redistribution
Albuterol	10-20 mg	Nebulized over 10 minutes	30 min/1-2 h	Acute	Stimulates intracellular K^+ uptake	Intracellular K^+ redistribution
Hemodialysis	4 hours	N/A	Immediate/variable	Acute	Removal from serum	Increased K^+ elimination
Sodium polystyrene sulfonate	15-60 g	Oral or rectal	1 h/variable	Nonacute	Resin exchanges Na^+ for K^+	Increased K^+ elimination
Patiromer	8.4-25.2 g	Oral	Hours/variable	Nonacute	Resin exchanges Ca^{++} for K^+	Increased K^+ elimination
Sodium zirconium cyclosilicate	5-15 g	Oral	1 h/variable	Nonacute	Resin exchanges Na^+ for K^+	Increased K^+ elimination

While specific treatment recommendations vary, it is generally accepted that asymptomatic patients with potassium concentrations below 6 mEq/L (mmol/L) can be treated conservatively. In patients with normal kidney function or those with stage 3 or 4 CKD, this typically involves the administration of furosemide to promote urinary potassium excretion. When given IV at a dosage of 40 to 80 mg, urine flow usually increases within minutes and

persists for approximately 4 to 6 hours. Oral furosemide can also be used, keeping in mind the IV:PO dose ratio (1:2) and delayed onset of action compared to IV. Close monitoring of the patient's volume status and other electrolyte concentrations is required while the patient is receiving furosemide. Of note, the effectiveness of diuretics in treating hyperkalemia has not been studied in a randomized, controlled fashion.

In symptomatic patients, or in those with severe hyperkalemia, emergency care is indicated. Initial therapy in this setting is the administration of IV calcium chloride or gluconate 1 g to treat or prevent life-threatening arrhythmias.[31] Calcium antagonizes the cardiac membrane effect of hyperkalemia by reducing the electrical threshold potential for cardiac myocytes and reverses ECG changes within minutes. IV calcium should not be given to patients receiving digoxin as it can lead to digoxin toxicity. Its duration of action is 30 to 60 minutes, and it can be repeated as needed based on ECG findings. IV calcium can be given as either the chloride or gluconate salt; each is available as a 10% solution by weight. Calcium chloride provides approximately three times more calcium than equal volumes of the gluconate salt; however, it can cause tissue necrosis if extravasation occurs. For this reason, calcium gluconate is more commonly administered, with the standard dose being 1 g IV bolus over 5 to 10 minutes.

Rapid correction of hyperkalemia may necessitate the administration of medications that result in an intracellular shift of potassium, such as insulin and dextrose, sodium bicarbonate, and a β_2-adrenergic receptor agonist (eg, albuterol). The treatment of choice depends on the underlying medical disorders accompanying hyperkalemia. For example, in patients with concomitant metabolic acidosis, a sodium bicarbonate bolus or infusion of 50 to 100 mEq (mmol) is the preferred therapy. Sodium bicarbonate helps correct the metabolic acidosis by raising the extracellular pH, in addition to causing a rapid intracellular potassium shift. It should be noted that sodium bicarbonate is much less effective when hyperkalemia is not related to metabolic acidosis.[1] Sodium bicarbonate is also less effective in patients with end-stage renal disease (ESRD), in whom a decrease in serum potassium may not be seen for as long as 4 hours. Use caution in patients sensitive to volume changes as sodium bicarbonate can also lead to hypernatremia and volume overload. Administration of a rapid-acting (eg, Insulin lispro 10 units IV) or regular insulin (10 units IV) and dextrose (10% or 50%) is an effective method of reducing potassium. Insulin increases the activity of the Na^+-K^+-ATPase pump, thereby intracellularly shifting potassium. Insulin therapy results in a reduction in potassium concentration of 0.6 to 1 mEq/L (mmol/L) that is sustained for up to 2 hours.[35] Glucose should routinely be given whenever insulin is used because hypoglycemia can develop as a result of the effects of the insulin therapy.[36] Alternative dosing strategies, such as low dose (eg, regular insulin 5 units) or weight-based regimens have been studied to combat hypoglycemia with varying results and cannot be routinely recommended.[37-39] A lower dose insulin strategy may be appropriate for patients with severe kidney impairment.[40] β_2-Adrenergic agonists have a dual mechanism for lowering serum potassium. First, they stimulate the Na^+-K^+-ATPase pump to promote intracellular potassium uptake. Second, they stimulate pancreatic β-receptors to increase insulin secretion. Albuterol can be administered via IV (0.5 mg given over 15 minutes) or via nebulizer (10-20 mg nebulized over 10 minutes). It should be noted that injectable albuterol is not available in the United States.

In patients with ESRD, decreases in the serum potassium concentration of 0.6 mEq/L (mmol/L) and 1 mEq/L (mmol/L) can be anticipated after inhalation of 10 and 20 mg of albuterol, respectively. Notice that the doses of inhaled albuterol used for hyperkalemia are at least four times higher than those typically used for bronchospasm, so adverse medication reactions are of greater concern. Adverse medication reactions include tachycardia, tremors, palpitations, mild anxiety, and increase blood glucose.[35] Furthermore, as many as 40% of patients may be resistant to the hypokalemic effects of albuterol and patients already receiving a nonselective β_2-receptor antagonist may not respond. Inconsistent bioavailability via the inhaled route must also be considered, as it could lead to potential over- or underdosing and an unpredictable response.

While not a fast-acting treatment based on pharmacokinetics, one ion exchange resin, sodium polystyrene sulfonate (SPS), is regularly used in hospitalized patients with acute hyperkalemia. It has been used in hospitalized patients for over 60 years. SPS (Kayexalate®) is a cation-exchange resin that can be administered orally or rectally by enema. SPS is available in powder form or prepackaged as a 33% sorbitol suspension. The usual oral SPS dose is 15 to 60 g in the 33% sorbitol suspension. The oral route is more effective than the enema and is better tolerated by patients. As the resin passes through the intestines, each gram of SPS exchanges 1 mEq (mmol) of sodium for 1 mEq (mmol) of potassium, which is in a relatively higher concentration in the large intestine. The onset of action of SPS is within 1 hour, and it can be repeated every 4 hours as needed. The medication should be separated from other oral medications by at least 3 hours as it may bind to and decrease the effectiveness of many oral medications.[41] The sorbitol component of the suspension promotes the excretion of the cationically modified potassium exchange resin by inducing diarrhea. SPS contains a large amount of sodium (100 mg [4.1 mEq or mmol] per gram of SPS) and package labeling advises against its use in patients who cannot tolerate even small increases in sodium loads.[42]

Colonic necrosis is associated with the use of SPS.[43,44] In 2009, the FDA mandated a boxed warning for SPS due to reports of colonic necrosis and other

serious GI toxicities.[42] The GI toxicities were believed to be associated with the 70% sorbitol; however, GI toxicity has also occurred with administration of 33% sorbitol solution. Toxicity appears to occur most commonly in patients who have undergone GI surgery or with current or history of bowel dysfunction. Therefore, the 33% sorbitol product is preferred over the 70% sorbitol product, rectal administration should be avoided, and use is contraindicated in patients with bowel dysfunction.

Several years ago, a Cochrane Review evaluated the emergency treatment of hyperkalemia and provided evidence for the efficacy of inhaled and nebulized β-agonists and IV insulin and glucose.[45] The combination of nebulized β-agonists with IV insulin and glucose appeared to be more effective than either agent alone. The meta-analysis results were equivocal for IV bicarbonate, and notably, SPS was not effective by 4 hours. Clinicians should exercise caution when extrapolating these findings to clinical practice. Nonetheless, the Cochrane database review corroborates the approach detailed in Fig. 70-2. Frequently, the management of hyperkalemia will be based on the clinician's personal judgment or institutional protocols. For example, the large majority (95%) of patients being treated for hyperkalemia in academic teaching hospitals receive SPS, with far fewer receiving insulin and IV calcium, and less than 10% of patient receive bicarbonate, albuterol, or hemodialysis.[46] In many emergency departments, insulin/glucose is the most commonly used agent and multimodal therapy is employed for treating initial serum potassium concentrations above 6 mEq/L (mmol/L).[47]

In nonhospitalized patients who have experienced chronic increases in serum potassium concentration, long-term management of hyperkalemia is focused on dietary restriction of potassium-rich foods and supplements, reducing and avoiding medications that impair potassium excretion in the kidney, and using diuretics or other medications to counteract the effects of medications that increase serum potassium concentrations. Medications used for chronic conditions that are known to cause hyperkalemia include NSAIDs, ACEIs, ARBs, direct renin inhibitors, and MRAs. These typically result in asymptomatic hyperkalemia without the need for emergent therapies. To prevent hyperkalemia, clinicians may attempt to lower the dose or switch to another medication without hyperkalemia as an adverse medication reaction (eg, calcium channel blocker). However, medications that inhibit the renin–angiotensin–aldosterone system (RAAS) have significant beneficial effects on morbidity and mortality in patients with chronic diseases such as diabetes mellitus, heart failure, and CKD. Therefore, reducing or avoiding the use of these medications to prevent hyperkalemia is not often appropriate. The use of a combination of ACEI and ARB is generally avoided due to the increased risk of hyperkalemia.[48] Mineralocorticoid receptor antagonists have a different mechanism of action and their use in combination with an ACEI or ARB is considered acceptable. In particular, finerenone has been shown to lower the rates of CKD progression and cardiovascular events in diabetic nephropathy when added to other RAAS inhibitors.[49,50] This provides the strongest evidence to date for the combination of MRA with an ACEI or ARB in patients with diabetic nephropathy and will likely expand the number of patients on dual RAAS inhibitors. As a third-generation non-steroidal MRA, it has equal distribution into cardiac and renal tissues, compared to spironolactone and eplerenone which favor distribution into renal tissue.[30] The starting dose of finerenone is 10 or 20 mg once daily based on eGFR and serum potassium with a target dose of 20 mg once daily. It should not be used with strong CYP3A4 inhibitors and inducers. The most common adverse medication reactions of finerenone are hyperkalemia, hypotension, and hyponatremia.[29] The extent of hyperkalemia is greater with a combination ACEI and MRA than a combination ACEI and ARB in patients with diabetic nephropathy, suggesting an extrarenal mechanism of this adverse medication reaction from MRAs.[51]

To allow for continued use of RAAS inhibitors, especially in patients prone to hyperkalemia, ion exchange resins may be used. A daily dose of SPS in patients with CKD receiving RAAS inhibitors effectively lowers and maintains serum potassium in the normal range.[52,53] Two other cation exchange agents, patiromer and sodium zirconium cyclosilicate, are available as alternatives to SPS in outpatients with hyperkalemia. Patiromer (Veltassa®) is a nonabsorbable polymer that exchanges calcium for potassium in the distal colon to increase the fecal elimination of potassium. The medication effectively achieves and maintains normokalemia in adults with stage 3 or 4 CKD on stable doses of RAAS inhibitors.[54,55] The most common adverse medication reactions of patiromer include constipation, hypomagnesemia, and diarrhea. The usual dose of patiromer is 8.4 to 25.2 g once daily. Patiromer contains sorbitol to increase medication stability, but at amounts 5- to 10-fold lower than SPS in sorbitol.[25] It should not be used to treat life-threatening hyperkalemia due to its delayed onset of action.[56] Additionally, patiromer can bind to many oral medications, which could lead to decreased absorption of other mediations and loss of efficacy. Therefore, it is recommended to administer other oral medications at least 3 hours before or after patiromer.[56]

Sodium zirconium cyclosilicate (ZS-9, Lokelma®) is a nonabsorbable inorganic compound that selectively exchanges sodium and hydrogen for potassium throughout the entire intestinal tract. The medication effectively decreases serum potassium concentrations as soon as 1 hour after administration of the first dose and for up to 48 hours after administration, with an average decrease of approximately 1 mEq/L (mmol/L) for the 10 g dose.[57,58] ZS-9 exhibits an acute onset of action, but is not FDA-approved for emergency treatment of life-threatening hyperkalemia. It is the only ion

exchange resin that is approved for treatment of hyperkalemia in patients with ESRD on hemodialysis. The most common adverse medication reaction ZS-9 is edema, likely from the exchange of sodium for potassium. The starting dose is 10 g three times daily for 48 hours followed by 5 to 15 g once daily. The dosing in patients on hemodialysis is 5 to 15 g on nondialysis days. Like SPS and patiromer, ZS-9 must be separated from other oral medications but the separation time is shorter at 2 hours.[59]

Evaluation of Therapeutic Outcomes

The frequency and rigor with which one evaluates patients to ascertain if they have achieved the desired therapeutic outcomes depends on the severity and acuity of hyperkalemia. For example, cautious waiting is more common for those with mild or moderate asymptomatic hyperkalemia compared to those with acute symptomatic, severe hyperkalemia. Many medications such as ACEIs, ARBs, direct renin inhibitors, spironolactone, and finerenone result in asymptomatic hyperkalemia and changes in dosage or to a different agent may be all that is warranted. In patients with normal kidney function, once these medications are initiated and the dose titrated, clinicians should check the potassium concentration at least monthly. More frequent monitoring of serum potassium is warranted with combination MRA and either ACEI or ARB. For those patients with impaired kidney function, monitoring should be biweekly until the dose is stabilized.

In patients who have acute symptomatic hyperkalemia (eg, ECG changes), frequent potassium concentration and ECG monitoring is warranted. The patient should receive continuous ECG telemetry monitoring until the serum potassium concentration decreases below 5 mEq/L (mmol/L), and the ECG abnormalities resolve. Similarly, while the patient is receiving emergent therapy, serial serum potassium concentrations should be obtained hourly until the potassium concentration decreases below 5 mEq/L (mmol/L). For patients who receive insulin and dextrose therapy for hyperkalemia, blood glucose monitoring should be performed hourly or more frequently if patients demonstrate signs and symptoms of hypoglycemia. For patients who receive large doses of sodium bicarbonate therapy for hyperkalemia, an arterial blood gas or serum chemistry profile should be obtained to assess their acid-base status. Furthermore, the patient should be evaluated for signs of fluid overload secondary to the high sodium load. Patients receiving albuterol therapy should be questioned regularly regarding the development of palpitations and tachycardia. The patient's medication records should be reviewed to assure the patient is not receiving medication therapy that increases the serum potassium concentration. Furthermore, the patient should be questioned regarding the occurrence of diarrheal stool output.

Clinical Bottom Line

Hyperkalemia commonly occurs in patients with reduced kidney function or other metabolic disturbances. It can rapidly evolve into a medical emergency; therefore, prompt identification and appropriate pharmacotherapy are needed. In patients with mild hyperkalemia, potassium binding resins or loop diuretics may be useful and should be used as first-line therapy. In severe hyperkalemia with ECG changes, IV calcium should be given to protect against cardiac dysrhythmias. Additionally, rapid-acting therapies such as IV insulin and β_2-adrenergic agonists are indicated to move potassium intracellularly.

DISORDERS OF MAGNESIUM HOMEOSTASIS

Magnesium plays a central role in cellular function and is an important cofactor in more than 300 biochemical reactions in the body, especially those systems that are dependent on adenosine triphosphate. Mitochondrial function, protein synthesis, cell membrane function, parathyroid hormone secretion, and glucose metabolism are just a few important functions affected by magnesium.[60] It is the fourth most abundant extracellular cation and the second most abundant intracellular cation, after potassium. Disorders of magnesium homeostasis are commonly encountered in clinical situations and most frequently are manifested as alterations in cardiovascular and neuromuscular functions. Life-threatening conditions such as paralysis and cardiac arrhythmias can occur, making the proper recognition and treatment of these problems of paramount importance. Altered magnesium balance also plays a key role in chronic disease states such as diabetes mellitus, CKD, osteoporosis, development of kidney stones, as well as heart and vascular disease.[61]

Magnesium is principally distributed in bone (67%) and muscle (20%). Because of its predominantly intracellular distribution, measurement of magnesium in the extracellular compartment may not accurately reflect the total-body magnesium content. The majority of magnesium in the extracellular fluid is in the ionized form as only 30% is bound to serum proteins. The normal range for serum magnesium is 1.4 to 1.8 mEq/L (1.7-2.3 mg/dL or 0.70-0.95 mmol/L).

The recommended daily dietary magnesium intake for adults is approximately 420 mg/day and 320 mg/day for men and women, respectively. The maintenance of magnesium homeostasis depends on the balance between intake and output. Ingested magnesium (30%-40%) is absorbed in the small bowel. The absorption of magnesium decreases as the dietary intake increases. Reductions in absorption have also been noted in older adults and those with CKD. A small amount is present in intestinal secretions and reabsorbed in the sigmoid colon. The kidneys play a major role in maintaining magnesium balance. Approximately 95% of the filtered magnesium is reabsorbed, thus in most patients less than 5% is excreted in the urine.[51] Renal magnesium handling is unique in that approximately 20% of the filtered magnesium is reabsorbed in the proximal tubule; the majority (up to 70%) of reabsorption occurs in the thick ascending limb of the loop of Henle. This explains why loop diuretics often cause profound urinary magnesium wasting. The remaining 10% is reabsorbed in the distal convoluted tubule.[62] Unlike most other important electrolytes, there is no hormonal regulation of the distribution of magnesium between bone and circulating or intracellular magnesium pools. Because of this, both hypomagnesemia and hypermagnesemia commonly occur.

CLINICAL PRESENTATION: Hypomagnesemia

General

- The dominant organ systems affected by hypomagnesemia are the neuromuscular and cardiovascular systems.

Symptoms

- Neuromuscular symptoms such as tetany, twitching, and generalized convulsions are common.
- Cardiac symptoms include heart palpitations.

Signs

- Neuromuscular: Presence of Chvostek sign, Trousseau sign, tremor, and tetany.
- Cardiovascular: Cardiac arrhythmias (ventricular fibrillation, torsade de pointes, or digoxin-induced arrhythmias), sudden cardiac death, and hypertension can be present. ECG abnormalities include widened QRS complex and peaked T waves with mild hypomagnesemia; and prolonged PR interval, progressive widening of QRS complex, and flattened T waves with moderate to severe hypomagnesemia.

Laboratory Tests

- Serum magnesium concentration less than 1.4 mEq/L (1.7 mg/dL [0.70 mmol/L]). Serum potassium and calcium concentrations can also be low.

HYPOMAGNESEMIA

Epidemiology

Hypomagnesemia is a common problem in both ambulatory and hospitalized patients. Although the exact prevalence is difficult to estimate, up to 65% of ICU patients may be magnesium-deficient. Although serum magnesium concentrations are not a reliable index of total-body magnesium content, they remain the primary diagnostic tool to evaluate body stores.

Hypomagnesemia is associated with an increase in mortality in critically ill patients. The incidence and associated risks of hypomagnesemia in hospitalized general medicine patients, even though they are at an increased risk of hypomagnesemia given the presence of comorbidities such as heart failure, CKD, and diabetes mellitus. Hypomagnesemia may be observed in as many as 20% of hospitalized general medicine patients and is associated with increased mortality.[63]

Etiology and Pathophysiology

Hypomagnesemia is usually associated with disorders of the intestinal tract or kidney.[64] Medications or conditions that interfere with intestinal absorption or increase renal excretion of magnesium can result in hypomagnesemia (Table 70-6). Decreased intestinal absorption as a result of small bowel disease is the most common cause of hypomagnesemia worldwide. These disorders include regional enteritis, radiation enteritis, ulcerative colitis, acute and chronic diarrhea, pancreatic insufficiency and other malabsorptive syndromes, small-bowel bypass surgery, and chronic laxative misuse. Proton pump inhibitors, especially when used chronically, can cause hypomagnesemia through impaired intestinal absorption. Hypomagnesemia is commonly associated with alcohol use disorder, where the etiology is multifactorial, including reduced intake, pancreatic insufficiency, chronic vomiting and diarrhea, and urinary magnesium wasting.

TABLE 70-6

Causes of Hypomagnesemia

GI
Reduced intake
Protein-calorie malnutrition
Prolonged parenteral fluid administration without magnesium
Alcohol use disorder
Reduced absorption
Primary hypomagnesemia
Malabsorption syndromes (eg, tropical sprue, celiac disease, radiation enteritis, or intestinal lymphectasia)
Short-bowel syndrome (eg, small-bowel resection or ileal bypass)
Pancreatic insufficiency
Proton pump inhibitors (long-term use)
Increased loss
Excessive vomiting
Prolonged nasogastric suction
Excessive laxative use
Intestinal and biliary fistulas
Prolonged diarrhea (ulcerative colitis, Crohn disease, or cancer of the colon)
Kidney
Primary tubular disorders
Primary renal magnesium wasting
Bartter syndrome
Renal tubular acidosis
Diuretic phase of acute tubular necrosis
Postobstructive diuresis
Postrenal transplant diuresis
Glomerulonephritis
Pyelonephritis
Drug-induced renal losses
Aminoglycosides
Amphotericin B
Cyclosporine
Tacrolimus
Diuretics
Digitalis

Cisplatin Pentamidine Foscarnet Hormone-induced renal losses Primary hyperparathyroidism Hyperthyroidism Aldosteronism “Hungry bone syndrome” after parathyroidectomy
Internal redistribution
Diabetic ketoacidosis Glucose, amino acid, or insulin administration Massive blood transfusion (citrate) Pancreatitis with lipedema (magnesium soap)
Other
Excessive sweating and lactation Hypercalcemia and hypercalciuria Phosphate depletion Chronic alcohol use disorder Extracellular fluid volume expansion

Primary renal magnesium wasting can be caused by a defect in renal tubular magnesium reabsorption, or inhibition of sodium reabsorption in those segments in which magnesium transport follows passively. The former condition is associated with hypercalciuria, nephrolithiasis, and progressive kidney disease, while the latter is associated with Gitelman and Bartter syndromes.[64] Much more common than these is renal magnesium wasting secondary to thiazide and loop diuretics. Other commonly used medications that can cause renal magnesium wasting include aminoglycosides, amphotericin B, cyclosporine, digoxin, tacrolimus, cisplatin, pentamidine, and foscarnet.[65]

Treatment

Desired Outcomes

The treatment goals in the management of hypomagnesemia are (a) resolution of the signs and symptoms, (b) restoration of normal magnesium concentrations, (c) correction of concomitant electrolyte abnormalities, and (d) identification and correction of the underlying cause of magnesium depletion.

General Approach to Treatment

Magnesium supplementation can be administered by the oral, intramuscular (IM), or IV route. The severity of the magnesium depletion and the presence of severe signs and symptoms should dictate the route of administration. Because IM administration is painful, it should be reserved for those patients with severe hypomagnesemia and limited venous access. IV bolus administration is associated with flushing, sweating, and a sensation of warmth; thus, bolus administration should be avoided if possible. Additionally, because calcium forms a complex with the sulfate moiety, which is then excreted, large amounts of IV magnesium sulfate should be administered with caution to patients with hypocalcemia, as it can further exacerbate calcium deficiency.[61] It is widely accepted that 8 to 12 g of magnesium sulfate be administered, in divided doses, in the first 24 hours followed by 4 to 6 g/day for 3 to 5 days to adequately replete body stores in those with severe hypomagnesemia.[66] Even if severe magnesium depletion is present,

approximately 50% of the administered dose is excreted in the urine. Consequently, magnesium replacement should be performed over 3 to 5 days, and continued supplementation should be provided for patients unable to eat. Table 70-7 lists the commonly used magnesium oral supplements and their respective elemental magnesium content.

TABLE 70-7

Common Magnesium Products and Their Elemental Magnesium Content

Product	Elemental Magnesium Content
Magnesium aspartate hydrochloride	122 mg in 1,230 mg dietary supplement granules
Magnesium carbonate	121 mg in 500 mg capsule
Magnesium chloride	64 mg in each 535 mg tablet
Magnesium citrate	48 mg in each 5 mL of the oral solution
Magnesium gluconate	27 mg in a 500 mg tablet
Magnesium glycerophosphate	97 mg in 1 g tablet
Magnesium hydroxide	167 mg in a 400 mg tablet or 5 mL oral suspension
Magnesium lactate	84 mg in an 84 mg tablet
Magnesium oxide	242 mg in a 400 mg tablet

Nonpharmacologic Therapy

There are no nonpharmacologic options for the management of hypomagnesaemia.

Pharmacologic Therapy

It is controversial whether all asymptomatic patients require magnesium supplementation when serum magnesium concentration falls below the normal range. In particular, for patients with type 2 diabetes mellitus, hypomagnesemia contributes to diabetic complications by affecting glucose transport and insulin secretion and utilization. Indeed, oral magnesium supplementation in patients with type 2 diabetes mellitus and hypomagnesemia improves insulin sensitivity and metabolic control.[67] On the other hand, hypomagnesemia may be a consequence of diabetes mellitus. Possible mechanisms of hypomagnesemia in these patients include reduced GI absorption, enhanced renal excretion secondary to an increased filtered magnesium load and tubular flow, and reduced tubular reabsorption. Metabolic abnormalities such as hypokalemia, hypophosphatemia, and metabolic acidosis may also contribute to its development.[68] While it seems reasonable to provide a supplement for diabetic patients with low serum magnesium concentrations, improved clinical outcomes have not been demonstrated.

Should treatment be warranted, those patients with serum magnesium concentrations greater than 1 mEq/L (1.2 mg/dL [0.5 mmol/L]) can be treated with oral supplements. Oral supplementation is preferred because magnesium uptake is a slow process that may require prolonged administration. Several magnesium products are available, including magnesium-containing antacids or laxatives, comprising a variety of magnesium salts in tablet or capsule formulations. Many of the oral products contain little magnesium, which necessitates three or four doses per day. As expected, diarrhea is the most common dose-limiting adverse medication reactions of oral therapy, which can greatly reduce patient compliance. Therefore, sustained-release magnesium products are preferred as they not only improve patient compliance but also reduce the occurrence of GI adverse medication reactions.

In patients with severe magnesium depletion (serum concentrations less than 1 mEq/L [1.2 mg/dL; 0.5 mmol/L]) or if signs and symptoms are present regardless of the serum concentration, IV magnesium should be administered. A dose of 4 to 6 g in 50 to 100 mL (maximum concentration 1 g/10 mL) should be administered in divided doses over 12 to 24 hours and repeated as necessary in order to maintain magnesium concentrations above 1 mEq/L (1.2 mg/dL [0.5 mmol/L]). Doses of 2 to 4 g in 50 mL infused over 1 hour are frequently used clinically; however, these result in transient benefit because of the extensive renal excretion and usually have to be repeated daily over 3 to 5 days for adequate repletion. Therapy should be continued until the signs and symptoms have completely resolved. In patients with impaired kidney function, some have reduced the does by 25% to 50%.

Evaluation of Therapeutic Outcomes

In patients with acute, asymptomatic mild-to-moderate hypomagnesemia, serum magnesium concentrations should be obtained at least daily during their hospitalization. Patients receiving oral magnesium therapy should be questioned regarding GI tolerance and the occurrence of diarrhea. Patients being treated for symptomatic severe hypomagnesemia should have their serum magnesium concentration monitored hourly until the serum concentration reaches 1.5 mEq/L (1.8 mg/dL [0.75 mmol/L]) and the symptoms resolve. At that point, the serum magnesium concentration can be monitored every 6 to 12 hours for the next 24 hours while receiving magnesium supplementation. Once the magnesium concentration is stable in the normal range, a concentration can be obtained daily. It should be reiterated that it typically takes 3 to 5 days to fully replete total-body magnesium stores. Patients receiving oral magnesium-containing antacids or supplements should be asked regularly about the occurrence of diarrhea.

Clinical Bottom Line

Hypomagnesemia is generally associated with kidney or GI tract disorders. Patients with mild, chronic magnesium loss, oral magnesium preparations can be used; however, the dose-limiting adverse medication reaction is diarrhea. For more severe hypomagnesemia, IV magnesium sulfate can be safely administered. Repeated doses may be needed as IV magnesium is rapidly eliminated in urine. In such cases, close monitoring of serum magnesium concentrations is needed.

HYPERMAGNESEMIA

Epidemiology

7 Hypermagnesemia (serum magnesium greater than 2 mEq/L [2.4 mg/dL; 1 mmol/L]) is a rare occurrence that is generally seen in patients with stage 4 or 5 CKD when magnesium intake exceeds the excretory capacity of the kidneys. Older adults are prone to hypermagnesemia because of their reduced GFR and because of their tendency to consume magnesium-containing antacids and vitamins.

Etiology and Pathophysiology

Because magnesium excretion decreases as GFR declines, serum magnesium concentrations tend to increase in patients with moderate-to-severe CKD. Indeed, magnesium concentrations steadily increase as the GFR decreases below 30 mL/min/1.73 m^2. As long as the patient maintains a normal diet, the serum magnesium concentration typically stabilizes at approximately 2.5 mEq/L (3 mg/dL [1.25 mmol/L]). If patients with stage 4 or 5 CKD are taking concomitant magnesium-containing antacids, the serum concentration can approach 6 mEq/L (7.3 mg/dL [3 mmol/L]), a value associated with signs and symptoms of toxicity. Critically ill patients with multiorgan system failure receiving enteral or parenteral nutrition are also prone to develop hypermagnesemia. Finally, the parenteral treatment of eclampsia with magnesium sulfate can lead to hypermagnesemia. Table 70-8 lists other causes of hypermagnesemia.

TABLE 70-8

Causes of Hypermagnesemia

Decreased renal excretion
Acute kidney injury
CKD with exogenous intake
Excessive intake
Treatment of toxemia of pregnancy
Ureteral irrigants (hemiacidrin)
Cathartics
Other
Lithium therapy
Hypothyroidism
Milk-alkali syndrome
Addison disease
Viral hepatitis
Acute diabetic ketoacidosis

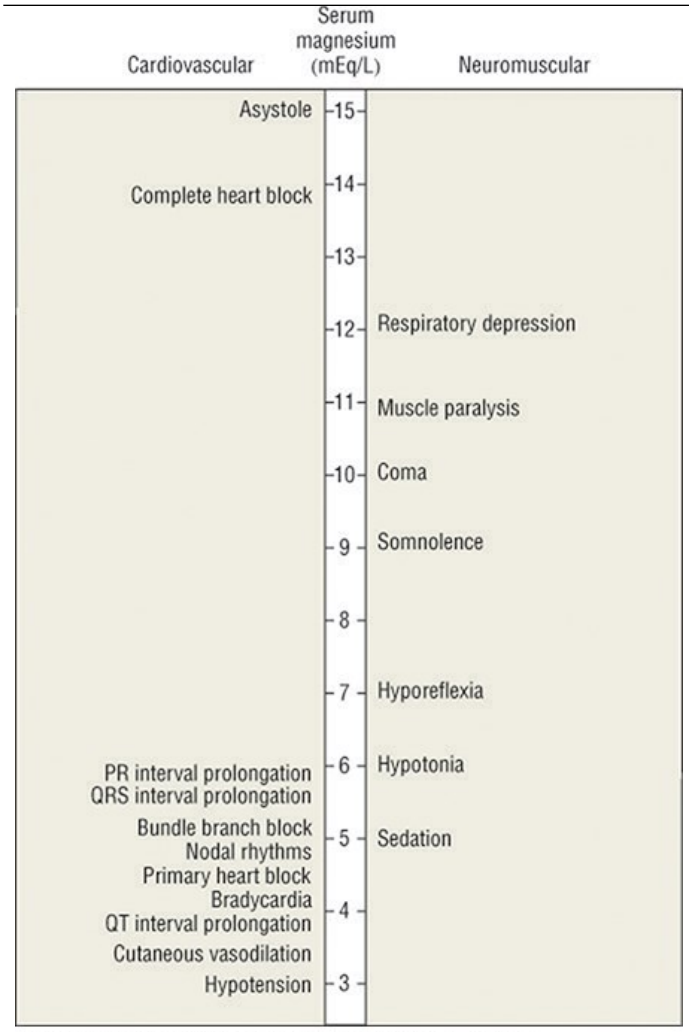
CKD, chronic kidney disease.

Clinical Presentation

The signs and symptoms of hypermagnesemia reflect magnesium's action on the neuromuscular and cardiovascular systems.[66,69] The main symptoms include lethargy, confusion, dysrhythmias, and muscle weakness. Symptoms are rare when the serum concentration is below 4 mEq/L (4.9 mg/dL [2 mmol/L]) (Fig. 70-3).

FIGURE 70-3

Clinical findings associated with hypermagnesemia. (Serum magnesium concentrations in mmol/L can be determined by multiplying the serum magnesium value expressed in mEq/L by 0.5.)



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Treatment

Desired Outcome

The goals of therapy are to (a) reverse the neuromuscular and cardiovascular manifestations of hypermagnesemia, (b) decrease the magnesium concentration toward normal values, and (c) identify and treat the underlying cause of hypermagnesemia.

Nonpharmacologic Therapy

There are no nonpharmacologic options for the management of hypermagnesemia.

Pharmacologic Therapy

There are three primary means of treating hypermagnesemia: (a) reduce magnesium intake, (b) enhance elimination of magnesium, and (c) antagonize the physiologic effects of magnesium. The optimal treatment regimen for the management of hypermagnesemia depends on the severity of the patient's signs and symptoms and the degree of serum concentration elevation. IV elemental calcium doses of 100 to 200 mg directly antagonize the neuromuscular and cardiovascular effects of hypermagnesemia. Oral calcium is not effective because of its relatively poor bioavailability and slow onset of action. The clinical effect of calcium is immediate, but the effect is transient; hence, repeated IV doses of 100 to 200 mg of elemental calcium

(eg, 2 g of calcium gluconate) might need to be administered hourly until the signs or symptoms abate and the magnesium concentration is normalized. Supportive care with cardiac pacing, vasopressors, and mechanical ventilation can be necessary in life-threatening situations. In patients with normal kidney function or those with stage 1, 2, or 3 CKD, forced diuresis with 0.45% NaCl and loop diuretics can promote magnesium elimination. An initial IV bolus of furosemide 40 mg or a similar equivalent can be used. Subsequent dosing can be determined based on the patient's clinical response. Patients with CKD can require long-term loop diuretic therapy to maintain adequate fluid and electrolyte balance. In patients with ESRD receiving dialysis, their hemodialysis prescription should be changed to employ magnesium-free dialysate.

Evaluation of Therapeutic Outcomes

Patients who are receiving IV calcium salts for the treatment of severe, symptomatic hypermagnesemia should have their serum magnesium concentration evaluated hourly until symptoms abate and the magnesium concentration decreases below 4 mg/dL (3.3 mEq/L [1.64 mmol/L]). Furthermore, the patient should be continuously monitored to detect ECG changes. In patients with CKD who can produce urine, forced diuresis with saline and furosemide should reduce the serum magnesium concentration within 6 to 12 hours. Close monitoring of the urine output and physical examination for signs of volume overload are important. Emergency hemodialysis will usually correct the hypermagnesemia within 4 hours and is a reasonable option for those who are receiving hemodialysis. To prevent further episodes of hypermagnesemia, the patient should receive dietary education regarding foods and beverages that contain large quantities of magnesium (Table 70-9).

TABLE 70-9

Magnesium Content of Selected Foods

Food	Elemental Magnesium Content per Serving (mg)
Halibut, cooked, 3 oz (85 g)	90
Almonds, dry roasted, 1 oz (28 g)	80
Spinach, boiled, one-half cup (~125 mL)	78
Cashews, dry roasted, 1 oz (28 g)	74
Peanuts, oil roasted, one-fourth cup (~60 mL)	63
Shredded wheat cereal, two large biscuits	61
Soymilk, plain, or vanilla, 1 cup (~250 mL)	61
Black beans, cooked, one-half cup (~125 mL)	60
Edamame, shelled, cooked, one-half cup (~125 mL)	50
Peanuts, dry roasted, 1 oz (28 g)	50
Peanut butter, smooth, 2 tablespoons (~30 mL)	49
Bread, whole wheat, 2 slices	46
Avocado, cubed, 1 cup (~250 mL)	44
Potato, baked with skin, 3.5 oz (~100 g)	43
Yogurt, plain, low fat, 8 oz (~225 g)	42
Rice, brown, cooked, one-half cup (~125 mL)	42
Breakfast cereals, fortified with 10% of the daily value for magnesium	40
Instant oatmeal, 1 cup (~250 mL)	36
Kidney beans, canned, one-half cup (~125 mL)	35
Banana, 1 medium	32

Clinical Bottom Line

Hypermagnesemia is generally associated with advanced CKD. Severe hypermagnesemia can result in neurologic symptoms or cardiac dysrhythmias. Should these symptoms occur, IV calcium can counteract these effects. Forced diuresis with saline and loop diuretics is useful in lowering magnesium in patients with mild to moderate kidney disease; hemodialysis should be reserved for patients with ESRD.

ABBREVIATIONS

ACEI	angiotensin-converting enzyme inhibitor
AKI	acute kidney injury
ARB	angiotensin-II receptor blocker
CKD	chronic kidney disease
ECG	electrocardiogram
ESRD	end-stage renal disease
FDA	Food and Drug Administration
GFR	glomerular filtration rate
GI	gastrointestinal
IM	intramuscular
IV	intravenous
MRA	mineralocorticoid receptor antagonist
NSAID	nonsteroidal anti-inflammatory drug
RAAS	renin–angiotensin–aldosterone system
SPS	sodium polystyrene sulfonate

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SELF-ASSESSMENT QUESTIONS

1. Which treatment for hyperkalemia works by preventing intestinal absorption of potassium?
   A. Albuterol
   B. Patiromer
   C. Sodium bicarbonate
   D. Insulin + dextrose
2. Which of the following medications is most commonly associated with the adverse medication reaction of hyperkalemia?
   A. Hydrochlorothiazide
   B. Fosinopril
   C. Furosemide
   D. Albuterol
3. For a patient presenting with lethargy, decreased deep tendon reflexes, and somnolence, what is the *most likely* condition?
   A. Hypokalemia
   B. Hyperkalemia

C. Hypomagnesemia

D. Hypermagnesemia

4. What is the *immediate first line* therapy for hyperkalemia associated with ECG changes?

A. Furosemide 40 mg PO

B. Calcium gluconate 1 gram IV

C. Hemodialysis

D. Regular insulin 10 Units IV

5. Which statement regarding IV potassium is *correct*?

A. The infusion rate should not exceed 20 mEq/hour (20 mmol/hour) in a peripheral line

B. IV potassium is preferred in all hospitalized patients

C. Potassium should be diluted in dextrose 5% water

D. Continuous ECG monitoring is always necessary when infusing potassium

6. Which adverse medication reaction is minimized by dividing the total daily dose of oral potassium supplements into smaller doses?

A. Itching

B. Hypoglycemia

C. GI upset

D. Muscle cramps

7. Which condition is *most likely* associated with a patient presenting with Trousseau sign?

A. Hypokalemia

B. Hyperkalemia

C. Hypomagnesemia

D. Hypermagnesemia

8. Which statement is *true* of sodium polystyrene sulfonate (SPS) compared to patiromer?

A. Both exchange potassium for sodium in the intestines

B. Both must be separated from other oral medications by 3 hours

C. Both are known to cause colonic necrosis

D. Both are commonly used to treat life-threatening hyperkalemia

9. Which is the most appropriate *first-line* treatment option for a patient who develops hyperkalemia (without ECG changes) as a result of severe metabolic acidosis?

A. IV calcium gluconate

B. Insulin + dextrose

C. Albuterol

D. Sodium bicarbonate

10. Which of the following is the *most likely* adverse medication reaction of intravenous magnesium replacement therapy?

A. Diarrhea

B. Kidney failure

C. Muscle pain

D. Flushing

11. An adult hospitalized patient receiving care from an internal medicine service has labs evaluated this morning, which include a serum potassium is 3.2 mEq/L (mmol/L) and serum magnesium is 0.9 mg/dL (0.74 mEq/L; 0.37 mmol/L). After receiving 40 mEq of liquid potassium chloride orally, repeat labs from 8 hours later include a serum potassium of 3.4 mEq/L (mmol/L) and serum magnesium 0.9 mg/dL (0.74 mmol/L; 0.37 mmol/L). What is the *most appropriate* therapy to increase the patient's serum potassium at this time?

A. Potassium chloride 60 mEq PO

B. Magnesium sulfate 2 grams IV

C. Potassium chloride 40 mEq IV

D. Magnesium oxide 400 mg PO

12. What is the mechanism that results in proton pump inhibitors causing hypomagnesemia?

A. Hormone-induced renal losses

B. Internal redistribution

C. Reduced gastrointestinal intake

D. Reduced gastrointestinal absorption

13. In addition to the cardiovascular system, which other system is *most commonly* affected by disorders of potassium?

A. Neuromuscular

B. Renal

C. Skeletal

D. Gastrointestinal

14. Which of the following *most commonly* affects potassium homeostasis?

A. Respiratory acidosis

B. Insulin secretion

C. Circulating acetylcholine

D. Cortisol production

15. Which patient is *most likely* to develop hypermagnesemia?

    A. A 45-year-old with alcohol use disorder receiving treatment for acute alcohol withdrawal

    B. A 60-year-old patient receiving treatment for fungemia with amphotericin B

    C. A 35-year-old patient with ESKD who has missed the past two sessions of dialysis

    D. A 17-year-old patient with newly diagnosed hypothyroidism

SELF-ASSESSMENT QUESTION-ANSWERS

1. **B.** Patiromer is one of three available potassium binders that decreases total body potassium. See the "Hyperkalemia (Pharmacologic Therapy)" and Table 70-1 for more information.

2. **B.** Angiotensin-converting enzyme inhibitors prevent renal potassium excretion and can lead to hyperkalemia. See the Hyperkalemia Associated with Decreased Renal Potassium Excretion" and "Hyperkalemia (Pharmacologic Therapy)" sections for more information.

3. **D.** The main symptoms of hypermagnesemia include lethargy, confusion, dysrhythmias, and muscle weakness. See the "Hypomagnesemia (Clinical Presentation)" section and Fig. 70-3 for more information.

4. **B.** In patients with hyperkalemia and ECG changes, IV calcium is the first line therapy. See the "General Approach to Therapy" and "Pharmacologic Therapy" sections and Fig. 70-2 for more information.

5. **A.** Generally, doses of 10 to 20 mEq (mmol) of potassium chloride are safe when administered through a peripheral vein over an hour. See the "Pharmacologic Therapy" section for more information.

6. **C.** Smaller doses of oral potassium supplements helps to minimize the common adverse medication reaction of GI upset. See the "Pharmacologic Therapy" section for more information.

7. **C.** Clinical presentations of hypomagnesemia can include specific neuromuscular effects such as Chvostek and Trousseau signs. See the "Disorders of Magnesium Homeostasis (Clinical Presentation Hypomagnesemia)" section for more information.

8. **B.** Administration of both SPS and patiromer must be separated from other oral medications by at least 3 hours. See the "Pharmacologic Therapy" section for more information.

9. **D.** In patients with concomitant metabolic acidosis sodium bicarbonate is the preferred therapy to treat hyperkalemia. See the "Pharmacologic Therapy" section and Fig. 70-2 for more information.

10. **D.** IV magnesium bolus administration is associated with flushing, sweating, and a sensation of warmth. See the "General Approach to Treatment" section for more information.

11. **B.** In patients with concomitant hypokalemia and hypomagnesemia, it is imperative to correct the hypomagnesemia first. See the "Etiology and Pathophysiology" and "Pharmacologic Therapy" sections for more information.

12. **D.** Proton pump inhibitors, especially when used chronically, can cause hypomagnesemia through impaired intestinal absorption. See the "Hypomagnesemia (Etiology and Pathophysiology)" section for more information.

13. **A.** Potassium disorders primarily affect the neuromuscular and cardiac systems. See the "Clinical Presentation (Hyperkalemia)" section for more information.

14. **B.** Insulin stimulates the cellular Na^+-K^+-ATPase pump to increase intracellular potassium transport in response to increasing serum potassium. See the "Control of Potassium Homeostasis" section for more information.

15. **C.** Decreased renal excretion is a common cause of hypermagnesemia. See the "Hypermagnesemia (Etiology and Pathophysiology)" section and Table 70-8 for more information.