# Clinical manifestations and treatment of hypokalemia in adults

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## INTRODUCTION

Although hypokalemia can be transiently induced by the entry of potassium into the cells, most cases result from unreplenished gastrointestinal or urinary losses due, for example, to vomiting, diarrhea, or diuretic therapy [1-3]. (See "Causes of hypokalemia in adults".)

Potassium replacement is primarily indicated when hypokalemia is due to potassium loss, and there is a significant deficit in body potassium. It is also warranted for acute therapy in disorders such as hypokalemic or thyrotoxic periodic paralysis in which the hypokalemia is due to redistribution of potassium into the cells, often in association with significant symptoms. Potassium is given cautiously in redistributive hypokalemia since the hypokalemia is transient and the administration of potassium can lead to rebound hyperkalemia when the underlying process is corrected and potassium moves back out of the cells. The recommended regimens for acute therapy in this disorder are presented elsewhere:

- (See "Hypokalemic periodic paralysis", section on 'Acute treatment'.)
- (See "Thyrotoxic periodic paralysis", section on 'Acute treatment'.)

Optimal therapy in patients with hypokalemia due to potassium loss is dependent upon the severity of the potassium deficit. In addition, somewhat different considerations are required to

minimize continued urinary losses due to diuretic therapy, or less often, to primary hyperaldosteronism.

The clinical manifestations and treatment of hypokalemia will be reviewed here. The causes of and evaluation of patients with hypokalemia are discussed separately:

- (See "Causes of hypokalemia in adults".)
- (See "Evaluation of the adult patient with hypokalemia".)

## MANIFESTATIONS OF HYPOKALEMIA

The severity of the manifestations of hypokalemia tends to be proportionate to the degree and duration of the reduction in serum potassium. Symptoms generally do not become manifest until the serum potassium is below 3.0 mEq/L, unless the serum potassium falls rapidly or the patient has a potentiating factor, such as a predisposition to arrhythmia due to the use of digitalis. Symptoms usually resolve with correction of the hypokalemia.

**Severe muscle weakness or rhabdomyolysis** — Muscle weakness usually does not occur at serum potassium concentrations above 2.5 mEq/L if the hypokalemia develops slowly [2]. However, significant muscle weakness can occur at serum potassium concentrations below 2.5 mEq/L or at higher values with hypokalemia of acute onset, as occurs in hypokalemic or thyrotoxic periodic paralysis. In addition, the pathophysiology of weakness in these disorders is more complex. (See "Myopathies of systemic disease", section on 'Hypokalemic myopathy'.)

The pattern of weakness in hypokalemia is similar to that associated with hyperkalemia. Weakness usually begins in the lower extremities, progresses to the trunk and upper extremities, and can worsen to the point of paralysis. (See "Clinical manifestations of hyperkalemia in adults", section on 'Severe muscle weakness or paralysis'.)

In addition to causing muscle weakness, severe potassium depletion (serum potassium less than 2.5 mEq/L) can lead to muscle cramps, rhabdomyolysis, and myoglobinuria [4-7]. Potassium release from muscle cells during exercise normally mediates vasodilation and an appropriate increase in muscle blood flow [8]. Decreased potassium release due to profound hypokalemia can diminish blood flow to muscles during exertion, leading to ischemic rhabdomyolysis [8]. The clinical and pathologic abnormalities are reversible with potassium repletion [4]. A potential diagnostic problem is that the release of potassium from the cells with rhabdomyolysis can mask the severity of the underlying hypokalemia or even lead to normal or

high values. (See "Rhabdomyolysis: Epidemiology and etiology", section on 'Electrolyte disorders'.)

Other manifestations of muscle dysfunction due to hypokalemia include:

- Respiratory muscle weakness, which can be severe enough to result in respiratory failure and death.
- Involvement of gastrointestinal muscles, resulting in ileus and its associated symptoms of distension, anorexia, nausea, and vomiting. The hypokalemia in some of these patients is caused by concomitant diarrhea. As an example, several reports have noted an association between colonic pseudo-obstruction (Ogilvie's syndrome) and hypokalemia due to secretory diarrhea with an abnormally high fecal potassium content [9,10]. (See "Acute colonic pseudo-obstruction (Ogilvie's syndrome)", section on 'Clinical manifestations'.)

**Cardiac arrhythmias and ECG abnormalities** — A variety of arrhythmias may be seen in patients with hypokalemia. These include premature atrial complex (PAC; also referred to a premature atrial beat, premature supraventricular complex, or premature supraventricular beat) and premature ventricular beats, sinus bradycardia, paroxysmal atrial or junctional tachycardia, atrioventricular block, atrial fibrillation, and ventricular tachycardia or fibrillation [2,11]. In addition, hypokalemia significantly increases the risk of ventricular fibrillation in the acute phase of ST-segment elevation myocardial infarction [12].

Hypokalemia produces characteristic changes on the ECG although they are not seen in all patients. There is depression of the ST segment, decrease in the amplitude of the T wave, and an increase in the amplitude of U waves which occur at the end of the T wave ( waveform 1). U waves are often seen in the lateral precordial leads V4 to V6. Hypokalemia also prolongs the QT interval [13-15]. (See "ECG tutorial: Miscellaneous diagnoses", section on 'Hypokalemia'.)

There is a large interpatient variability in the serum potassium concentration that is associated with progression of ECG changes or arrhythmias. In a carefully controlled trial of thiazide therapy (hydrochlorothiazide 50 mg/day), there was a two-fold increase in ventricular arrhythmias (as detected by Holter monitoring) in the small proportion of patients in whom the serum potassium concentration fell to or below 3.0 mEq/L [16]. In addition, the presence of concomitant factors, such as coronary ischemia, digitalis, increased beta-adrenergic activity, and magnesium depletion, can promote arrhythmias; the last two of these cofactors can also lower the serum potassium concentration:

- Epinephrine released during a stress response (as with coronary ischemia) drives potassium into the cells, possibly worsening preexisting hypokalemia. A similar effect can

be seen with bronchodilator therapy with a beta-adrenergic agonist. (See "Causes of hypokalemia in adults", section on 'Elevated beta-adrenergic activity'.)

- Hypokalemia may be associated with magnesium depletion (due, for example, to diuretics or diarrhea), both of which promote the development of arrhythmias. Hypokalemia and hypomagnesemia are associated with an increased risk of torsades de pointes, particularly in patients treated with drugs that prolong the QT interval or those with a genetic predisposition to the long QT syndrome. In addition to its direct proarrhythmic effect, hypomagnesemia can increase urinary potassium losses and lower the serum potassium concentration. (See "Acquired long QT syndrome: Definitions, pathophysiology, and causes", section on 'Metabolic abnormalities' and 'Hypomagnesemia and redistributive hypokalemia' below.)

**Kidney abnormalities** — Prolonged hypokalemia can cause multiple structural and functional changes in the kidney [17-19]. These include:

- Impaired concentrating ability
- Increased ammonia production
- Increased bicarbonate reabsorption
- Altered sodium reabsorption
- Hypokalemic nephropathy
- Elevation in blood pressure
- Decreased phosphate reabsorption

These changes are discussed in detail elsewhere. (See "Hypokalemia-induced kidney dysfunction" and "Potassium and hypertension".)

**Glucose intolerance** — Hypokalemia reduces insulin secretion, which may play an important role in thiazide-associated diabetes. However, worsening glucose tolerance is much less common in the era of low-dose thiazide therapy (eg, 12.5 to 25 mg of hydrochlorothiazide) ( figure 1). (See "Pathogenesis of type 2 diabetes mellitus", section on 'Drug-induced hyperglycemia'.)

## PATHOGENESIS OF SYMPTOMS

The neuromuscular and cardiac symptoms induced by hypokalemia are related to alterations in the generation of the action potential [2]. The ease of generating an action potential (called membrane excitability) is related both to the magnitude of the resting membrane potential and to the activation state of membrane sodium channels. Opening the sodium channels leads to

the passive diffusion of extracellular sodium into the cells, which is the primary step in this process.

According to the Nernst equation, the resting membrane potential is related to the ratio of the intracellular to the extracellular potassium concentration. In skeletal muscle, a reduction in the serum (extracellular) potassium concentration will increase this ratio and therefore hyperpolarize the cell membrane (that is, make the resting potential more electronegative); this impairs the ability of the muscle to depolarize and contract, leading to weakness. However, in some cardiac cells (such as Purkinje fibers in the conducting system), hypokalemia causes K2P1 channels, which are normally selective for potassium, to transport sodium into the cells, causing depolarization [20,21]. This leads to increased membrane excitability and arrhythmias.

Hypokalemia also delays ventricular repolarization by inhibiting the activity of potassium channels responsible for this component of the cardiac electrical cycle [14]. (See "Reentry and the development of cardiac arrhythmias".)

In addition, hypokalemia causes ventricular arrhythmias through downregulation of cardiac Na-K-ATPase activity [22,23]. This produces an increase in intracellular sodium, which impedes removal of intracellular calcium by the Na-Ca exchanger, leading to intracellular calcium overload. The ensuing activation of calmodulin kinase II activity reduces repolarization reserve by activating late sodium and calcium currents [24]. This, in turn, predisposes the heart to early afterdepolarization-associated arrhythmias, such as Torsades de pointes and polymorphic ventricular tachycardia [24].

The same intracellular calcium overload that is seen in ventricular myocytes can be demonstrated in a minority of atrial myocytes that possess the t-tubules that are abundant in ventricular myocytes. By contrast, atrial myocytes that lack t-tubules do not show the same increase in intercellular calcium with hypokalemia, and electrical excitability is driven instead by changes in sodium and potassium currents [25]. This suggests a distinct mechanism for hypokalemia-associated atrial fibrillation.

## DIAGNOSIS AND EVALUATION

Once the presence of hypokalemia has been documented, attempts should be made from the history and laboratory findings to identify the cause of the hypokalemia, which is often apparent from the history (eg, vomiting, diarrhea, diuretic therapy). The patient should be evaluated for the functional manifestations of hypokalemia, and the potassium deficit should

be estimated. (See "Evaluation of the adult patient with hypokalemia" and 'Estimation of the potassium deficit' below.)

The assessment of the hypokalemic patient begins with evaluation of muscle strength and obtaining an electrocardiogram to assess the cardiac consequences of the hypokalemia, with particular attention to the QT interval. At serum potassium concentrations below 2.5 mEq/L, severe muscle weakness and/or marked electrocardiographic changes may be present and require immediate treatment. (See 'Manifestations of hypokalemia' above and "ECG tutorial: Miscellaneous diagnoses", section on 'Hypokalemia'.)

Telemetry or continuous ECG monitoring is indicated for hypokalemic patients with a prolonged QT, other ECG changes associated with hypokalemia, and/or underlying cardiac issues that predispose to arrhythmia in the setting of hypokalemia (digoxin toxicity, myocardial infarction, underlying long QT syndrome, etc) [26,27].

## TREATMENT

**General issues** — The goals of therapy in hypokalemia are to prevent or treat life-threatening complications (arrhythmias, paralysis, rhabdomyolysis, and diaphragmatic weakness), to replace the potassium deficit, and to diagnose and correct the underlying cause. The urgency of therapy depends upon the severity of hypokalemia, associated and/or comorbid conditions, and the rate of decline in serum potassium concentration. The risk of arrhythmia from hypokalemia is highest in older patients, patients with organic heart disease, and patients on digoxin or antiarrhythmic drugs [28].

Potassium replacement is the mainstay of therapy in hypokalemia. Such therapy is clearly warranted in patients with hypokalemia due to renal or gastrointestinal losses. It should also be considered when hypokalemia is due to redistribution of potassium from the extracellular fluid into the cells (eg, hypokalemic periodic paralysis, insulin therapy) if serious complications such as paralysis, rhabdomyolysis, or arrhythmias are present or imminent. (See "Causes of hypokalemia in adults", section on 'Increased entry into cells'.)

Continued replacement over a matter of days is usually required, given that the total body potassium deficit can be marked in severe hypokalemia. Absorption into intracellular compartments may be slow, leading to the potential for transient hyperkalemia as potassium repletion is administered; therefore, serum potassium should be monitored closely during repletion.

**Hypomagnesemia and redistributive hypokalemia** — The underlying cause of the hypokalemia should be identified as quickly as possible, particularly the presence of hypomagnesemia or redistributive hypokalemia:

- Patients with hypokalemia may also have hypomagnesemia due to concurrent loss with diarrhea or diuretic therapy or, in patients with hypomagnesemia as the primary abnormality, renal potassium wasting [29,30]. Such patients can be refractory to potassium replacement alone [31]. Thus, measurement of serum magnesium should be considered in patients with hypokalemia and, if present, hypomagnesemia should be treated. (See "Hypomagnesemia: Clinical manifestations of magnesium depletion", section on 'Hypokalemia' and "Hypomagnesemia: Evaluation and treatment".)

- A potential complication of potassium therapy in redistributive hypokalemia is rebound hyperkalemia as the initial process causing redistribution resolves or is corrected. Such patients can develop fatal hyperkalemic arrhythmias [3,32-35]. The risk of rebound hyperkalemia is particularly high in patients with hypokalemic or thyrotoxic periodic paralysis in whom rebound hyperkalemia has been described in 40 to 60 percent of treated attacks. (See "Thyrotoxic periodic paralysis", section on 'Acute treatment'.)

- When increased sympathetic tone is thought to play a major role, the administration of a nonspecific beta blocker, such as propranolol, should be considered. The greatest experience is with acute attacks of hypokalemic thyrotoxic periodic paralysis [36], although head injury and theophylline toxicity can also result in redistributive hypokalemia [37-40], presumably due to sympathetic activation and elevated epinephrine levels [41]. In such patients, high-dose oral propranolol or intravenous propranolol rapidly reverses the hypokalemia and paralysis seen in acute attacks, without rebound hyperkalemia. (See "Thyrotoxic periodic paralysis", section on 'Acute treatment'.)

**Estimation of the potassium deficit** — Estimation of the potassium deficit assumes that there is a normal distribution of potassium between the cells and the extracellular fluid. The most common settings in which this estimation **does not apply** is diabetic ketoacidosis or nonketotic hyperglycemia, and in redistributive causes of hypokalemia such as hypokalemic periodic paralysis. (See "Causes of hypokalemia in adults", section on 'Increased entry into cells'.)

The goals of potassium replacement in patients with hypokalemia due to potassium losses are to rapidly raise the serum potassium concentration to a safe level and then replace the remaining deficit at a slower rate over days to weeks to allow for equilibration of potassium between plasma and intracellular stores [3,28,42]. Estimation of the potassium deficit and careful monitoring of the serum potassium helps to prevent hyperkalemia due to excessive

supplementation. This is not an uncommon outcome in hospitalized patients since, in one report, one in six patients developed mild hyperkalemia following potassium administration for hypokalemia [43]. The risk of overcorrection is increased in patients with a reduced glomerular filtration rate.

The potassium deficit varies directly with the severity of hypokalemia. In different studies, the serum potassium concentration fell by approximately 0.27 mEq/L for every 100 mEq reduction in total body potassium stores [3,42,44] and, in chronic hypokalemia, a potassium deficit of 200 to 400 mEq is required to lower the serum potassium concentration by 1 mEq/L [44]. However, these estimates are only an approximation of the amount of potassium replacement required to normalize the serum potassium concentration and careful monitoring is required.

**Uncontrolled diabetes** — In diabetic ketoacidosis or a hyperosmolar hyperglycemic state (nonketotic hyperglycemia), hyperosmolality and insulin deficiency favor the movement of potassium out of cells. As a result, the serum potassium concentration at presentation may be normal or even elevated despite a marked potassium deficit due to urinary and, in some patients, gastrointestinal losses [45]. The initiation of insulin therapy and fluid replacement will lower the serum potassium toward the level appropriate for the potassium deficit. Potassium supplementation is usually begun once the serum potassium concentration is 4.5 mEq/L or lower.

Occasional patients with uncontrolled diabetes (eg, 6 percent in one study) have more marked potassium loss and are hypokalemic at presentation [46]. Such patients require aggressive potassium replacement (20 to 30 mEq/hour), which can be achieved by the addition of 40 to 60 mEq of potassium chloride to each liter of one-half isotonic saline. Since insulin will worsen the hypokalemia, insulin therapy should be **delayed** until the serum potassium is above 3.3 mEq/L to avoid possible complications of hypokalemia such as cardiac arrhythmias and respiratory muscle weakness. (See 'Intravenous potassium repletion' below and 'Manifestations of hypokalemia' above.)

These issues are discussed in detail elsewhere. (See "Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Treatment", section on 'Potassium replacement'.)

**Potassium preparations** — Potassium can be administered as potassium chloride, potassium phosphate, potassium bicarbonate or its precursors (potassium citrate, potassium acetate) or potassium gluconate [3,28,42].

The choice among these preparations varies with the clinical setting:

- Potassium bicarbonate or its precursors are preferred in patients with hypokalemia and metabolic acidosis (eg, renal tubular acidosis or diarrhea) [28,42]. Only potassium acetate is available for intravenous use.

- Potassium phosphate should be considered only in the rarely seen patients with hypokalemia and hypophosphatemia, as might occur with proximal (type 2) renal tubular acidosis associated with Fanconi syndrome and phosphate wasting [42,47,48].

- Potassium chloride is preferred in all other patients for two major reasons [1]:

  - Patients with hypokalemia and metabolic alkalosis are often chloride depleted due, for example, to diuretic therapy or vomiting. In such patients, chloride depletion contributes to maintenance of the metabolic alkalosis by enhancing renal bicarbonate reabsorption and may contribute to potassium wasting as sodium is reabsorbed in exchange for secreted potassium rather than with chloride [3,49,50]. It has been estimated that administration of non-chloride-containing potassium salts in the presence of metabolic alkalosis results in the retention of only 40 percent as much potassium as the administration of potassium chloride [50]. (See "Pathogenesis of metabolic alkalosis", section on 'Chloride depletion' and "Treatment of metabolic alkalosis", section on 'Treatment'.)

  - Potassium chloride raises the serum potassium concentration at a faster rate than potassium bicarbonate. Chloride is primarily an extracellular anion that does not enter cells to the same extent as bicarbonate, thereby promoting maintenance of the administered potassium in the extracellular fluid [51] In addition, potassium bicarbonate may partially offset the benefits of potassium administration by aggravating metabolic alkalosis, if present.

Oral potassium chloride can be given in crystalline form (salt substitutes), as a liquid, or in a slow-release tablet or capsule. Salt substitutes contain 50 to 65 mEq per level teaspoon; they are safe, well tolerated, and much less expensive than the other preparations [52]. Liquid forms of potassium chloride are also inexpensive but are often unpalatable. Nevertheless, they may be preferred in patients with an enteral feeding tube or who are unable to swallow tablets. Slow-release tablets are better tolerated, but they have been associated with gastrointestinal ulceration and bleeding, which have been ascribed to local accumulation of high concentrations of potassium [53]. The risk is relatively low, and even lower with microencapsulated preparations (eg, microK or Klor-Con) compared to wax matrix tablets [3].

Increasing the intake of potassium-rich foods, such as oranges and bananas ( table 1), is **less effective**, in part because dietary potassium is predominantly in the form of potassium

phosphate or potassium citrate which, as mentioned earlier in this section, results in the retention of only 40 percent as much potassium as potassium chloride [50]. In addition, the potassium concentration is relatively low in fruit (eg, approximately 2.2 mEq/inch [0.9 mEq/cm] in bananas) [54]. As a result, it would take two to three bananas to provide 40 mEq.

**Intravenous therapy** — Potassium chloride can be given intravenously to patients who are unable to take oral therapy or as an adjunct to oral replacement in patients who have severe symptomatic hypokalemia. (See 'Intravenous potassium repletion' below.)

**Ongoing losses and the steady state** — The recommendations for potassium replacement in the following sections assume that there are no ongoing losses (eg, vomiting, diarrhea, nasogastric suction, diuretic therapy) and that the patient does not have a chronic potassium wasting condition such as diuretic therapy, primary aldosteronism, or Gitelman or Bartter syndrome:

- Among patients with ongoing losses, the rate of potassium administration recommended below must be increased by the rate of potassium loss to produce the desired rate of potassium repletion.
- Stable patients with chronic diuretic therapy (at a fixed dose), primary aldosteronism (unless aldosterone secretion increases), or Gitelman or Bartter syndrome typically do **not** develop progressive hypokalemia because the increased urinary potassium losses are balanced by hypokalemia-induced potassium retention. The net effect is a new steady state in which potassium intake and output are in balance, with a lower-than-normal serum potassium concentration. A potassium-sparing diuretic is usually required in such patients who do not respond adequately to potassium supplementation. (See "General principles of disorders of water balance (hyponatremia and hypernatremia) and sodium balance (hypovolemia and edema)", section on 'The steady state'.)

**Potassium-sparing diuretics** — There are two classes of potassium-sparing diuretics: blockers of the cortical collecting tubule sodium channels (amiloride and triamterene); and the aldosterone (mineralocorticoid receptor) antagonists (spironolactone and eplerenone). With respect to treating hypokalemia, these drugs are used in patients with renal potassium wasting in whom, as noted in the preceding section, potassium supplements may not be sufficiently effective.

Amiloride is usually preferred to a mineralocorticoid receptor antagonist because it is better tolerated (see "Triamterene nephrotoxicity"). Primary aldosteronism is an important exception since spironolactone or eplerenone is preferred to block apparent adverse effects of excess aldosterone on the heart and vascular system in patients diagnosed with this disorder. (See

"Treatment of primary aldosteronism", section on 'First line: Mineralocorticoid receptor antagonists' and "Pathophysiology and clinical features of primary aldosteronism", section on 'Cardiovascular risk'.)

A potassium-sparing diuretic in combination with potassium supplements should be used only with careful monitoring of the serum potassium since the risk of hyperkalemia is increased. This may be a particular problem in patients with moderately severe to severe heart failure in whom several factors may act together to markedly reduce urinary potassium excretion (decreased kidney perfusion due to the fall in cardiac output, therapy with an angiotensin inhibitor, and therapy with spironolactone or eplerenone). Among patients with heart failure, mineralocorticoid receptor antagonists should be given only if the serum creatinine is less than or equal to 2.5 mg/dL (221 micromol/L) in men and 2.0 mg/dL (177 micromol/L) in women and the serum potassium is less than 5.0 mEq/L. (See "Primary pharmacologic therapy for heart failure with reduced ejection fraction", section on 'Cautions and side effects' and "Primary pharmacologic therapy for heart failure with reduced ejection fraction", section on 'Dosing and monitoring'.)

**Mild to moderate hypokalemia** — Most hypokalemic patients have a serum potassium concentration of 3.0 to 3.4 mEq/L. This degree of potassium depletion usually produces no symptoms. Exceptions include patients with heart disease (particularly if they are taking digitalis or certain other antiarrhythmic drugs or are undergoing cardiac surgery [55,56]) and patients with cirrhosis, in whom hypokalemia can increase ammonia generation and promote the development of hepatic encephalopathy.

Treatment of mild to moderate hypokalemia depends upon the cause of the hypokalemia and acid-base status:

- Patients with gastrointestinal losses are treated with potassium chloride if they have metabolic alkalosis (as usually seen with vomiting) or a normal serum bicarbonate concentration, and with potassium bicarbonate (or potassium citrate or acetate) in the presence of metabolic acidosis (as seen with diarrhea or renal tubular acidosis). Treatment is usually started with 10 to 20 mEq of potassium given two to four times per day (20 to 80 mEq/day), depending upon the severity of the hypokalemia. (See 'Potassium preparations' above.)

- By contrast, potassium supplements at usual doses produce only modest elevations in serum potassium in patients with hypokalemia due to renal potassium wasting (eg, chronic diuretic therapy, primary aldosteronism). As soon as the serum potassium rises, there is less hypokalemia-induced potassium retention and most of the administered

potassium is excreted in the urine. Thus, a potassium-sparing diuretic is likely to be more effective. Amiloride is usually preferred to a mineralocorticoid receptor antagonist because it is better tolerated. Primary aldosteronism is an important exception since spironolactone or eplerenone is preferred to block apparent adverse effects of excess aldosterone on the heart and vascular system. (See 'Ongoing losses and the steady state' above and 'Potassium-sparing diuretics' above.)

Patients with mild to moderate hypokalemia who are treated with potassium supplements are typically treated with oral therapy. Patients who cannot take oral therapy require intravenous repletion. Sequential monitoring of the serum potassium is essential to determine the response.

**Severe or symptomatic hypokalemia** — Potassium must be given more rapidly to patients with hypokalemia that is severe (serum potassium less than 2.5 to 3.0 mEq/L) or symptomatic (arrhythmias, marked muscle weakness, or rhabdomyolysis).

A potential diagnostic and therapeutic problem in patients with hypokalemia-induced rhabdomyolysis is that the release of potassium from the muscle cells can mask the severity of the underlying hypokalemia or even lead to normal or elevated values at presentation or after potassium supplementation. If the serum potassium is normal or elevated at baseline, it will not be possible to be certain that underlying hypokalemia was responsible for the rhabdomyolysis and initial potassium therapy in such patients is not warranted and may be dangerous. In patients who present with hypokalemia, potassium therapy can be initiated with repeated monitoring of the serum potassium (eg, every four to six hours initially).

Particular caution must be exercised when repleting potassium in patients with a concurrent disorder that, when treated, will tend to drive potassium into the cells and worsen the hypokalemia. The two main examples are insulin therapy in diabetic ketoacidosis or nonketotic hyperglycemia, and bicarbonate therapy in metabolic acidosis with a normal anion gap.

Potassium repletion is most easily accomplished orally but can be given intravenously. The serum potassium concentration can transiently rise by as much as 1 to 1.5 mEq/L after an oral dose of 40 to 60 mEq, and by as much as 2.5 to 3.5 mEq/L after 135 to 160 mEq [57,58]. The serum potassium concentration will then fall back toward baseline over a few hours, as most of the exogenous potassium is taken up by the cells [59]. A patient with a serum potassium concentration of 2.0 mEq/L, for example, may have a 400 to 800 mEq potassium deficit [44]. In patients with severe hypokalemia, potassium chloride can be given orally in doses of 40 mEq, three to four times per day or, particularly in patients also treated with intravenous potassium, 20 mEq every two to three hours.

As noted in the preceding section, potassium supplements at usual doses produce only modest elevations in serum potassium in patients with hypokalemia due to renal potassium wasting (eg, chronic diuretic therapy, primary aldosteronism). Thus, a potassium-sparing diuretic is likely to be more effective.

Careful monitoring is essential in patients treated with potassium. We suggest that the serum potassium should initially be measured every two to four hours to ascertain the response to therapy. If tolerated, this regimen should be continued until the serum potassium concentration is persistently above 3.0 to 3.5 mEq/L and symptoms or signs attributable to hypokalemia have resolved. Thereafter, the dose and frequency of administration can be reduced to that used in mild to moderate hypokalemia since aggressive repletion is no longer required and gastric irritation can be avoided. (See 'Mild to moderate hypokalemia' above.)

**Intravenous potassium repletion** — Potassium chloride can be given intravenously as an adjunct to oral replacement in patients who have severe symptomatic hypokalemia and in patients with less severe hypokalemia who are unable to take oral medications. Potential constraints to intravenous therapy for severe hypokalemia include a risk of volume overload in susceptible subjects and hyperkalemia due to excessive repletion.

A saline rather than a dextrose solution should be used for initial therapy since the administration of dextrose stimulates the release of insulin which drives extracellular potassium into the cells. This can lead to a transient 0.2 to 1.4 mEq/L reduction in the serum potassium concentration, particularly if the solution contains only 20 mEq/L of potassium [3,60]. The transient reduction in serum potassium can induce arrhythmias in susceptible patients, such as those taking digitalis [60].

The necessity for aggressive intravenous potassium replacement most commonly occurs in patients with diabetic ketoacidosis or hyperosmolar hyperglycemic state (nonketotic hyperglycemia). These patients typically have a substantial reduction in potassium stores due to urinary losses, but usually present with normal or even high serum potassium levels due to transcellular potassium shifts. Patients who present with hypokalemia have an even larger potassium deficit [61]. Furthermore, treatment with insulin and intravenous fluids will exacerbate the hypokalemia and minimize the efficacy of potassium repletion. Thus, insulin therapy should be **delayed** until the serum potassium is above 3.3 mEq/L to avoid possible complications of hypokalemia such as cardiac arrhythmias, cardiac arrest, and respiratory muscle weakness. (See "Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Clinical features, evaluation, and diagnosis", section on 'Serum potassium' and 'Manifestations of hypokalemia' above and "Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Treatment", section on 'Potassium replacement'.)

Although isotonic saline is often the initial replacement fluid used in treating diabetic ketoacidosis or nonketotic hyperglycemia, the addition of potassium will make this a hypertonic fluid (since potassium is as osmotically active as sodium), thereby delaying reversal of the hyperosmolality. Thus, 40 to 60 mEq of potassium per liter in one-half isotonic saline is preferred. (See "Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Treatment", section on 'Potassium replacement'.)

In contrast to patients with marked potassium depletion, patients with hypokalemia due to potassium redistribution (eg, hypokalemic periodic paralysis) have no potassium deficit and even low rates of potassium administration can result in hyperkalemia once the redistributed potassium returns to the extracellular fluid. In a report of patients with hypokalemic thyrotoxic periodic paralysis (baseline serum potassium concentration 2.0 mEq/L), administration of potassium at a rate of 10 mEq/hour (80 mEq/L) resulted in hyperkalemia (>5.5 mEq/L) in 40 percent of patients, one-half of whom had ECG changes [35]. Appropriate therapy in these patients is discussed separately. (See "Hypokalemic periodic paralysis", section on 'Acute treatment' and "Thyrotoxic periodic paralysis", section on 'Acute treatment'.)

**Adverse effects of intravenous potassium** — Pain and phlebitis can occur during parenteral infusion of potassium into a peripheral vein. This primarily occurs at rates above 10 mEq/hour but can be seen at lower rates. If pain occurs, either the infusion rate or, preferably, the potassium concentration should be reduced.

Another potential problem with administering high potassium concentrations in a single infusion container is inadvertent administration of a large amount of potassium in a short period of time, which is more likely to occur when an infusion pump is not used. Since the total extracellular potassium is normally 50 to 70 mEq, rapid infusion of 40 to 60 mEq of potassium can result in severe hyperkalemia. The following recommended approach should minimize this risk, but careful monitoring is still required. (See 'Careful monitoring' below.)

**Recommended approach** — For patients with severe hypokalemia due to gastrointestinal or renal losses, the recommended maximum rate of potassium administration is 10 to 20 mEq/hour in most patients. However, initial rates as high as 40 mEq/hour have been used for life-threatening hypokalemia [2,61-63]. Rates above 20 mEq/hour are highly irritating to peripheral veins. Such high rates should be infused into a large central vein or into multiple peripheral veins.

Potassium can be given intravenously via a peripheral or a large central vein. To decrease the risk of inadvertent administration of a large absolute amount of potassium, we suggest the

following maximum amounts of potassium that should be added to each particular sized infusion container [62,64]:

- In any 1000 mL-sized container of appropriate non-dextrose fluid, we suggest a maximum of 60 mEq of potassium.
- In a small-volume mini-bag of 100 to 200 mL of water that is to be infused into a peripheral vein, we suggest 10 mEq of potassium.
- In a small-volume mini-bag of 100 mL of water that is to be infused into a large central vein, we suggest a maximum of 40 mEq of potassium.

Intravenous potassium is most often infused in a peripheral vein at concentrations of 20 to 60 mEq/L in a non-dextrose-containing saline solution. Use of an infusion pump is preferred to prevent overly rapid potassium administration in any intravenous container with more than 40 mEq of potassium or if the desired rate of potassium administration is more than 10 mEq/hour. For patients with severe hypokalemia, administration in a large central vein is preferred if this access is available.

**Careful monitoring** — Careful monitoring of the physiologic effects of severe hypokalemia (ECG abnormalities, muscle weakness, paralysis) is essential. Continuous ECG monitoring or telemetry is warranted in patients with arrhythmias caused by hypokalemia, prolonged QT and/or other ECG abnormalities attributable to hypokalemia [26,27], underlying cardiac issues that predispose to arrhythmia in the setting of hypokalemia (digoxin toxicity, myocardial infarction, underlying long QT syndrome), intravenous potassium repletion at a rate greater than 10 mEq per hour, and patients at risk for rebound hyperkalemia (most often due to thyrotoxic periodic paralysis). Once the hypokalemia is no longer severe, the rate of intravenous potassium repletion should be reduced or changed to oral therapy. (See 'Mild to moderate hypokalemia' above.)

Careful monitoring of the serum potassium is also essential. We suggest that the serum potassium should initially be measured every two to four hours to ascertain the response to therapy. If tolerated, this regimen should be continued until the serum potassium concentration is persistently above 3.0 to 3.5 mEq/L and symptoms or signs attributable to hypokalemia have resolved. Thereafter, the dose and frequency of administration can be reduced to that used in mild to moderate hypokalemia since aggressive repletion is no longer required and gastric irritation can be avoided. (See 'Mild to moderate hypokalemia' above.)

## SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Fluid and electrolyte disorders in adults".)

## INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Hypokalemia (The Basics)")

## SUMMARY AND RECOMMENDATIONS

- **Etiology** – The most common causes of hypokalemia are gastrointestinal or urinary losses due to vomiting, diarrhea, or diuretic therapy. Hypokalemia may also result from the transient entry of potassium into cells, which is called redistributive hypokalemia. (See 'Introduction' above.)

- **Clinical manifestations** – Manifestations of hypokalemia include severe muscle weakness, cardiac arrhythmias, kidney abnormalities, and glucose intolerance. These signs and symptoms are generally proportionate to the degree and rapidity of the reduction in serum potassium and resolve with correction of the hypokalemia. The risk of arrhythmias from hypokalemia is highest in older patients, patients with organic heart disease, and patients on digoxin or antiarrhythmic drugs. (See 'Manifestations of hypokalemia' above and 'General issues' above.)

- **Management** – The underlying cause of the hypokalemia should be identified, particularly the presence of hypomagnesemia or redistributive hypokalemia. Patients with

hypomagnesemia can be refractory to potassium replacement alone, and potassium replacement can result in rebound hyperkalemia in patients with redistributive hypokalemia. Among patients with redistributive hypokalemia due to increased sympathetic tone (as in hypokalemic thyrotoxic periodic paralysis), the administration of a nonselective beta blocker, such as propranolol, can rapidly reverse the hypokalemia and associated symptoms. (See 'Hypomagnesemia and redistributive hypokalemia' above and "Thyrotoxic periodic paralysis", section on 'Acute treatment'.)

- **Mild to moderate hypokalemia** – For patients with mild to moderate hypokalemia (serum potassium 3.0 to 3.4 mEq/L) who do not have ongoing urinary potassium losses, we suggest initial oral administration of 10 to 20 mEq of potassium given two to four times per day (20 to 80 mEq/day) (**Grade 2B**). (See 'Mild to moderate hypokalemia' above.)

  Oral potassium preparations include potassium chloride, potassium bicarbonate or its precursors (potassium citrate, potassium acetate), and potassium phosphate. Potassium chloride can be given in crystalline form (salt substitutes), as a liquid, or in a slow-release tablet or capsule. Potassium bicarbonate or its precursors are preferred in patients with hypokalemia and metabolic acidosis. Potassium phosphate should be considered only in patients with hypokalemia and hypophosphatemia, as might occur with proximal (type 2) renal tubular acidosis associated with Fanconi syndrome and phosphate wasting. (See 'Potassium preparations' above.)

  In patients who have chronic, stable renal potassium wasting, a potassium-sparing diuretic, such as amiloride, may be required should potassium repletion not be successful. (See 'Ongoing losses and the steady state' above and "General principles of disorders of water balance (hyponatremia and hypernatremia) and sodium balance (hypovolemia and edema)", section on 'The steady state'.)

  Patients with primary aldosteronism also present with hypokalemia due to renal potassium wasting: Spironolactone or eplerenone is preferred for patients diagnosed with this disorder. (See "Treatment of primary aldosteronism", section on 'First line: Mineralocorticoid receptor antagonists' and "Pathophysiology and clinical features of primary aldosteronism", section on 'Renal actions of aldosterone'.)

  If a potassium-sparing diuretic is used in combination with potassium supplements, we recommend close monitoring of potassium levels, along with dietary assessment and limitation of dietary potassium intake. This combination must be used with extreme caution in patients with decreased kidney function and in patients on an ACE inhibitor,

renin inhibitor, and/or angiotensin receptor blocker. We suggest monitoring the serum potassium concentration approximately every three to four months in all patients receiving chronic potassium supplementation, or more often if clinically indicated.

- **Severe hypokalemia** – Careful monitoring of the physiologic effects of severe hypokalemia (ECG abnormalities, muscle weakness, paralysis) is essential. Continuous ECG monitoring or telemetry is warranted in patients with arrhythmias caused by hypokalemia, prolonged QT and/or other ECG abnormalities attributable to hypokalemia, underlying cardiac issues that predispose to arrhythmia in the setting of hypokalemia (eg, digoxin toxicity, myocardial infarction, underlying long QT syndrome), and also when intravenous potassium repletion is given at a rate greater than 10 mEq per hour, or if patients are at risk for rebound hyperkalemia (most often due to thyrotoxic periodic paralysis). (See 'Careful monitoring' above.)

  Potassium must be given more rapidly to patients with hypokalemia that is severe (serum potassium less than 2.5 to 3.0 mEq/L) or symptomatic (arrhythmias, marked muscle weakness, or rhabdomyolysis). In such patients, potassium chloride can be given orally in doses of 40 mEq, three to four times per day or, particularly in patients also treated with intravenous potassium, 20 mEq every two to three hours. Careful monitoring of the serum potassium is also essential. We suggest that the serum potassium should initially be measured every two to four hours to ascertain the response to therapy. If tolerated, this regimen should be continued until the serum potassium concentration is persistently above 3.0 to 3.5 mEq/L and symptoms or signs attributable to hypokalemia have resolved. (See 'Severe or symptomatic hypokalemia' above.)

  For patients with severe manifestations of hypokalemia or those who are unable to take oral medications, we recommend intravenous potassium chloride (**Grade 1B**). (See 'Manifestations of hypokalemia' above and 'Intravenous therapy' above.)

  Depending upon the severity of symptoms, intravenous potassium may be given at doses ranging from 20 mEq every two to three hours to a recommended maximum rate of potassium administration of 10 to 20 mEq/hour for most patients; rates as high as 40 mEq/hour have been used for life-threatening hypokalemia. Rates above 20 mEq/hour are highly irritating to peripheral veins. When such high rates are given, they should be infused into a large central vein or into multiple peripheral veins.

  In addition, the maximum amount of potassium that is added to each particular sized infusion container should be limited in order to decrease the risk of inadvertent

administration of a large absolute amount of potassium. We suggest the following:

- In any 1000 mL-sized container of appropriate non-dextrose fluid, we suggest a maximum of 60 mEq of potassium.
- In a small-volume mini-bag of 100 to 200 mL of water that is to be infused into a peripheral vein, we suggest 10 mEq of potassium.
- In a small-volume mini-bag of 100 mL of water that is to be infused into a large central vein, we suggest a maximum of 40 mEq of potassium.

Intravenous potassium is most often infused in a peripheral vein at concentrations of 20 to 60 mEq/L in a non-dextrose-containing saline solution. Use of an infusion pump is preferred to prevent overly rapid potassium administration in any intravenous container with more than 40 mEq of potassium or if the desired rate of potassium administration is more than 10 mEq/hour. (See 'Recommended approach' above.)

Pain and phlebitis can occur during parenteral infusion of potassium into a peripheral vein. This primarily occurs at rates above 10 mEq/hour but can be seen at lower rates. If pain occurs, either the infusion rate or, preferably, the potassium concentration should be reduced. (See 'Adverse effects of intravenous potassium' above.)

Once the hypokalemia is no longer severe, the rate of intravenous potassium repletion should be reduced or changed to oral therapy. Patients should be treated until the serum potassium concentration is persistently above 3.0 to 3.5 mEq/L and symptoms or signs attributable to hypokalemia have resolved. (See 'Careful monitoring' above.)



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Topic 2297 Version 37.0

## GRAPHICS

### Hypokalemia


An increase in the amplitude of U waves, which occur at the end of the T wave, are characteristic of hypokalemia.

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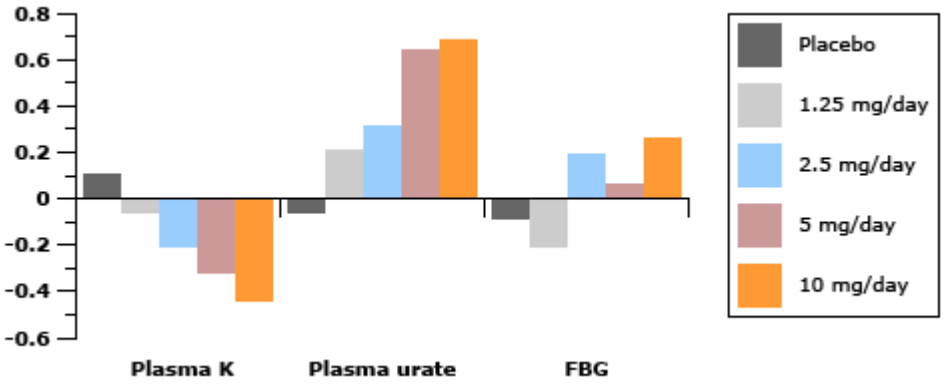
Graphic 73888 Version 2.0

## Dose dependence of thiazide-induced side effects




Metabolic complications induced by bendrofluazide in relation to daily dose (multiply by 10 to get equivalent doses of hydrochlorothiazide). Increasing the dose led to progressive hypokalemia and hyperuricemia and a greater likelihood of a mild elevation in the FBG, all without a further reduction in the systemic blood pressure. Each treatment group contained approximately 52 patients.

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FBG: fasting blood glucose.

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*Data from: Carlsen JE, Kober L, Torp-Pedersen C, Johansen P. Relation between dose of bendrofluazide, antihypertensive effect, and adverse biochemical effects. BMJ 1990; 300:975.*

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Graphic 69912 Version 5.0

## Foods with high levels of potassium

| Highest content (>25 mEq/100 g) |
| --- |
| Dried figs |
| Molasses |
| Seaweed |
| **Very high content (>12.5 mEq/100 g)** |
| Dried fruits (dates, prunes) |
| Nuts |
| Avocados |
| Bran cereals |
| Wheat germ |
| Lima beans |

| High content (>6.2 mEq/100 g) |
| --- |
| **Vegetables** |
| Spinach |
| Tomatoes |
| Broccoli |
| Winter squash |
| Beets |
| Carrots |
| Cauliflower |
| Potatoes |
| **Fruits** |
| Bananas |
| Cantaloupe |
| Kiwis |
| Oranges |
| Mangos |
| **Meats** |
| Ground beef |
| Steak |
| Pork |
| Veal |
| Lamb |

*Adapted from: Gennari FJ. Hypokalemia. N Engl J Med 1998; 339:451.*

Graphic 53492 Version 5.0