Life-threatening electrolyte abnormalities

Electrolyte abnormalities are common in hospitalized patients. Prompt recognition and treatment of imbalances in the calcium, potassium, magnesium, or sodium levels may reduce complications and the risk of morbidity and mortality.

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Article at a glance

- Because electrolyte abnormalities can have dire consequences, it is important to correct them, particularly in severely ill patients, to avoid further complications.
- When managing patients with abnormal serum electrolytes, it is always good practice not only to correct the abnormality but also to investigate the underlying cause.
- The patient's medical history and medication list should be reviewed, along with previous laboratory tests, to determine whether the patient is suffering from an acute or chronic event.

Uncorrected electrolyte abnormalities may have life-threatening sequelae that encompass multiple organ systems, including the cardiovascular, GI, and central nervous systems. Severe electrolyte abnormalities can result in paralysis, seizures, coma, intractable nausea and vomiting, cardiac and respiratory arrest, and even death. We review the clinical presentation and treatment of the most commonly encountered electrolyte abnormalities in hospitalized patients.

CALCIUM

Changes in serum calcium are directly related to serum albumin concentrations. For every increase in albumin of 1.0 mg/dL, there is a 0.8-mg/dL increase in calcium concentration. Corrected calcium is calculated as follows:

$$\text{Corrected Ca} = (4.0\ \text{g/dL} - \text{plasma albumin}) \times 0.8 + \text{serum Ca}$$

The concentration of ionized calcium is inversely proportional to the albumin concentration. The higher the serum albumin, the lower the plasma ionized calcium concentration will be. The lower the serum albumin, the higher the plasma ionized calcium concentration will be. Measured total serum calcium concentration is dependent on changes in serum albumin. Therefore, ionized calcium levels may be normal when total calcium levels are low. One setting in which ionized calcium should be followed instead of total serum calcium is in the ICU, where there is a high false-positive and a high false-negative rate for hypercalcemia and hypocalcemia, respectively, when calculating for changes in serum albumin.[1]

Hypocalcemia

Normal plasma calcium concentrations range from 8.5 to 10.5 mg/dL (4.2-5.2 mg/dL for ionized calcium). Hypocalcemia is defined as a calcium level of less than 8.5 mg/dL or an ionized calcium level of less than 4.2 mg/dL. Symptoms may occur when ionized calcium drops below 2.5 mg/dL.[2]

The most common sequela of hypocalcemia is tetany. Symptoms may range from mild, such as circumoral numbness and paresthe-

sias, to severe, including muscle contractions and carpopedal spasm. Latent tetany may result in the classic Trousseau's and Chvostek's signs. Hypocalcemia may also have neurologic sequelae, such as grand mal, petit mal, or focal seizures, which may occur independently of tetany. Hallucinations or psychosis may also develop. Cardiovascular manifestations of acute hypocalcemia include congestive heart failure (CHF) due to decreased myocardial contractility, bradycardia, and a prolonged QT syndrome that may progress to torsades de pointes.[3,4]

Hypocalcemia may stem from hyperphosphatemia as a result of rhabdomyolysis or renal failure, pancreatitis and the formation of calcium soaps, hypovitaminosis D from liver or kidney disease, cancers with a high proclivity for bone metastasis (such as prostate and breast cancer), tumor lysis syndrome, or postthyroidectomy.[2,5,6] Magnesium depletion may also lower calcium levels. There is an increased parathyroid hormone (PTH) resistance when serum magnesium concentrations fall below 0.8 mEq/L (1.0 mg/dL). More severe forms of hypomagnesemia result in decreased PTH secretion.

Express Stop

Serum calcium levels above 15 mg/dL may result in complete heart block or even cardiac arrest.

Treatment of hypocalcemia

Patients with symptomatic hypocalcemia should have ionized calcium measured to rule out hypoalbuminemia as the cause. In addition, serum phosphate, PTH, magnesium, potassium, and creatinine levels should be ordered. Acute symptomatic hypocalcemia should be treated with 9 mEq, or 2 g, of calcium gluconate in 100 mL of 0.9% sodium chloride (NaCl) or dextrose 5% in water (D5W) infused over 15 minutes. If symptoms persist, this should be followed by 27 mEq, or 6 g, of calcium gluconate in 1 L of 0.9% NaCl or D5W infused over 6 to 12 hours. Calcium gluconate is preferred to calcium chloride because it is less likely to cause tissue necrosis if a peripheral IV line extravasates. Serum calcium should be monitored every 4 to 6 hours. After the serum calcium is corrected, an evaluation for the cause should be initiated.

Hypercalcemia

Hypercalcemia is measured as a serum calcium concentration of greater than 10.5 mg/dL (5.2 mg/dL for ionized calcium) and may result from increased bone resorption, decreased renal loss, or increased GI absorption (see "Stages of hypercalcemia," page 21).

Hyperparathyroidism accounts for 90% of elevated serum calcium levels in ambulatory patients, whereas cancer is the most common cause in hospitalized patients, accounting for 65% of cases. Hypercalcemia in cancer patients carries a poor prognosis: The 30-day mortality risk is nearly 50%.[7]

Elevated serum PTH may result from a parathyroid gland adenoma (primary hyperparathyroidism) or neuroendocrine tumors, such as squamous cell carcinoma of the lung (secondary hyperparathyroidism). Hypercalcemia associated with cancer may be secondary to bony metastasis with increased production of inflammatory cytokines and PTH-related protein, neuroendocrine tumors, or lymphomas that secrete 1,25-dihydroxyvitamin D (1,25[OH]2D).[7,8]

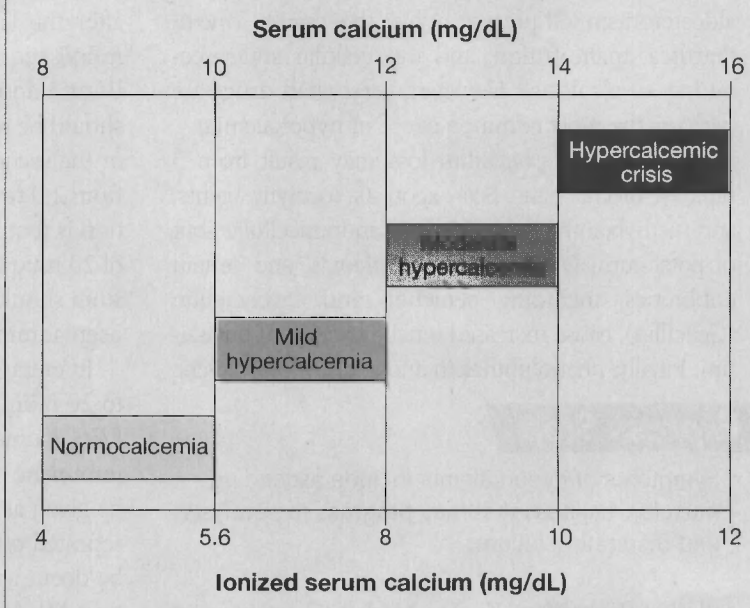
Medications, including lithium, thiazide diuretics, and large doses of beta carotene, may also be responsible for increased serum calcium concentrations. Calcium carbonate overuse can lead to hypercalcemia, alkalosis, and renal insufficiency in the milk-alkali syndrome. Medications should always be considered in the evaluation of high serum calcium levels.[9]

Patients with levels of serum calcium from 10.5 to 12 mg/dL are typically asymptomatic. Above 12 mg/dL, multiple manifestations may occur, involving organ systems included in the mnemonic "stones, bones, psychic moans, and abdominal groans." Renal involvement may present with nephrolithiasis, nephrogenic diabetes insipidus, and dehydration. Musculoskeletal symptoms such as bone pain, arthritis, and osteoporosis may be present. Hypercalcemia may also cause nausea, vomiting, abdominal pain, constipation, peptic ulcers, and pancreatitis. Serious side effects affect the CNS: Confusion, lethargy, and fatigue in mild hypercalcemia, if untreated, may progress to stupor and coma.

Cardiovascular findings depend on the severity of

hypercalcemia. Initially, elevated serum calcium levels increase myocyte contractility. Once the level reaches 15 mg/dL, myocardial depression may occur. The QT interval shortens when serum calcium levels are higher than 13 mg/dL with subsequent prolongation of the PR and QRS intervals and an increased risk for cardiac arrhythmias. Serum calcium levels above 15 mg/dL, a level indicative of hypercalcemic crisis, may result in complete heart block or even cardiac arrest.[2]

Stages of hypercalcemia



Adapted with permission from Carroll MF, Schade DS. A practical approach to hypercalcemia. *Am Fam Physician*. 2003;67:1959-1966.

Treatment of hypercalcemia

Patients with mild hypercalcemia generally do not derive benefit from treatment. However, it is essential that those with calcium levels above 14 mg/dL, or those who are symptomatic with calcium levels above 12 mg/dL, receive immediate intervention.

For patients with mild hypercalcemia who have adequate renal and cardiovascular function, it is recommended that they receive IV fluids to generate a urine output of 200 mL/h. Severe hypercalcemia requires an infusion rate of 300 to 500 mL/h until urine output equals fluid intake. When fluid input and output are balanced, the rate can be lowered to 100 to 200 mL/h.[2] After intravascular volume has been restored, if serum calcium levels are still elevated, a loop diuretic can be considered. During this time, magnesium and potassium levels should be monitored, and concentrations replenished as necessary. If a patient suffers from resistant, life-threatening hypercalcemia, hemodialysis is the treatment of choice.

POTASSIUM

Abnormal serum potassium levels are the most common electrolyte abnormality in hospitalized patients, with nearly 20% having a level below 3.6 mEq/L.[10-12] Serum potassium concentration is controlled by 3 mechanisms: intake, distribution between intracellular and extracellular fluid, and renal excretion.

Cellular distribution is affected by insulin and beta-adrenergic receptors that stimulate activation of Na^+/K^+-ATPase channels and cause an influx of potassium into the cell. Renal excretion occurs mainly at the cortical collecting tubule in response to increased serum potassium levels and the plasma aldosterone concentration.

Rapid or severe changes in serum potassium levels may have life-threatening consequences. Adjustments may affect not only membrane potential but also serum pH. Changes in serum potassium result in an inverse change in serum pH. Also, changes in serum pH will affect serum potassium levels: A rise in pH will cause hydrogen to exit cells in an attempt to buffer the rising pH, which will cause a fall in serum potassium levels. Falling pH has the converse effect. In patients who suffer from illnesses that cause changes in pH, such as diabetic ketoacidosis, uremia, and lactic acidosis, serum potassium levels should be monitored.

Hypokalemia

Only 0.4% of the total concentration of extracellular potassium is measurable in plasma. Hypokalemia is defined as a serum potassium level of less than 3.5 mEq/L. Pathophysiologic causes of low serum potas-

sium include renal loss from diseases such as hyperaldosteronism; GI potassium loss that may be due to diarrhea; malnutrition; and intracellular shifts secondary to alkalosis.[2] However, prescribed drugs are perhaps the most common cause of hypokalemia.

Drug-induced potassium loss may result from 3 separate mechanisms. Beta$_2$-agonists, tocolytic agents, and methylxanthines may induce an intracellular shift of potassium. Diuretics, glucocorticoids, and certain antibiotics, including penicillin and carbenicillin (Geocillin), cause increased renal excretion of potassium. Finally, phenolphthalein and sodium polystyrene sulfonate (Kayexalate, Kionex, Marlexate) can increase GI loss of potassium. Therefore, it is important to review a patient's drug record when treating hypokalemia.

Express Stop

Symptoms of hyperkalemia include ascending muscle weakness that may progress to paralysis and respiratory failure.

Typically, patients with mild hypokalemia (serum potassium 3.0-3.5 mEq/L) are asymptomatic. Serum potassium levels from 2.5 to 3.0 mEq/L may cause constipation and weakness. Levels less than 2.5 mEq/L may result in muscle necrosis, and levels less than 2.0 mEq/L may cause an ascending muscle paralysis and subsequent respiratory failure.[12] In patients with a history of cardiac disease, even mild to moderate changes in serum potassium can cause cardiac arrhythmias. Hypokalemia can result in prolonged QT syndrome with subsequent development of torsades de pointes. In patients receiving digoxin (Lanoxin) therapy, low serum potassium levels can increase its arrhythmogenic effects.

Treatment of hypokalemia

The cornerstone of treatment is potassium replacement. However, potassium supplementation is also the most common cause of severe hyperkalemia, especially with the use of IV potassium.

Oral potassium is the preferred method of repletion, if possible.[12] Patients with serum potassium levels of 3.0 to 3.5 mEq/L should receive 80 mEq in either 4 doses of 20 mEq IV or two doses of 40 mEq po. Serum potassium should be checked 2 hours after the last dose. Potassium levels of 2.5 to 2.9 mEq/L require 120 mEq, given as 6 doses of 20 mEq IV or 3 doses of 40 mEq po. Serum potassium levels should be rechecked 2 hours after the fourth IV dose or the second oral dose. For serum potassium levels from 2.0 to 2.4 mEq/L, 160 mEq of potassium repletion is required. This can be administered as 8 doses of 20 mEq IV or 4 doses of 40 mEq po. Serum potassium should be checked 2 hours after 120 mEq have been administered.

In emergent conditions, patients may be given 10 to 20 mEq/h of potassium. This requires continuous ECG monitoring. If cardiac arrest is believed to be imminent, higher concentrations of potassium may be given at 10 mEq IV over 5 minutes. This may be repeated once if needed.[2] If this step is taken, it must be documented that the injection was intentional to treat life-threatening hypokalemia.

Hyperkalemia

Hyperkalemia may be defined as mild (potassium of 5.0-6.0 mEq/L), moderate (potassium 6.0-7.0 mEq/L), or severe (potassium greater than 7.0 mEq/L). Moderate and severe hyperkalemia require immediate treatment. Causes of hyperkalemia include metabolic acidosis, insulin deficiency and hyperglycemia, increased tissue catabolism (such as rhabdomyolysis), renal tubular acidosis, tumor lysis syndrome secondary to chemotherapy, and beta-adrenergic blockade. Many other drugs can also cause hyperkalemia (see Table 1, page 23). Medication lists should be reviewed when treating patients for high serum potassium levels.

Keep laboratory error in mind when evaluating hyperkalemia. Drawing blood from a line through which potassium is being infused, technician error, hemolysis, leukocytosis, thrombocytosis, and traumatic venipuncture can all cause falsely elevated values of serum potassium.[13]

Hyperkalemia manifests itself with very few symptoms and these tend to occur only at levels exceeding 7.0 mEq/L or when levels rise acutely. Symptoms include ascending muscle weakness that may progress to paralysis and respiratory failure. The ECG changes that occur with hyperkalemia start

with peaking of the T waves, which then progresses to flattened P waves, first-degree heart block, widening of the QRS complex, deep S waves, and merging of the S and T waves. If the condition is left untreated, a sine-wave pattern may develop with subsequent cardiac arrest.

Treatment of hyperkalemia

Initially, one should evaluate the patient for all exogenous sources of potassium and medications that can elevate serum potassium concentrations. Treatment is based on severity level (see Table 2, page 24).

MAGNESIUM

Physiologically, magnesium aids in cellular transport of calcium, potassium, and sodium and acts to stabilize excitable cellular membranes. Magnesium homeostasis is maintained in healthy individuals by absorption through the brush border in the small intestine via both facilitated transport and passive diffusion. It is also excreted from the small intestine, with a large amount being reabsorbed in the large intestine. Balance is maintained in the kidney, where approximately 100 mg of magnesium is excreted in the urine daily.

Hypomagnesemia

Defined as a serum magnesium concentration of less than 1.3 mEq/L, hypomagnesemia is relatively common, occurring in more than 10% of hospitalized patients. The 2 main mechanisms by which hypomagnesemia occurs are GI and renal losses.

GI loss may be the result of chronic diarrhea, small bowel bypass surgery, malabsorption, or pancreatitis. Necrotic fat within the pancreas is able to utilize magnesium, as it does calcium, in the saponification process. Renal losses may result from the use of loop or thiazide diuretics via loss of sodium-dependent magnesium reabsorption. They may also be secondary to nephron damage. Nephrotoxic drugs, such as cisplatin (Platinol), pentamidine (Nebupent, Pentam), and cyclosporine (Neoral, Sandimmune, SangCya), are all associated with tubular necrosis and hypomagnesemia.

Symptomatic hypomagnesemia often occurs concomitantly with hypokalemia and hypocalcemia.

TABLE 1
Agents that may cause hyperkalemia

ACE inhibitors and ARBs
Amiloride (Midamor) and triamterene (Dyrenium)
Amino acids
Azole antifungals
Beta-blockers
Cyclosporine (Neoral, Sandimmune, SangCya)
Digoxin (Lanoxin) (at toxic levels)
Eplerenone (Inspra)
Ethinyl estradiol/drospirenone (Yasmin)
Fluoride toxicity
Glucose infusions or insulin deficiency
Heparins
Herbal remedies with digitalis-like effect
NSAIDs
Nutritional and herbal supplements
Packed RBCs
Penicillin G potassium
Potassium supplements or salt substitutes
Spironolactone (Aldactone)
Succinylcholine (Anectine, Quelcin)
Tacrolimus (Prograf)
Trimethoprim (Primsol, Proloprim) and pentamidine (Nebupent, Pentam 300)

Key: ARB, angiotensin receptor blocker.

Hypokalemia is strongly linked to low serum magnesium levels because they are both associated with renal and GI loss. Severe hypomagnesemia (serum magnesium lower than 1.0 mg/dL) may be associated with hypocalcemia because of increased resistance to PTH on receptor cells via inhibition of G-protein-activated cAMP production, although this has not been proved. Because magnesium aids in the stabilization of excitable membranes, low serum magnesium levels may result in neurologic manifestations similar to those in patients with hypocalcemia. Tetany, respiratory and skeletal muscle weakness, convulsions, and Trousseau's and Chvostek's signs may all be present in patients with hypomagnesemia.

Magnesium deficiency has also been associated with increased severity of cardiovascular disease. The incidence of atherosclerosis, diabetes, hypertension, and platelet-dependent thrombosis is higher in

TABLE 2
Treatment of hyperkalemia

Serum potassium level	Treatment
5.5-7.0 mEq/L (mild to moderate elevation)	Sodium polystyrene sulfonate (Kayexalate, Kionex, Marlexate) and loop diuretics If the patient is asymptomatic without significant ECG findings, treatment is mainly focused on potassium excretion.
>7.0 mEq/L (severe elevation)	Insulin and glucose, calcium chloride, sodium bicarbonate, sodium polystyrene sulfonate, and loop diuretics Regardless of symptoms or ECG findings, this degree of elevation requires rapid decrease of serum potassium levels, with stabilization of myocardial membranes.

patients with hypomagnesemia.[14,15] ECG findings may include widening of the QRS complex and peaked T waves, which may progress to long QT syndrome with subsequent polymorphic ventricular tachycardia, or torsades de pointes.[3,4] Symptoms may include chest pain, shortness of breath, and syncope. Unfortunately, many patients who progress to long QT syndrome have no prior symptoms and are found after sudden cardiac arrest.

Low serum magnesium concentrations may also be a poor prognostic indicator for patients in the ICU. One study revealed that patients who developed hypomagnesemia while in the ICU had a longer length of stay, a higher prevalence of severe sepsis and septic shock, and increased mortality.[16]

Treatment of hypomagnesemia

Cellular repletion of magnesium is a slow process and requires 3 to 5 days to correct. For a serum magnesium concentration of 1.3 to 2.0 mEq/L, 2 g of magnesium sulfate should be given in 100 mL of 0.9% NaCl or D5W at a rate of 1 g/h. For severe hypomagnesemia (less than 0.8 mEq/L), 2 g of magnesium sulfate should be given IV over 10 minutes followed by a continuous infusion at 0.5 g/h IV for 72 hours or 1 to 2 g IV q4h for 72 hours. For torsades de pointes, patients should receive 2 g of magnesium sulfate over 1 to 2 minutes. Patients with seizures require 2 g of magnesium sulfate IV over 10 minutes. Given the association of hypomagnesemia with hypocalcemia, it is prudent to administer calcium in these patients.

Hypermagnesemia

Hypermagnesemia, defined as a serum magnesium level greater than 2.2 mEq/L, is mainly seen either in patients with impaired renal function or in those who have received a large magnesium load orally, rectally, or IV. Renal excretion is the only regulatory mechanism for plasma magnesium concentration. In hospitalized patients with renal failure, medications such as laxatives and antacids may cause hypermagnesemia even at therapeutic dosages and are thus contraindicated. Parenteral magnesium is utilized in women with preeclampsia to decrease neuromuscular activation, and serum magnesium concentrations of 5 to 7 mEq/L (6.0-8.4 g/dL) are tolerated. Elderly patients with GI disease who are on cathartics may develop hypermagnesemia and should be monitored.

In most cases, the elevation in serum magnesium concentrations is mild, and patients are usually asymptomatic. Patients generally become symptomatic when magnesium levels exceed 4 mEq/L (4.8 mg/dL). Magnesium levels with expected symptoms may be stratified as shown in Table 3 (see page 25).

Treatment of hypermagnesemia

First-line treatment for elevated magnesium levels is to give calcium, which is able to remove magnesium from serum, and to remove sources of magnesium intake. Infusion of a 10% calcium chloride solution (5-10 mL or 500-1000 mg) may be administered to correct for arrhythmias, more than once if necessary. For severe hypermagnesemia that is refractory to calcium chloride, dialysis is the treatment of choice. In the interim, the patient may receive IV saline and furosemide (Lasix) to eliminate some of the magnesium as long as there is normal cardiac and renal function.[2]