Causes and evaluation of hyperkalemia in adults

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INTRODUCTION

Hyperkalemia is a common clinical problem. Potassium enters the body via oral intake or intravenous infusion, is largely stored in the cells, and is then excreted in the urine. The major causes of hyperkalemia are increased potassium release from the cells and, most often, reduced urinary potassium excretion (table 1).

This topic will review the causes and evaluation of hyperkalemia. The clinical manifestations, treatment, and prevention of hyperkalemia, as well as a detailed discussion of hypoaldosteronism (an important cause of hyperkalemia), are presented elsewhere:

- (See "Clinical manifestations of hyperkalemia in adults".)
- (See "Treatment and prevention of hyperkalemia in adults".)
- (See "Etiology, diagnosis, and treatment of hypoaldosteronism (type 4 RTA)".)

BRIEF REVIEW OF POTASSIUM PHYSIOLOGY

An understanding of potassium physiology is helpful when approaching patients with hyperkalemia. Total body potassium stores are approximately 3000 mEq or more (50 to 75 mEq/kg body weight) [1]. In contrast to sodium, which is the major cation in the extracellular fluid and has a much lower concentration in the cells, potassium is primarily an intracellular cation, with the cells containing approximately 98 percent of body potassium. The intracellular

potassium concentration is approximately 140 mEq/L compared with 4 to 5 mEq/L in the extracellular fluid. The difference in distribution of the two cations is maintained by the Na-K-ATPase pump in the cell membrane, which pumps sodium out of and potassium into the cell in a 3:2 ratio.

The ratio of the potassium concentrations in the cells and the extracellular fluid is the major determinant of the resting membrane potential across the cell membrane, which sets the stage for the generation of the action potential that is essential for normal neural and muscle function. Thus, both hyperkalemia and hypokalemia can cause muscle paralysis and potentially fatal cardiac arrhythmias. (See "Clinical manifestations of hyperkalemia in adults" and "Clinical manifestations and treatment of hypokalemia in adults", section on 'Manifestations of hypokalemia'.)

The causes of hyperkalemia can be best understood after a brief review of normal potassium homeostasis. The plasma potassium concentration is determined by the relationship among potassium intake, the distribution of potassium between the cells and the extracellular fluid, and urinary potassium excretion.

Regulation of urinary potassium excretion — In normal individuals, dietary potassium is absorbed in the intestines and then largely excreted in the urine, a process that is primarily determined by potassium secretion by the principal cells in the two segments that follow the distal tubule: the connecting segment and cortical collecting tubule (figure 1) [2-5]. There are three major factors that stimulate principal cell potassium secretion [2-5]:

- An increase in plasma potassium concentration and/or potassium intake
- An increase in aldosterone secretion
- Enhanced delivery of sodium and water to the distal potassium secretory sites

Ingestion of a potassium load leads initially to the uptake of most of the excess potassium by cells in muscle and the liver, a process that is facilitated by insulin and the beta-2-adrenergic receptors, both of which increase the activity of Na-K-ATPase pumps in the cell membrane [4-7]. Some of the ingested potassium remains in the extracellular fluid, producing a mild elevation in the plasma potassium concentration.

The increase in plasma potassium stimulates the secretion of aldosterone, which directly enhances sodium reabsorption and indirectly enhances potassium secretion in the principal cells (figure 1). The increase in sodium reabsorption is mediated primarily by an increase in the number of open sodium channels in the luminal membrane of the principal cells. The reabsorption of cationic sodium makes the lumen more electronegative, thereby enhancing the electrical gradient that promotes the secretion of potassium from the cells into the tubular fluid

via potassium channels in the luminal membrane (figure 1). Additionally, the aldosterone-independent activation of apical secretory potassium channels by dietary potassium loading increases the capacity for potassium secretion [5,8]. Aldosterone also increases the number and activity of basolateral Na-K-ATPase pumps in principal cells, which facilitates both sodium reabsorption and potassium secretion. The net effect is that most of the potassium load is excreted within six to eight hours.

Both cellular uptake and urinary excretion of an acute potassium load are impaired in patients with advanced acute or chronic kidney disease. (See 'Acute and chronic kidney disease' below.)

Potassium adaptation — Hyperkalemia is a rare occurrence in normal individuals because the cellular and urinary responses prevent significant potassium accumulation in the extracellular fluid. Furthermore, the efficiency of potassium excretion is enhanced if potassium intake is increased, thereby allowing what might otherwise be a fatal potassium load to be tolerated. This phenomenon, called **potassium adaptation**, is mostly due to the ability to more rapidly excrete potassium in the urine [4,5].

Studies in rats have shown that potassium adaptation begins after a single potassium-containing meal. In one study, for example, rats fed a meal with potassium, when compared with rats given a potassium-free meal, were better able to excrete a potassium load several hours later, leading to a lesser rise in the plasma potassium concentration after the second potassium load [9]. The net effect is that adapted animals excrete more potassium at a given plasma potassium concentration than animals that have not adapted (figure 2).

The efficacy of potassium adaptation in humans was demonstrated in a study evaluating the response of healthy adults to increasing potassium intake from 100 to 400 mEq/day [10]. Urinary potassium excretion rose to equal intake by the end of the second day, an effect that was accompanied by an elevation in both aldosterone secretion and the plasma potassium concentration (from 3.8 to 4.8 mEq/L) (figure 3). At day 20, urinary potassium excretion continued to match the high level of intake, but plasma aldosterone levels had returned to near baseline, and the plasma potassium concentration had fallen to 4.2 mEq/L (figure 3).

The increased efficiency of potassium excretion with potassium adaptation appears to be mediated by three changes that occur in the potassium-secreting principal cells in the connecting segment and cortical collecting tubule (figure 1):

- A largely aldosterone-independent increase in the density and activity of apical secretory potassium channels [3,8,11].

- Increased Na-K-ATPase activity, which enhances potassium uptake into the cell across the basolateral (peritubular) membrane, thereby increasing the size of the potassium secretory pool [12,13].

- Increased activity of apical epithelial sodium channels (ENaC), through both aldosterone-independent and aldosterone-dependent mechanisms [8,11,14]. This induction increases the electrogenic driving force for apical potassium excretion.

Additionally, by inhibiting the function of the thiazide-sensitive Na-Cl cotransporter (NCC) within the distal convoluted tubule, potassium loading and hyperkalemia increase the delivery of sodium to principal cells within the downstream connecting tubule, thereby increasing potassium secretion. NCC is tightly regulated by complex interactions among potassium, the renin-angiotensin-aldosterone system, and the chloride-sensitive WNK signaling system [5,15-17].

Conclusions — The preceding observations lead to the following conclusions concerning the causes of hyperkalemia:

- Increasing potassium intake alone is **not** a common cause of hyperkalemia unless it occurs acutely. Acute hyperkalemia can rarely be induced (primarily in infants because of their small size) by the administration of potassium penicillin as an intravenous bolus, the accidental ingestion of a potassium-containing salt substitute, or the use of stored blood for exchange transfusions. In addition, moderate increases in potassium intake can be an important contributor to the development of hyperkalemia in patients with impaired potassium excretion due, for example, to hypoaldosteronism and/or kidney function impairment. (See 'Reduced urinary potassium excretion' below.)

- The net release of potassium from the cells (due to enhanced release or decreased entry) can, if large enough (eg, increased tissue breakdown), cause a transient elevation in the serum potassium concentration. (See 'Increased potassium release from cells' below.)

- Persistent hyperkalemia requires **impaired urinary potassium excretion**. In view of the factors described above, this is generally associated with a reduction in aldosterone secretion or responsiveness, acute or chronic kidney disease, and/or diminished delivery of sodium and water to the distal potassium secretory sites. (See 'Reduced urinary potassium excretion' below.)

- Potassium secretion is tightly regulated by a complex interplay among individual mediators in the renin-angiotensin-aldosterone system, sodium and potassium transport pathways, and the chloride-sensitive WNK signaling system [5,15-17]. Due to aldosterone-

independent regulatory pathways in potassium homeostasis, hyperkalemia is not a universal feature of hypoaldosteronism.

Many of the causes of hyperkalemia are discussed in detail elsewhere and will only be listed below (table 1).

INCREASED POTASSIUM RELEASE FROM CELLS

Pseudohyperkalemia — Pseudohyperkalemia refers to those conditions in which the elevation in the measured serum potassium concentration is usually due to potassium movement out of the cells during or after the blood specimen has been drawn [18]. The possible presence of pseudohyperkalemia should be suspected when there is no apparent cause for the hyperkalemia in an asymptomatic patient who has no electrocardiographic manifestations of hyperkalemia.

Technique of blood drawing — Pseudohyperkalemia can be seen in a variety of settings. The most common causes are related to the technique of blood drawing and can involve one or both of the following mechanisms:

- Mechanical trauma during venipuncture can result in the release of potassium from red cells and a characteristic reddish tint of the serum due to the concomitant release of hemoglobin.

  Red serum can also represent severe intravascular hemolysis rather than a hemolyzed specimen [19]. When intravascular hemolysis is present, the measured serum potassium may represent the true circulating value.

- Potassium moves out of muscle cells with exercise. As a result, repeated fist clenching during blood drawing can acutely raise the serum potassium concentration by more than 1 to 2 mEq/L in that forearm [20]. (See 'Exercise' below.)

In these settings, venipuncture without a tourniquet, repeated fist clenching, or trauma will demonstrate the true serum potassium concentration [21]. If a tourniquet is required, the tourniquet should be released after the needle has entered the vein, followed by waiting for **one to two minutes** before drawing the blood sample.

Less common causes of an increase in serum potassium related to collection and storage include cooling of the sample and specimen deterioration because of prolonged length of storage [18,22].

Other causes — There are several other settings in which pseudohyperkalemia can occur:

- Potassium moves out of platelets after clotting has occurred. Thus, the serum potassium concentration normally exceeds the true value in plasma by 0.1 to 0.5 mEq/L [23]. Although this difference in normal individuals is not clinically important, the increase in the measured serum potassium concentration can be much greater in normokalemic patients with thrombocytosis, rising by approximately 0.15 mEq/L per 100,000/microL elevation in the platelet count [23]. In one study, hyperkalemia in a serum sample occurred in 34 percent of patients with a platelet count above 500,000/microL compared with 9 percent of patients with a platelet count less than 250,000/microL [23]. The concentration of potassium in plasma (obtained by centrifugation of heparinized, unclotted blood) was normal.

  A similar phenomenon has been reported in acute myeloid leukemia [24]. However, **hypokalemia** is more common in this disorder, due to movement of potassium into rapidly proliferating cells after the blood has been drawn (pseudohypokalemia) or to renal potassium wasting (true hypokalemia). (See "Acute myeloid leukemia: Overview of complications", section on 'Hypokalemia'.)

- High white blood cell counts (>120,000/microL) caused by chronic lymphocytic leukemia can lead to falsely elevated potassium concentrations due to cell fragility. Unlike thrombocytosis, this form of pseudohyperkalemia occurs in **both** serum and plasma samples and may be more prominent when blood is sampled in heparinized tubes [25]. Centrifugation of a heparinized tube causes in vitro cell destruction and release of potassium as these cells are freely suspended in plasma.

  Accurate assessment of the potassium concentration in this setting can be achieved by allowing clotting to separate serum (plasma without the clotting factors) from cells **before** centrifugation. The fibrin clot entraps and protects fragile leukemic cells, minimizing cell lysis.

  Pseudohyperkalemia in patients with very high white blood cell counts due to leukemia or lymphoma has also been reported after mechanical disruption of white blood cells during transport of blood samples via pneumatic tube systems [26,27].

- Potassium can move out of red cells after the specimen is collected in patients with hereditary (familial) forms of pseudohyperkalemia, which are caused by an increase in the passive potassium permeability of erythrocytes. Pseudohyperkalemia may be the only manifestation of the disorder, or it may be accompanied by abnormal red cell morphology (eg, stomatocytosis), varying degrees of hemolysis, and/or perinatal edema in specific

kindreds. This genetically heterogeneous condition is discussed in detail elsewhere. (See "Hereditary stomatocytosis (HSt) and hereditary xerocytosis (HX)", section on 'Clinical manifestations'.)

Metabolic acidosis — In patients with metabolic acidosis other than organic acidosis due to lactic acidosis or ketoacidosis, buffering of excess hydrogen ions in the cells leads to potassium movement into the extracellular fluid, a transcellular shift that is obligated in part by the need to maintain electroneutrality (figure 4). (See "Potassium balance in acid-base disorders", section on 'Metabolic acidosis'.)

Although this shift will tend to raise the plasma potassium concentration, some patients have concurrent potassium losses due to gastrointestinal disease (eg, diarrhea) or increased urinary losses (eg, renal tubular acidosis [RTA]). In these settings, the measured serum potassium concentration may be normal or reduced despite the presence of metabolic acidosis. However, the plasma potassium will be higher than it would have been if the same degree of potassium loss had occurred in the absence of metabolic acidosis. (See "Overview and pathophysiology of renal tubular acidosis and the effect on potassium balance".)

Absent effect in lactic acidosis or ketoacidosis — In contrast to the above finding, hyperkalemia due to an acidosis-induced shift of potassium from the cells into the extracellular fluid does **not** occur in the organic acidoses lactic acidosis and ketoacidosis [28-31]. A possible contributory factor in both disorders is the ability of the organic anion and the hydrogen ion to enter into the cell via a sodium-organic anion cotransporter. The transport mechanisms involved and how they minimize potassium movement out of the cells are discussed in detail elsewhere [29].

As described below, the development of hyperkalemia in patients with diabetic ketoacidosis is primarily due to insulin deficiency and hyperosmolality, not acidemia. (See 'Insulin deficiency, hyperglycemia, and hyperosmolality' below and "Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Clinical features, evaluation, and diagnosis", section on 'Serum potassium'.)

Smaller effect in respiratory acidosis — Hyperkalemia due to respiratory acidosis is not a common clinical problem. The effect of respiratory acidosis on the plasma potassium concentration has been primarily evaluated in acute rather than chronic respiratory acidosis. In a review of the available human data, respiratory acidosis produced **no** significant effect on the plasma potassium, although the degree of acidemia in the reviewed studies was usually mild (fall in plasma pH approximately 0.1); in addition, the increase in plasma potassium for a given reduction in pH was smaller when the fall in pH was induced by respiratory as compared with

metabolic acidosis [28]. The effect of respiratory acidosis on the plasma potassium is greater with more severe acidosis and with a longer duration of acidosis [32]. The mechanisms responsible for the lesser increase in plasma potassium in respiratory acidosis compared with metabolic acidosis are not well defined [29].

Studies in animal models of acute respiratory acidosis have shown variable increases in plasma potassium with the severity and duration of the acidosis. The following illustrates the range of findings:

- In a study in dogs, severe acute respiratory acidosis (a decrease in mean plasma pH from 7.4 to 7) had no effect on the plasma potassium at 10 minutes but, at two and six hours, the plasma potassium had increased from 4 to 6 mEq/L (approximately 0.5 mEq/L per 0.1 reduction in plasma pH) [33]. The increase in plasma potassium was due to potassium movement out of cells and was approximately twice as large when the ureters were ligated, suggesting a role for urinary excretion of some of the excess potassium.

- As might be expected, other studies in dogs with less severe acute respiratory acidosis found no [34] or only small elevations in the plasma potassium concentration [35].

Insulin deficiency, hyperglycemia, and hyperosmolality — Insulin promotes potassium entry **into** cells. Thus, the ingestion of glucose (which stimulates endogenous insulin secretion) minimizes the rise in the serum potassium concentration induced by concurrent potassium intake (figure 5) [36], while glucose ingestion alone in patients without diabetes modestly lowers the serum potassium (figure 6) [37].

The findings are different in uncontrolled diabetes mellitus. In this setting, the combination of insulin deficiency (either impaired secretion or insulin resistance) and hyperosmolality induced by hyperglycemia frequently leads to hyperkalemia even though there may be marked potassium depletion due to urinary losses caused by the osmotic diuresis (figure 6) [37-39]. (See "Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Clinical features, evaluation, and diagnosis", section on 'Serum potassium'.)

The increase in plasma osmolality results in osmotic water movement from the cells into the extracellular fluid. This is accompanied by potassium movement out of the cells by two proposed mechanisms:

- The loss of cell water raises the cell potassium concentration, thereby creating a favorable gradient for passive potassium exit through potassium channels in the cell membrane.

- The friction forces between solvent (water) and solute can result in potassium being carried along with water through the water pores in the cell membrane. This phenomenon of solvent drag is independent of the electrochemical gradient for potassium diffusion.

Causes other than diabetes mellitus — Disorders other than diabetes mellitus have been associated with hyperkalemia due to insulin deficiency and/or hyperosmolality. As examples:

- Insulin levels fall in response to therapy with somatostatin or the somatostatin agonist, octreotide, and can lead to elevations in serum potassium [40-43]. The magnitude of this effect varies with the clinical setting. In one study, for example, the mean increase in serum potassium was 0.5 to 0.6 mEq/L in normal individuals and patients with type 2 diabetes; in contrast, there was no change in serum potassium in patients with type 1 diabetes since they make little or no insulin [40]. The effect of somatostatin or octreotide is much greater in patients with end-stage kidney disease (ESKD) requiring dialysis in whom the serum potassium can rise above 7 mEq/L [41,42].

- Fasting is associated with an appropriate reduction in insulin levels that can lead to an increase in plasma potassium. This may be a particular problem in patients on dialysis. (See 'Acute and chronic kidney disease' below.)

  The risk of hyperkalemia during preoperative fasting can be minimized by the administration of insulin and glucose in patients with diabetes, or glucose alone in patients without diabetes (figure 6) [37].

- In addition to hyperglycemia induced by insulin deficiency, hyperkalemia induced by hyperosmolality has also been described with hypernatremia [44], sucrose contained in intravenous immune globulin [45], radiocontrast media [46], and the administration of hypertonic mannitol [47]. Most of the reported patients had kidney failure. (See "Complications of mannitol therapy", section on 'Volume expansion, hyponatremia, hyperkalemia, hypokalemia, and metabolic acidosis'.)

Increased tissue catabolism — Any cause of increased tissue breakdown leads to the release of intracellular potassium into the extracellular fluid. Hyperkalemia can occur in this setting, particularly if kidney failure is also present. Clinical examples include trauma (including noncrush trauma), rhabdomyolysis, the administration of cytotoxic or radiation therapy to patients with lymphoma or leukemia (the tumor lysis syndrome), and severe accidental hypothermia [48-50]. (See "Crush-related acute kidney injury", section on 'Biochemical abnormalities' and "Tumor lysis syndrome: Pathogenesis, clinical manifestations, definition, etiology and risk factors", section on 'Clinical manifestations' and "Accidental hypothermia in adults", section on 'Pathophysiology'.)

Beta blockers — Increased beta-2-adrenergic activity drives potassium into the cells and lowers the serum potassium. (See "Causes of hypokalemia in adults", section on 'Elevated beta-adrenergic activity'.)

Beta blockers interfere with the beta-2-adrenergic facilitation of potassium uptake by the cells, particularly after a potassium load (figure 7) [51,52]. An increase in serum potassium is primarily seen with nonselective beta blockers (such as propranolol and labetalol). In contrast, beta-1-selective blockers such as atenolol have little effect on serum potassium since beta-2 receptor activity remains intact [53].

The rise in serum potassium with nonselective beta blocker therapy is usually less than 0.5 mEq/L. True hyperkalemia is rare unless there is a large potassium load, marked exercise (as described in the next section), or an additional defect in potassium handling that prevents excretion of the excess extracellular potassium, such as hypoaldosteronism or kidney failure [52,54]. In one report, for example, three kidney transplant recipients developed severe hyperkalemia after the administration of labetalol for postoperative hypertension [52].

Exercise — Potassium is normally released from muscle cells during exercise. The increase in plasma potassium is rarely important clinically, with the one major exception that fist clenching during blood drawing can interfere with accurate assessment of the serum potassium concentration. Repeated fist clenching during blood drawing can acutely raise the serum potassium concentration by more than 1 mEq/L in that forearm, thereby representing a form of pseudohyperkalemia [20]. (See 'Pseudohyperkalemia' above.)

The increase in plasma potassium during exercise may be mediated by two factors:

- A delay between potassium exit from the cells during depolarization and subsequent reuptake into the cells via the Na-K-ATPase pump.
- With marked exercise, an increased number of open potassium channels in the cell membrane. These channels are inhibited by ATP, an effect that is removed by the exercise-induced decline in ATP levels [55].

The release of potassium during exercise may have a physiologically important role. The **local** increase in potassium concentration has a vasodilator effect, thereby increasing blood flow and energy delivery to the exercising muscle.

The degree of elevation in the plasma potassium concentration in the **systemic circulation** is less pronounced and varies directly with the degree of exercise: 0.3 to 0.4 mEq/L with slow walking; 0.7 to 1.2 mEq/L with moderate exertion (including prolonged aerobic exercise with

marathon running); and as much as 2 mEq/L following exercise to exhaustion [54,56-59], which may be associated with both ECG changes [58] and lactic acidosis [59].

The peak increase in plasma potassium during exercise is **less** pronounced with prior physical conditioning (perhaps due to increased Na-K-ATPase activity) [60] and **more** pronounced in patients treated with nonselective beta blockers [56] or those with ESKD even though there is often a lesser degree of attained exercise [61]. (See 'Beta blockers' above.)

The rise in plasma potassium concentration induced by exercise is reversed after several minutes of rest and is typically associated with a mild rebound hypokalemia (averaging 0.4 to 0.5 mEq/L below the baseline level) [57-59]. It has been suggested that the changes in plasma potassium might be arrhythmogenic in susceptible patients, such as those with angina pectoris [58].

Hyperkalemic periodic paralysis — Hyperkalemic periodic paralysis is an autosomal dominant disorder in which episodes of weakness or paralysis are usually precipitated by cold exposure, rest after exercise, fasting, or the ingestion of small amounts of potassium. The most common abnormality in hyperkalemic periodic paralysis is a point mutation in the gene for the alpha subunit of the skeletal muscle cell sodium channel. (See "Hyperkalemic periodic paralysis", section on 'Pathogenesis'.)

Other — Other rare causes of hyperkalemia due to translocation of potassium from the cells into the extracellular fluid include:

- Digitalis overdose, due to dose-dependent inhibition of the Na-K-ATPase pump [62]. Hyperkalemia can also occur after poisoning with structurally related digitalis glycosides, as may occur after ingestion of the plants, common oleander or yellow oleander [63], or extracts of the cane toad, Bufo marinus (bufadienolides) [64]. (See "Digitalis (cardiac glycoside) poisoning", section on 'Electrolyte abnormalities' and "Potentially toxic plant ingestions in children: Clinical manifestations and evaluation", section on 'Cardiac glycosides (eg, oleander, foxglove)'.)

- Red cell transfusion, due to leakage of potassium out of the red cells during storage. Hyperkalemia primarily occurs in infants and with massive transfusions. (See "Red blood cell transfusion in infants and children: Administration and complications", section on 'Metabolic toxicity'.)

- Administration of succinylcholine to patients with burns, extensive trauma, prolonged immobilization, chronic infection, or neuromuscular disease [65-67]. Acetylcholine receptors are normally concentrated within the neuromuscular junction, and the efflux of

intracellular potassium caused by depolarization of these receptors is confined to this space. Hyperkalemia occurs when succinylcholine is given under conditions that cause upregulation and widespread distribution of acetylcholine receptors throughout the entire muscle membrane [65].

- Administration of arginine hydrochloride, which is metabolized in part to hydrochloric acid and has been used to treat refractory metabolic alkalosis. The entry of cationic arginine into the cells presumably obligates potassium exit to maintain electroneutrality [68]. The drug aminocaproic acid can cause hyperkalemia by the same mechanism since it is structurally similar to arginine [69,70]. (See "Treatment of metabolic alkalosis", section on 'Hydrochloric acid in selected patients'.)

- Use of drugs that activate ATP-dependent potassium channels in cell membranes, such as calcineurin inhibitors (eg, cyclosporine and tacrolimus), nicorandil, and isoflurane [71]. In particular, there are multiple reports of hyperkalemia from nicorandil in susceptible patients [72-74]. As described elsewhere, other mechanisms are also involved in calcineurin inhibitor-induced hyperkalemia, including hyporeninemic hypoaldosteronism and inhibition of the luminal potassium channel through which potassium is secreted (figure 1). (See 'Reduced aldosterone secretion' below and "Cyclosporine and tacrolimus nephrotoxicity", section on 'Hyperkalemia'.)

REDUCED URINARY POTASSIUM EXCRETION

Urinary potassium excretion is primarily mediated by potassium secretion in the principal cells in the two segments that follow the distal tubule: the connecting segment and cortical collecting tubule (figure 1). Three major factors are required for adequate potassium secretion at these sites: **adequate aldosterone secretion**, **adequate responsiveness to aldosterone**, and **adequate distal sodium and water delivery** [75]. The widely used term hypoaldosteronism applies to both reduced aldosterone secretion and reduced response to aldosterone. (See 'Brief review of potassium physiology' above.)

The four major causes of hyperkalemia due to reduced urinary potassium secretion are:

- Reduced aldosterone secretion
- Reduced response to aldosterone (aldosterone resistance)
- Reduced distal sodium and water delivery as occurs in effective arterial blood volume depletion
- Acute and chronic kidney disease in which one or more of the above factors are present

Other mechanisms for reduced urinary potassium secretion have rarely been described. (See 'Other mechanisms of impaired potassium secretion' below.)

In addition to directly causing hyperkalemia, impaired urinary potassium excretion can also contribute to hyperkalemia induced by potassium release from the cells (table 1). (See 'Increased potassium release from cells' above.)

Reduced aldosterone secretion — Any cause of decreased aldosterone release, such as that induced by hyporeninemic hypoaldosteronism or certain drugs, can diminish the efficiency of potassium secretion and lead to hyperkalemia and metabolic acidosis (called type 4 renal tubular acidosis [RTA]) (table 2). Drugs commonly implicated include angiotensin inhibitors [76], nonsteroidal antiinflammatory drugs, calcineurin inhibitors, and heparin. (See "Etiology, diagnosis, and treatment of hypoaldosteronism (type 4 RTA)", section on 'Etiology'.)

Hyperkalemia is a common problem in patients treated with the calcineurin inhibitors, cyclosporine and tacrolimus. These drugs can induce hyporeninemic hypoaldosteronism and can also interfere with the effect of aldosterone on the potassium-secreting cells in the connecting segment and cortical collecting tubule. (See "Cyclosporine and tacrolimus nephrotoxicity", section on 'Hyperkalemia'.)

The rise in plasma potassium concentration induced by reductions in aldosterone secretion or aldosterone response directly stimulates potassium secretion, partially overcoming the relative absence of aldosterone. The net effect is that the rise in the plasma potassium concentration is generally small in patients with normal kidney function but can be clinically important in the presence of underlying kidney function impairment and/or other causes of hyperkalemia (table 1).

Reduced response to aldosterone — There are a number of causes of hyperkalemia that are due to a reduced response to aldosterone, also called aldosterone or mineralocorticoid resistance. The most common are the administration of potassium-sparing diuretics and acute and chronic kidney disease in which other factors may also contribute. (See 'Acute and chronic kidney disease' below.)

Potassium-sparing diuretics — Two classes of diuretic medications impair renal potassium secretion despite normal or high levels of aldosterone: aldosterone antagonists that compete with aldosterone for receptor sites (spironolactone and eplerenone), and drugs that directly block the sodium channels in the apical (luminal) membrane of the principal cells in the collecting tubule (amiloride and triamterene) (figure 1).

The antibiotics trimethoprim (TMP) and pentamidine share structural similarity with amiloride and also inhibit apical sodium channels [77,78]; in perfused cortical collecting ducts, TMP inhibits both sodium reabsorption and potassium secretion [79]. Hyperkalemia associated with TMP was initially reported in patients with HIV treated for *Pneumocystis* pneumonia with high doses of trimethoprim-sulfamethoxazole [80]. Standard doses of TMP may also produce hyperkalemia; in one study of hospitalized patients, for example, hyperkalemia occurred in greater than 50 percent, with serum potassium concentrations >5.5 mmol/L in 21 percent [81]. (See "Trimethoprim-sulfamethoxazole: An overview" and "Etiology, diagnosis, and treatment of hypoaldosteronism (type 4 RTA)", section on 'Antibiotics'.)

Risk factors for hyperkalemia in patients treated with potassium-sparing diuretics include kidney function impairment, hyporeninemic hypoaldosteronism, and treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs).

Voltage-dependent renal tubular acidosis — In some patients with distal RTA, the primary defect is impaired sodium reabsorption in the principal cells in the two segments that follow the distal tubule (the connecting segment and the cortical collecting tubule). The movement of sodium from the lumen into the principal cells makes the lumen electronegative, thereby promoting the secretion of both hydrogen ions and potassium (figure 1). In contrast, an impairment in sodium reabsorption will reduce both hydrogen and potassium secretion, which will promote the development of metabolic acidosis and hyperkalemia. This disorder, which has been called voltage-dependent RTA, has been associated with urinary tract obstruction [82], lupus nephritis [83], sickle cell disease [84], and renal amyloidosis [85]. (See "Overview and pathophysiology of renal tubular acidosis and the effect on potassium balance".)

A somewhat similar defect is induced by hypoaldosteronism since aldosterone normally increases the number of open sodium channels in the luminal membrane. In contrast to hypoaldosteronism, voltage-dependent RTA is associated with normal or even high aldosterone levels and an inability to normally acidify the urine, as the urine pH is above 5.5. (See 'Reduced aldosterone secretion' above and "Etiology and diagnosis of distal (type 1) and proximal (type 2) renal tubular acidosis".)

Pseudohypoaldosteronism type 1 — Pseudohypoaldosteronism type 1 is a rare hereditary disorder that is characterized by aldosterone resistance. The autosomal recessive form affects the collecting tubule sodium channel (ENaC) (figure 1), and the autosomal dominant form in most patients affects the mineralocorticoid receptor. (See "Etiology, diagnosis, and treatment of hypoaldosteronism (type 4 RTA)", section on 'Pseudohypoaldosteronism type 1'.)

Reduced distal sodium and water delivery — Even in the presence of normal or increased plasma aldosterone levels, potassium secretion and therefore urinary potassium excretion can be impaired if there is a substantial reduction in sodium and water delivery to the potassium secretory sites in the distal nephron (connecting segment and cortical collecting tubule). As an example, potassium secretion by perfused rabbit cortical collecting ducts is dramatically inhibited at a luminal sodium concentration of 8 mmol/L and essentially stops at a luminal sodium concentration of 0 mmol/L [86]. Dietary sodium intake also influences potassium excretion; the potassium secretory capacity is enhanced by excess sodium intake and reduced by sodium restriction [87].

The most common cause of reduced distal sodium and water delivery is effective arterial blood volume depletion, which may be accompanied by other factors that promote the development of hyperkalemia. Measurement of urinary sodium concentration, combined with a therapeutic response to saline hydration, can help confirm this pathophysiology.

Effective arterial blood volume depletion — The effective arterial blood volume (also called effective circulating volume) refers to the arterial blood volume that is effectively perfusing the tissues. Effective arterial blood volume depletion includes any cause of true volume depletion (eg, gastrointestinal or renal losses) as well as heart failure and cirrhosis in which decreased tissue perfusion is due to a reduced cardiac output and vasodilation, respectively. (See "General principles of disorders of water balance (hyponatremia and hypernatremia) and sodium balance (hypovolemia and edema)", section on 'Effective arterial blood volume'.)

Any cause of effective arterial blood volume depletion can lead sequentially to decreased delivery of sodium and water to the sites of potassium secretion in the distal nephron (connecting segment and cortical collecting tubule), impaired potassium secretion into the tubular lumen, and hyperkalemia (figure 1) [88,89]. (See 'Brief review of potassium physiology' above.) However, the effect of impaired potassium secretion can be minimized or overcome, possibly resulting in hypokalemia, if there are concurrent potassium losses, as in patients with vomiting or diarrhea, or those treated with diuretic therapy.

In addition to decreased distal delivery of sodium and water, other potentially important contributing factors to hyperkalemia in patients with heart failure and cirrhosis include angiotensin inhibitor therapy in heart failure (but not cirrhosis) and aldosterone antagonists in both heart failure and cirrhosis. (See "Renal effects of ACE inhibitors in heart failure", section on 'Hyperkalemia' and "Ascites in adults with cirrhosis: Initial therapy", section on 'Avoidance of angiotensin inhibition' and "Ascites in adults with cirrhosis: Initial therapy", section on 'Diuretic regimen' and "Primary pharmacologic therapy for heart failure with reduced ejection fraction", section on 'Mineralocorticoid receptor antagonist'.)

Acute and chronic kidney disease — Hyperkalemia is a common complication of acute and chronic kidney disease. In patients with acute kidney injury, hyperkalemia is most prevalent in oliguric patients who also have increased potassium release from cells due, for example, to rhabdomyolysis or tumor lysis syndrome.

In patients with chronic kidney disease, the ability to excrete potassium at near-normal levels without the development of hyperkalemia generally persists as long as both the secretion of and responsiveness to aldosterone are intact and distal delivery of sodium and water are maintained [90]. Hyperkalemia is most commonly seen in patients who are oliguric or have an additional problem such as a high-potassium diet, increased tissue breakdown, reduced aldosterone secretion or responsiveness, or fasting in patients on dialysis, which may both lower insulin levels and cause resistance to beta-adrenergic stimulation of potassium uptake [38,90-92]. In patients on dialysis who fasted prior to surgery, the administration of insulin and glucose or, to a lesser degree, glucose alone in patients without diabetes can minimize the elevation in the serum potassium concentration [92]. (See 'Insulin deficiency, hyperglycemia, and hyperosmolality' above.)

Impaired cell uptake of potassium also contributes to the development of hyperkalemia in advanced kidney failure (figure 5). Diminished Na-K-ATPase activity may be particularly important in this setting. How this occurs is not clear, but retained uremic toxins may decrease the transcription of mRNA for the alpha1 isoform of the Na-K-ATPase pump in skeletal muscle [91,93,94].

Multiple factors — The presence of multiple factors that impair potassium secretion can lead to more severe and possibly life-threatening hyperkalemia. One setting in which this can occur is in patients with moderate to severe heart failure [95-99]. These patients often have reduced distal sodium and water delivery due to the associated kidney hypoperfusion, relatively decreased aldosterone release (from treatment with ACE inhibitors and/or ARBs), and reduced aldosterone effect (from treatment with spironolactone or eplerenone) [98]. (See "Major side effects of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers", section on 'Hyperkalemia' and "Overview of the management of heart failure with reduced ejection fraction in adults" and "Primary pharmacologic therapy for heart failure with reduced ejection fraction", section on 'Mineralocorticoid receptor antagonist'.)

Other mechanisms of impaired potassium secretion — In addition to the common mechanisms of hyperkalemia due to reduced urinary potassium excretion described above, there are other, less common causes of hyperkalemia in which urinary potassium excretion is impaired due to mechanisms not directly related to reduced secretion of or response to aldosterone or to reduced distal sodium and water delivery.

Selective impairment in potassium secretion — Some patients with hyperkalemia have impaired urinary potassium excretion despite normal aldosterone release and normal distal sodium and water delivery. This seemingly selective impairment in potassium secretion, which does not respond to exogenous mineralocorticoid, has been described with lupus nephritis, acute transplant rejection, and sickle cell disease [100-102]. These patients do not have sodium wasting and have a normal antinatriuretic response to mineralocorticoids, indicating a selective potassium defect, **not** aldosterone resistance [101,102]. In at least some cases, the potassium secretory defect may be due to interstitial nephritis [100].

A selective impairment in potassium secretion can also occur in patients treated with cyclosporine or tacrolimus. One or more mechanisms involved in tubular potassium secretion may be impaired. (See "Cyclosporine and tacrolimus nephrotoxicity", section on 'Hyperkalemia'.)

Pseudohypoaldosteronism type 2 (Gordon's syndrome) — An inherited syndrome of hyperkalemia, volume expansion, hypertension, and otherwise normal kidney function has been called pseudohypoaldosteronism type 2, Gordon's syndrome, or familial hyperkalemic hypertension. The reduction in aldosterone secretion represents an **appropriate** response to volume expansion. (See "Etiology, diagnosis, and treatment of hypoaldosteronism (type 4 RTA)", section on 'Pseudohypoaldosteronism type 2 (Gordon's syndrome)'.)

Ureterojejunostomy — A rise in the serum potassium concentration can occur in patients with a urinary diversion procedure in which the ureters are inserted into the jejunum (called a ureterojejunostomy). Hyperkalemia in this setting is presumably due to absorption of urinary potassium by the jejunum [103]. (See "Acid-base and electrolyte abnormalities with diarrhea".)

EVALUATION

Evaluation of the patient with hyperkalemia usually begins with a careful history, evaluation for clinical manifestations of hyperkalemia such as muscle weakness and characteristic changes on the electrocardiogram, and laboratory testing for the causes of hyperkalemia (algorithm 1). (See "Clinical manifestations of hyperkalemia in adults".)

Exclude pseudohyperkalemia — Pseudohyperkalemia, which is discussed above, refers to those conditions in which the elevation in the measured serum potassium concentration is due to potassium movement out of the cells during or after the blood specimen has been drawn. It is usually related to the technique of blood drawing, but it can also occur in patients with marked elevations in platelet or white blood cell counts. (See 'Pseudohyperkalemia' above.)

Pseudohyperkalemia should be suspected when there is no apparent cause for the hyperkalemia in an asymptomatic patient who has no clinical or electrocardiographic manifestations of hyperkalemia. One clue to the possible presence of pseudohyperkalemia is wide variability in repeated measurements of the serum potassium concentration (eg, from 5 to 6.5 mEq/L, often including some normal values). In contrast, patients with normokalemia and those with true chronic hyperkalemia, most often due to hypoaldosteronism or chronic kidney disease, tend to have stable values over the short term, although higher values can occur over time if there is progression of the underlying disease.

If an artifact of blood drawing is suspected or there is no apparent cause for hyperkalemia, venipuncture without a tourniquet, repeated fist clenching, or trauma will demonstrate the true serum potassium concentration [21]. If a tourniquet is required, the tourniquet should be released after the needle has entered the vein, followed by waiting for one to two minutes before drawing the blood sample. The diagnosis of pseudohyperkalemia in patients with thrombocytosis or markedly elevated white blood cell counts is described above. (See 'Other causes' above.)

Acute rise in serum potassium — In the absence of pseudohyperkalemia or recent potassium administration, an acute rise in serum potassium is often due to increased release of potassium from the cells, and the cause is identified from the history and laboratory data. Increased tissue catabolism is a classic example that is most often due to trauma or cytotoxic or radiation therapy in patients with lymphoma or leukemia (the tumor lysis syndrome). Diabetic ketoacidosis is another cause of an acute rise in serum potassium, a change that is more pronounced if kidney function is impaired. (See 'Increased tissue catabolism' above and 'Insulin deficiency, hyperglycemia, and hyperosmolality' above and 'Metabolic acidosis' above.)

Increasing potassium intake is **not** a major cause of hyperkalemia in individuals without another risk factor such as reduced aldosterone secretion or responsiveness or acute or chronic kidney disease. In healthy adults, raising potassium intake from a normal value of 100 mEq/day to a much higher value of 400 mEq/day only produces a modest elevation in serum potassium from 3.8 mEq/L at baseline to 4.8 mEq/L at the end of day 2 and 4.2 mEq/L at day 20 (figure 3) [10]. Urinary potassium excretion increases to the level of intake by the end of the second day, an effect that is mediated by both the elevation in plasma potassium and increased secretion of aldosterone. (See 'Potassium adaptation' above.)

Persistent hyperkalemia — Given the ability of healthy individuals to handle large potassium loads with only a small rise in serum potassium (figure 3) [10], the most common causes of persistent hyperkalemia are associated with impaired urinary potassium excretion due to reduced secretion of or response to aldosterone, acute or chronic kidney disease, and/or

effective arterial blood volume depletion. Effective arterial blood volume depletion may be due to true volume depletion or to heart failure or cirrhosis, in which decreased tissue perfusion is due to a reduced cardiac output and vasodilation, respectively (table 1). (See 'Reduced urinary potassium excretion' above.)

Administration of angiotensin inhibitors and aldosterone antagonists in patients with heart failure can contribute to the development of hyperkalemia but can also improve patient outcomes [104]. Limiting potassium intake and the use of loop diuretics may minimize the degree of hyperkalemia and allow these potentially life-saving therapies to be continued. (See "Treatment and prevention of hyperkalemia in adults", section on 'Prevention' and "Primary pharmacologic therapy for heart failure with reduced ejection fraction", section on 'Mineralocorticoid receptor antagonist' and "Primary pharmacologic therapy for heart failure with reduced ejection fraction", section on 'Hyperkalemia'.)

Urinary potassium excretion — Measurement of 24-hour urinary potassium excretion is of **limited utility** in patients with persistent **stable** hyperkalemia because urinary potassium excretion is primarily determined by and roughly equal to potassium intake. These patients have an impairment in urinary potassium excretion since a higher-than-normal plasma potassium concentration is required to excrete the daily potassium load.

Although uncommon, 24-hour urinary potassium excretion above 80 to 100 mEq/day (normal potassium intake) suggests that increased potassium intake (as with ingestion of a salt substitute) may be contributing to the hyperkalemia. However, as noted above, increasing potassium intake alone is not sufficient in healthy adults. In this setting, raising potassium intake from 100 to 400 mEq/day only increases the serum potassium from 3.8 mEq/L at baseline to 4.8 mEq/L at the end of day 2 and 4.2 mEq/L by day 20, a time at which intake and output are again equal (figure 3) [10]. (See 'Potassium adaptation' above.)

Transtubular potassium gradient — It would be desirable to assess the degree of aldosterone activity in patients with hyperkalemia by estimating the tubular fluid potassium concentration at the most distal site of potassium secretion in the cortical collecting tubule. Although this measurement cannot be made in humans, it was proposed that the potassium concentration at this site could be estimated clinically from calculation of the transtubular potassium gradient (TTKG) [105-107].

However, in a later publication, the authors of the original studies suggested that the assumptions underlying the TTKG were **not valid** [108], suggested that the equation did not consider the effects of distal tubular urea reabsorption on potassium excretion, and concluded that the TTKG was not a reliable test for the diagnosis of hyperkalemia. However, these

criticisms are theoretical and not supported by animal experiments [109]. Thus, it is unclear whether use of the TTKG is appropriate for assessment of the renal response to hyperkalemia. An alternative is the potassium:creatinine ratio; however, this calculation has not been extensively validated in hyperkalemia.

Diagnosis of hypoaldosteronism — Patients with persistent hyperkalemia in whom the etiology has not been identified should be evaluated for the presence and cause of hypoaldosteronism. This disorder can result from reduced aldosterone secretion or from aldosterone resistance, which most often occurs in patients treated with potassium-sparing diuretics and can be one of several factors that can contribute to hyperkalemia in acute and chronic kidney disease. (See 'Reduced aldosterone secretion' above and 'Reduced response to aldosterone' above.)

The approach to the diagnosis of hypoaldosteronism is discussed in detail elsewhere. (See "Etiology, diagnosis, and treatment of hypoaldosteronism (type 4 RTA)", section on 'Diagnosis of hypoaldosteronism'.)

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 topics (see "Patient education: Hyperkalemia (The Basics)")

SUMMARY

- Ingestion of a potassium load leads initially to the uptake of most of the excess potassium by cells in muscle and the liver, a process that is facilitated by insulin and the beta-2-adrenergic receptors, both of which increase the activity of Na-K-ATPase pumps in the cell membrane. Some of the ingested potassium remains in the extracellular fluid, producing a mild elevation in the plasma potassium concentration. The increase in plasma potassium stimulates the secretion of aldosterone, which enhances both sodium reabsorption and potassium secretion by principal cells (figure 1). (See 'Brief review of potassium physiology' above.)

- Increasing potassium intake alone is **not** a common cause of hyperkalemia unless it occurs acutely. The net release of potassium from the cells (due to enhanced release or decreased entry) can, if large enough (eg, increased tissue breakdown), cause a transient elevation in the serum potassium concentration. Persistent hyperkalemia requires **impaired urinary potassium excretion**. This is generally associated with a reduction in aldosterone secretion or responsiveness, acute or chronic kidney disease, and/or diminished delivery of sodium and water to the distal potassium secretory sites (table 1). (See 'Brief review of potassium physiology' above.)

- The following are causes of hyperkalemia due to increased potassium release from cells (see 'Increased potassium release from cells' above):

  - Pseudohyperkalemia – Pseudohyperkalemia includes those conditions in which the elevation in the measured serum potassium concentration is due to potassium movement out of the cells during or after the blood specimen has been drawn. The most common is mechanical trauma during venipuncture, which can result in the release of potassium from red cells and a characteristic reddish tint of the serum due to the concomitant release of hemoglobin. (See 'Pseudohyperkalemia' above.)

  - Metabolic acidosis – In patients with metabolic acidosis other than organic acidosis due to lactic acidosis or ketoacidosis, buffering of excess hydrogen ions in the cells leads to potassium movement into the extracellular fluid, a transcellular shift that is obligated in part by the need to maintain electroneutrality (figure 4). (See 'Metabolic acidosis' above.)

- Insulin deficiency, hyperglycemia, and hyperosmolality – Insulin promotes potassium entry into cells, minimizing the rise in the serum potassium concentration induced by concurrent potassium intake (figure 5). In uncontrolled diabetes mellitus, the combination of insulin deficiency/resistance and hyperosmolality induced by hyperglycemia frequently leads to hyperkalemia even though there may be marked potassium depletion due to urinary losses caused by the osmotic diuresis (figure 6). (See 'Insulin deficiency, hyperglycemia, and hyperosmolality' above.)

- Increased tissue catabolism – Any cause of increased tissue breakdown leads to the release of intracellular potassium into the extracellular fluid. Hyperkalemia can occur in this setting, particularly if kidney failure is also present. (See 'Increased tissue catabolism' above.)

- Beta blockers – Beta blockers interfere with the beta-2-adrenergic facilitation of potassium uptake by the cells, particularly after a potassium load (figure 7). An increase in serum potassium is primarily seen with nonselective beta blockers (such as propranolol and labetalol).

Other causes of hyperkalemia due to increased potassium release from cells include exercise, hyperkalemic periodic paralysis, red cell transfusion, and various drugs including digitalis. (See 'Exercise' above and 'Hyperkalemic periodic paralysis' above and 'Other' above.)

- The four major causes of hyperkalemia due to reduced urinary potassium secretion are (table 1) (see 'Reduced urinary potassium excretion' above):

  - Reduced aldosterone secretion – Any cause of decreased aldosterone release, such as that induced by hyporeninemic hypoaldosteronism or certain drugs, can diminish the efficiency of potassium secretion and lead to hyperkalemia and metabolic acidosis (called type 4 renal tubular acidosis [RTA]) (table 2). (See 'Reduced aldosterone secretion' above.)

  - Reduced response to aldosterone (aldosterone resistance) – There are a number of causes of hyperkalemia that are due to a reduced response to aldosterone, also called aldosterone or mineralocorticoid resistance. The most common are the administration of potassium-sparing diuretics and acute and chronic kidney disease. (See 'Reduced response to aldosterone' above.)

  - Reduced distal sodium and water delivery – Potassium secretion can be impaired if there is a substantial reduction in sodium and water delivery to the potassium

secretory sites in the distal nephron (connecting segment and cortical collecting tubule). The most common cause is reduced effective arterial blood volume, including any cause of true volume depletion (eg, gastrointestinal or renal losses) as well as heart failure and cirrhosis in which decreased tissue perfusion is due to a reduced cardiac output and vasodilation, respectively. (See 'Reduced distal sodium and water delivery' above.)

- Acute and chronic kidney disease – In patients with acute kidney injury, hyperkalemia is most prevalent in oliguric patients who also have increased potassium release from cells due, for example, to rhabdomyolysis or tumor lysis syndrome. In patients with chronic kidney disease, the ability to excrete dietary potassium without the development of hyperkalemia generally persists as long as both the secretion of and responsiveness to aldosterone are intact and distal delivery of sodium and water are maintained. However, moderate increases in potassium intake can be an important contributor to the development of hyperkalemia in patients with impaired potassium excretion due to kidney function impairment, particularly in combination with other predisposing factors (hyporeninemic hypoaldosteronism, angiotensin-converting enzyme [ACE] inhibitor therapy, etc). (See 'Acute and chronic kidney disease' above.)

Other causes of impaired urinary potassium excretion include Gordon's syndrome and ureterojejunostomy. (See 'Other mechanisms of impaired potassium secretion' above.)

- Evaluation of the patient with hyperkalemia usually begins with a careful history, evaluation for clinical manifestations of hyperkalemia such as muscle weakness and characteristic changes on the electrocardiogram, and laboratory testing for the causes of hyperkalemia (algorithm 1). (See 'Evaluation' above.)

- Pseudohyperkalemia should be suspected when there is no apparent cause for the hyperkalemia in an asymptomatic patient who has no clinical or electrocardiographic manifestations of hyperkalemia. (See 'Exclude pseudohyperkalemia' above.)

- In the absence of pseudohyperkalemia or recent potassium administration, an acute rise in serum potassium is often due to increased release of potassium from the cells, and the cause is identified from the history and laboratory data. (See 'Acute rise in serum potassium' above.)

- Given the ability of healthy individuals to handle large potassium loads with only a small rise in serum potassium (figure 3), the most common causes of persistent hyperkalemia are associated with impaired urinary potassium excretion due to reduced secretion of or response to aldosterone, acute or chronic kidney disease, and/or effective

arterial blood volume depletion. Measurement of 24-hour urinary potassium excretion is of **limited utility** in patients with persistent **stable** hyperkalemia. The transtubular potassium gradient (TTKG) may be used for the diagnosis of hyperkalemia, in combination with assessment of urine sodium. Patients with persistent hyperkalemia in whom the etiology has not been identified should be evaluated for the presence and cause of hypoaldosteronism. (See 'Persistent hyperkalemia' above.)

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Topic 2377 Version 21.0

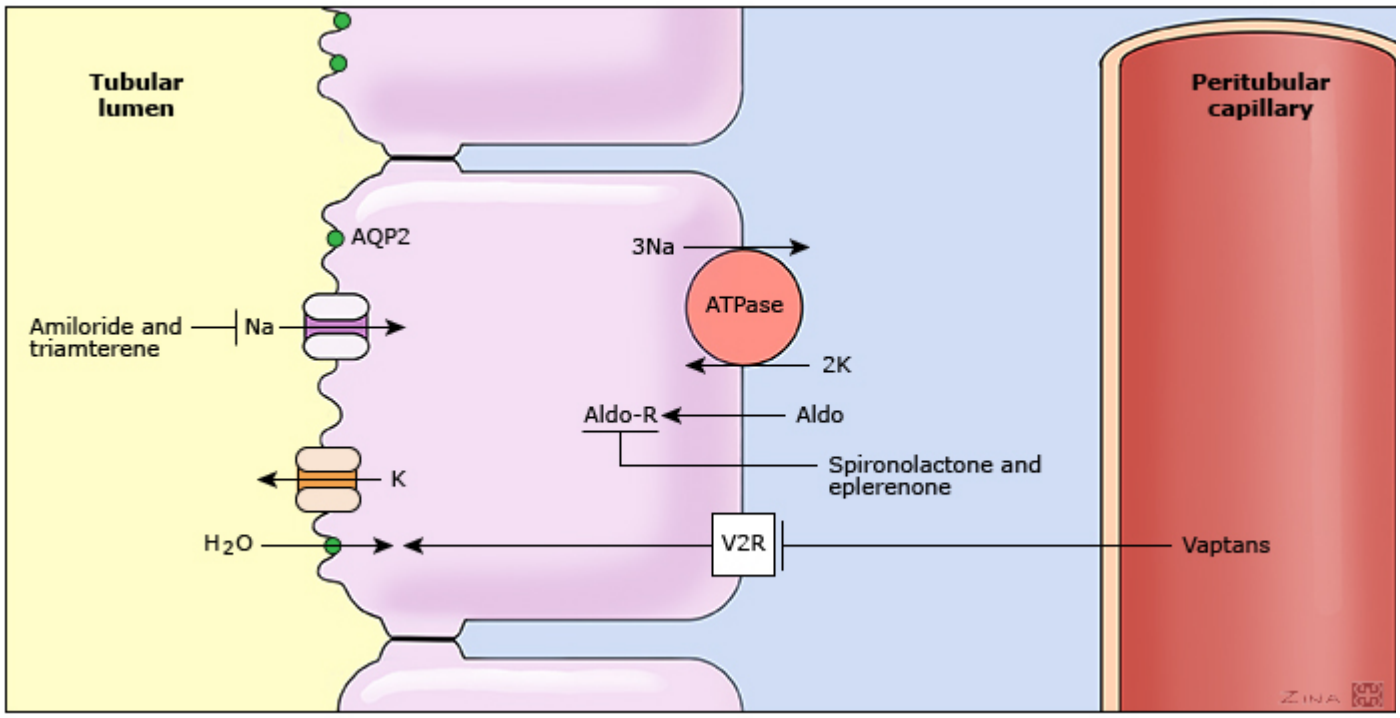
GRAPHICS

Major causes of hyperkalemia

Increased potassium release from cells
Pseudohyperkalemia
Metabolic acidosis
Insulin deficiency, hyperglycemia, and hyperosmolality
Increased tissue catabolism
Beta blockers
Exercise
Hyperkalemic periodic paralysis
Other
Overdose of digitalis or related digitalis glycosides
Red cell transfusion
Succinylcholine
Arginine hydrochloride
Activators of ATP-dependent potassium channels (eg, calcineurin inhibitors, diazoxide, minoxidil, and some volatile anesthetics)
Reduced urinary potassium excretion
Reduced aldosterone secretion
Reduced response to aldosterone
Reduced distal sodium and water delivery
Effective arterial blood volume depletion
Acute and chronic kidney disease
Other
Selective impairment in potassium secretion
Gordon's syndrome
Ureterojejunostomy

Graphic 58157 Version 6.0

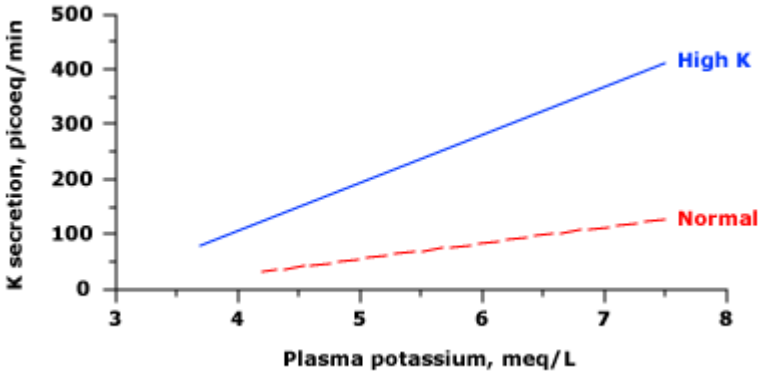
Ion transport in collecting tubule principal cells



Schematic representation of sodium (Na) and potassium (K) transport in the sodium-reabsorbing principal cells in the collecting tubules. The entry of filtered sodium into these cells is mediated by selective sodium channels in the apical (luminal) membrane (ENaC); the energy for this process is provided by the favorable electrochemical gradient for sodium (cell interior electronegative and low cell sodium concentration). Reabsorbed sodium is pumped out of the cell by the Na-K-ATPase pump in the basolateral (peritubular) membrane. The reabsorption of cationic sodium makes the lumen electronegative, thereby creating a favorable gradient for the secretion of potassium into the lumen via potassium channels (ROMK and BK) in the apical membrane. Aldosterone (Aldo), after combining with the cytosolic mineralocorticoid receptor (Aldo-R), leads to enhanced sodium reabsorption and potassium secretion by increasing both the number of open sodium channels and the number of Na-K-ATPase pumps. The potassium-sparing diuretics (amiloride and triamterene) act by directly inhibiting the epithelial sodium channel; spironolactone acts by competing with aldosterone for binding to the mineralocorticoid receptor.

Graphic 60693 Version 16.0

Increased potassium secretion in potassium adaptation

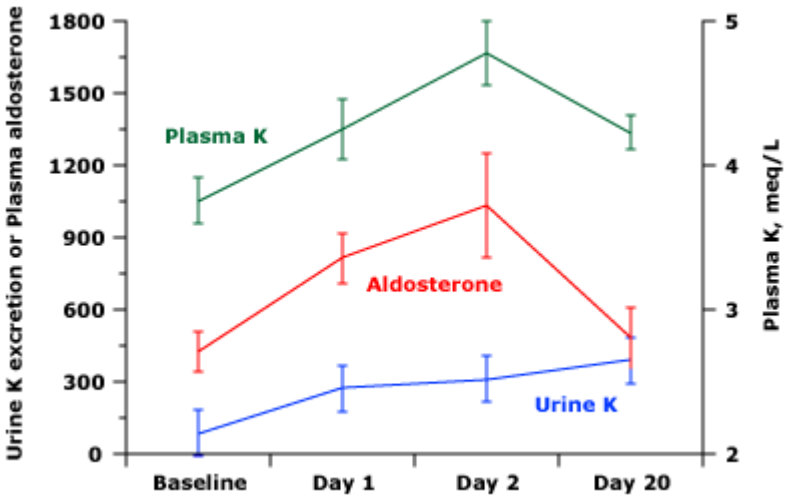


Relationship between the plasma potassium concentration (which is raised by potassium chloride infusion) and distal potassium secretion in normal animals (dashed line) and those treated with a high-potassium diet for four weeks (solid line). A high-potassium diet leads to potassium adaptation: at any plasma potassium concentration, distal potassium secretion is two to four times higher in adapted animals compared to normals.

Data from: Stanton BA. Am J Physiol 1989; 257:R989.

Graphic 67129 Version 2.0

Response to potassium load

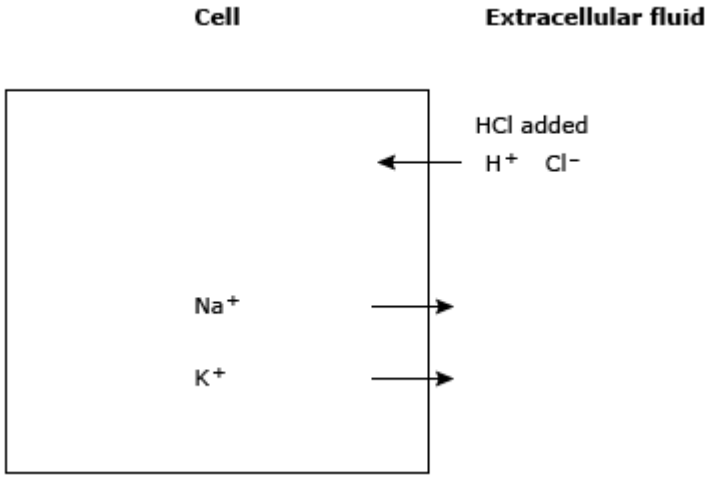


Response to increasing potassium intake from 100 to 400 meq/day in normal subjects. Urinary potassium excretion rises to over 300 meq/day within two days, a response that is driven by increases in both aldosterone release and the plasma potassium concentration. By day 20, potassium excretion is almost 400 meq/day, the plasma aldosterone level is near normal, and there is only a small rise in the plasma potassium concentration to 4.2 meq/L.

Data from: Rabelink TJ, Koomans HA, Hené RJ, et al. Kidney Int 1990; 38:942.

Graphic 50808 Version 2.0

Ion redistribution after acid load

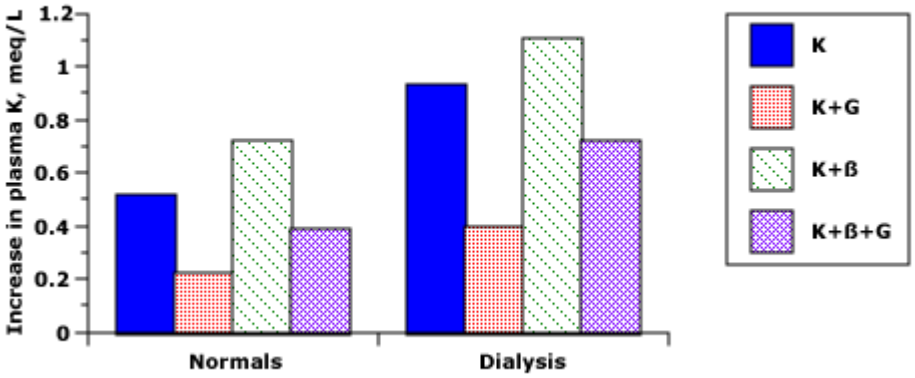


Effect of an HCl load on the distribution of Cl^-, Na^+, and K^+. As H^+ enters the cells to be buffered, intracellular Na^+ and K^+ leave the cells and move into the extracellular fluid, tending to raise the plasma K^+ concentration. These ion shifts are reversed when H^+ are removed from the extracellular fluid.

HCl: hydrogen chloride; H^+: hydrogen; Cl^-: chloride; Na^+: sodium; K^+: potassium.

Graphic 68866 Version 4.0

Effects of glucose and beta-blockade on response to potassium load in normals and dialysis patients

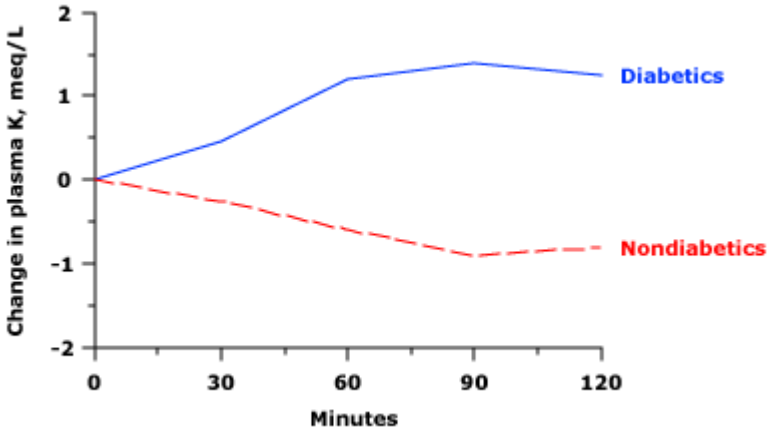


Peak increase in the plasma potassium concentration in normals and dialysis patients following the ingestion of 0.25 meq/kg of potassium alone (K) or with glucose (K+G), a beta blocker (K+β), or a beta blocker and glucose (K+β+G). The degree of hyperkalemia was minimized by glucose (via enhanced release of insulin), increased by a beta blocker, and made more prominent (by as much as 0.4 meq/L) with all interventions in dialysis patients, indicating decreased cell uptake of potassium in renal failure.

Data from: Allon M, Dansby L, Shanklin N. Am J Med 1993; 94:475.

Graphic 52424 Version 3.0

Glucose-induced hyperkalemia in diabetes

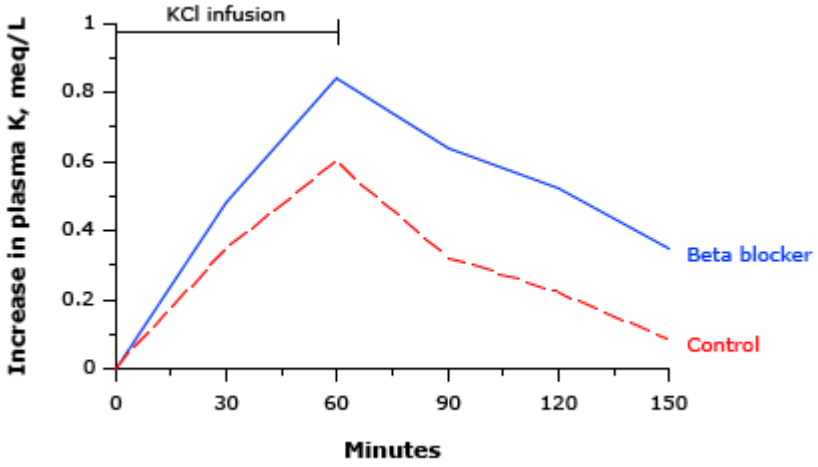


Effect of a glucose load on the plasma potassium concentration in diabetics (solid line) and nondiabetics (dashed line). Glucose led to a fall in the plasma potassium concentration in nondiabetics due to stimulation of insulin release but a rise in diabetics due to the elevation in plasma osmolality.

Data from: Nicolis GL, Kahn T, Sanchez A, et al. Arch Intern Med 1981; 141:49.

Graphic 64207 Version 2.0

Beta blocker enhances kalemic response to a potassium load



Change in the plasma potassium concentration after a potassium chloride infusion in control subjects (dashed line) and those treated with a beta blocker (solid line). The rise in the plasma potassium concentration was signficantly greater in the presence of beta blockade.

Data from: Rosa RM, Silva P, Young JB, et al. N Engl J Med 1980; 302:431.

Graphic 62538 Version 4.0

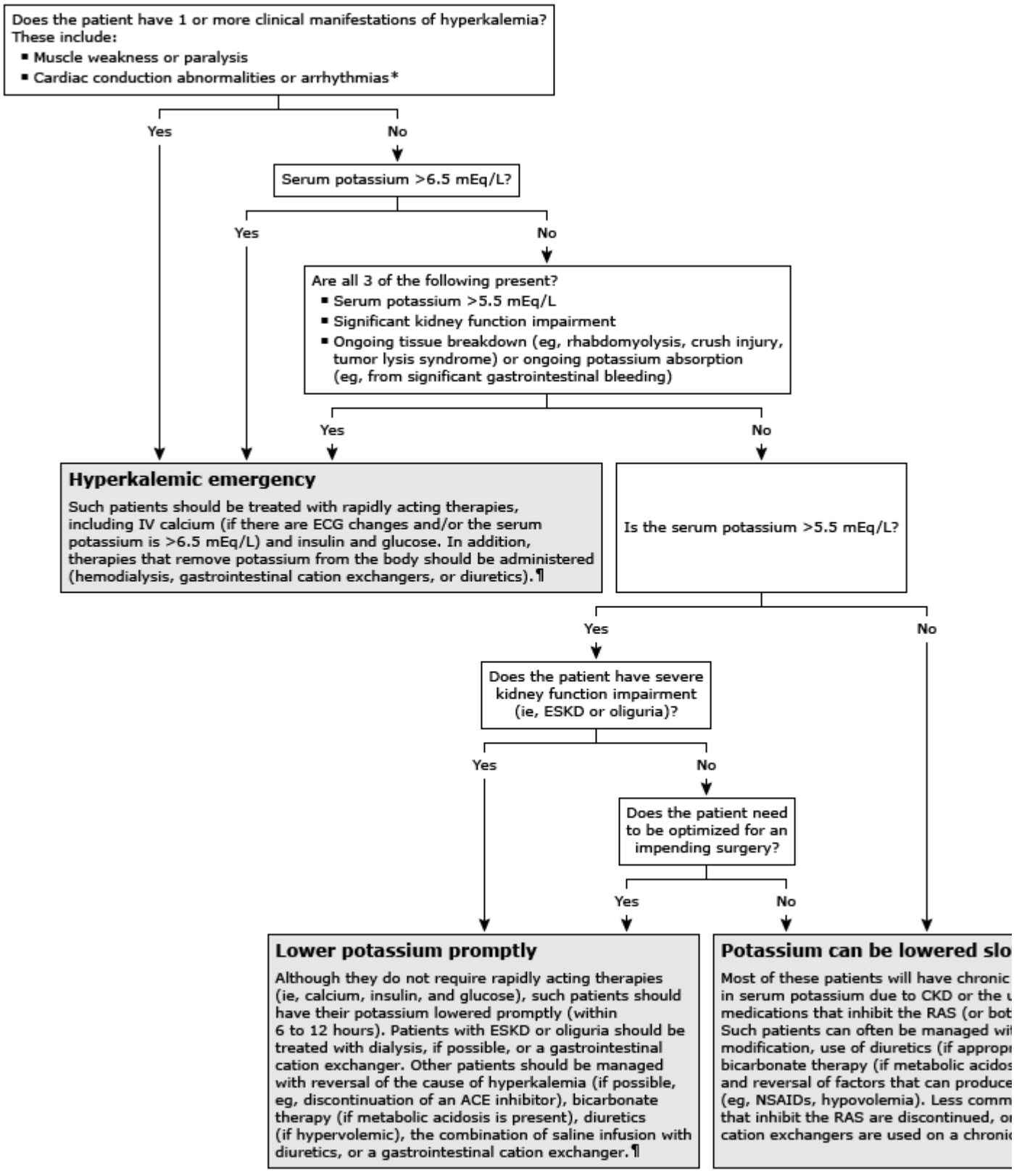
Major causes of hypoaldosteronism

Reduced aldosterone production
Hyporeninemic hypoaldosteronism
Kidney disease, most often diabetic nephropathy
Nonsteroidal antiinflammatory drugs
Calcineurin inhibitors
Volume expansion, as in acute glomerulonephritis
Angiotensin inhibitors, such as ACE inhibitors, angiotensin II receptor blockers, and direct renin inhibitors
Chronic heparin therapy (impairs aldosterone synthesis)
Primary adrenal insufficiency
Severe illness
Inherited disorders
Congenital hypoaldosteronism (21-hydroxylase deficiency and isolated hypoaldosteronism)
Pseudohypoaldosteronism type 2 (Gordon's syndrome)
Aldosterone resistance
Inhibition of the epithelial sodium channel
Potassium-sparing diuretics, such as spironolactone, eplerenone, amiloride, and triamterene
Antibiotics, trimethoprim, and pentamidine
Pseudohypoaldosteronism type 1
Voltage defects
Markedly reduced distal sodium delivery
Acquired or congenital defects in sodium reabsorption by the distal tubule principal cells (obstructiv uropathy), SLE, and sickle cell disease

ACE: angiotensin-converting enzyme; SLE: systemic lupus erythematosus.

Graphic 82440 Version 17.0

Treatment of hyperkalemia in adults



ESKD: end-stage kidney disease; ACE: angiotensin-converting enzyme; CKD: chronic kidney disease; RAS: renin-angiotensin system; NSAIDs: nonsteroidal antiinflammatory drugs; IV: intravenous; ECG: electrocardiogram.

* Cardiac manifestations of hyperkalemia are discussed in detail in the topic on clinical manifestations of hyperkalemia.

¶ Some experts given IV calcium only to patients with ECG changes. Details are presented in the topic on treatment of hyperkalemia.

Graphic 109740 Version 3.0