Hypokalemia—Consequences, Causes, and Correction

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Hypokalemia is one of the most commonly encountered fluid and electrolyte abnormalities in clinical medicine. It can be an asymptomatic finding identified only on routine electrolyte screening, or it can be associated with symptoms ranging from mild weakness to sudden death. The correction of hypokalemia can be simple, but if inappropriately performed can lead to worsening symptoms, and even death.

The purpose of this article is to discuss the management of hypokalemia in sufficient detail to allow practitioners to care for patients who have this condition. We shall discuss the epidemiology of hypokalemia and its consequences on renal and extrarenal tissues and shall briefly discuss the physiology of potassium handling and the differential diagnosis of hypokalemia. Finally, we shall consider the important factors that should influence therapy and shall provide general recommendations for patient management. Space limitations preclude extensive reference to many of the primary sources of information; thus, comprehensive reviews are frequently cited.

Epidemiology

The occurrence of hypokalemia is strongly dependent on the patient population. In otherwise healthy adults not receiving any medications, less than 1% will develop hypokalemia, as defined by a serum potassium level of less than 3.5 mEq/liter. This very low frequency of hypokalemia is a testament to two factors: the adequacy of potassium in the typical Western diet, and potent mechanisms for renal potassium conservation in states of potassium depletion. The presence of spontaneous hypokalemia in otherwise healthy adults who are not receiving any medications should suggest the possibility of underlying disease and indicate the need to search for an etiology.

Most cases of hypokalemia occur in the setting of specific disease states. Patients receiving diuretics are at the highest risk, with as many as 50% developing serum potassium levels of less than 3.5 mEq/liter (1). As we will later discuss, thiazide diuretics are more likely to cause hypokalemia than "loop" or osmotic diuretics. Individuals with secondary hyperaldosteronism, whether due to congestive heart failure, hepatic insufficiency, or nephrotic syndrome, constitute a second group at high risk. Finally, those patients with diseases that alter renal potassium conservation through interaction with salt delivery to the cortical collecting duct (CCD) are also at high risk for hypokalemia.

Consequences

Potassium deficiency alters the function of several organs and most prominently affects the cardiovascular system, neurologic system, muscles, and kidneys (2). These effects ultimately determine the morbidity and mortality related to this condition. Unfortunately, the correlation between degree of potassium deficiency and adverse side-effects is poor, possibly because the occurrence of side-effects is related to both the potassium deficiency and the underlying disease state. Overall, children and young adults tolerate more severe degrees of hypokalemia with less risk of severe side-effects than the elderly.

Cardiovascular

Two major side-effects of hypokalemia affect the cardiovascular system: hypokalemia-related hypertension and hypokalemia-induced ventricular arrhythmias. Both contribute to increased morbidity and mortality.

Hypokalemia contributes to hypertension in many patients (3) but is frequently unrecognized as an important factor that may produce or worsen this serious health problem. Several lines of evidence reveal that potassium deficiency can increase blood pressure. Cross-sectional studies show that low-potassium diets, especially in the presence of a high sodium intake, are linked with the prevalence of hypertension (3). This association is most marked in African Americans. Epidemiologic and prospective studies confirm this association in both healthy volunteers and in essential hypertensive patients (4). The antihypertensive effect of thiazide diuretics is reduced by hypokalemia and enhanced by potassium repletion (5). Finally, blood pressure may be more highly sodium-dependent in the presence of hypokalemia (3). Thus evidence strongly indicates that hypokalemia contributes to hypertension.

The mechanism of hypokalemia-induced hypertension is not completely clear. One component of this type of hypertension appears to be salt retention (4). Hypokalemia leads to intravascular volume expansion as a result of renal NaCl retention. Hypokalemia may also potentiate the hypertensive effects of various neurohumoral agents (6,7).

Ventricular arrhythmias are a second cardiovascular side-effect of hypokalemia. Several prospective studies show that hypokalemia predisposes patients to the development of a variety of ventricular arrhythmias, including ventricular fibrillation (8). Patients at the highest risk for arrhythmias, the
elderly and those patients with underlying ischemic heart disease, appear to have the highest risk for hypokalemia-related complications (9,10). Diuretic-induced hypokalemia is of particular concern because the incidence of sudden death in hypertensive individuals treated with the thiazide diuretic hydrochlorothiazide is greater than that in matched control subjects (11). The effect is dose-related and is decreased by the concomitant use of potassium-sparing diuretics (11).

**Hormonal**

Hypokalemia impairs both insulin release and end-organ sensitivity to insulin, resulting in worsening hyperglycemia in diabetic patients (12,13). Hyperglycemia and diabetes mellitus are major public health concerns in industrialized nations. Because increasing evidence suggests that end-organ complications from diabetes mellitus are related to the degree of hyperglycemia (14,15), treatment of hypokalemia may decrease the devastating effects of diabetes mellitus.

**Muscular**

Potassium depletion can result in several muscular-related complications (16). Hypokalemia can hyperpolarize skeletal muscle cells, impairing their ability to develop the depolarization necessary for muscle contraction. It can also reduce blood flow to skeletal muscles. The reduced blood flow can predispose patients to rhabdomyolysis (17), especially when vigorous exercise is combined with impaired blood-flow regulation. The combination of these effects frequently leads to muscle weakness, easy fatigability, cramping, and myalgias (16). Paralysis, although uncommon, can occur in cases of profound potassium deficiency (16).

**Acid-Base**

Hypokalemia can profoundly affect systemic acid-base homeostasis through its effects on multiple components of renal acid-base regulation. The most common abnormality is metabolic alkalosis. Hypokalemic metabolic alkalosis results from the effects of hypokalemia on several components of net acid excretion. The most direct effects include stimulation of proximal tubule HCO$_3^-$ reabsorption and ammoniagenesis (18,19); collecting duct proton secretion, possibly via stimulation of both the gastric (HKa$_1$) and colonic (HKa$_2$) isoforms of H$^+$-K$^+$-ATPase (20); and decreasing urinary citrate excretion. Hypokalemia may produce these widespread effects on renal acid-base homeostasis because of intracellular acidification (21). Hypokalemia also inhibits aldosterone secretion (22), which possibly minimizes such effects on acid-base homeostasis. In rare cases, severe hypokalemia leads to respiratory muscle weakness and the development of respiratory acidosis. In patients with hypokalemia as a result of renal tubular acidosis, the concomitant development of respiratory acidosis can be life-threatening.

**Polyuria**

Another complication of hypokalemia is the development of mild polyuria, averaging 2 to 3 liters per day (2). The polyuria is related to both increased thirst and mild nephrogenic diabetes insipidus (23). Increased thirst is associated with increased central nervous system levels of angiotensin II, a hormone that, besides its other effects, regulates thirst. Hypokalemia also impairs the kidney's ability to concentrate the urine maximally (2). This appears to occur because hypokalemia causes defective activation of renal adenylate cyclase, preventing antidiuretic hormone-stimulated urinary concentration (24).

**Renal Cystic Disease**

Hypokalemia, in association with hyperaldosteronism, can lead to renal cystic disease. These cysts appear to arise in the collecting duct epithelium and are frequently associated with interstitial scarring (25). Correcting the hypokalemia leads to cyst regression (25). The mechanism of cyst development is unclear. Hypokalemia leads to increased ammoniagenesis and medullary ammonia accumulation, which may activate the complement system. It has been postulated that hypokalemia, by leading to activation of complement in the medullary interstitium, leads to interstitial fibrosis (26). Consistent with this hypothesis is the observation that bicarbonate supplementation, by inhibiting ammoniagenesis, decreases the interstitial fibrosis associated with hypokalemia; this effect is independent of changes in serum potassium (26).

**Hepatic Encephalopathy**

Hypokalemia can contribute to the development, or worsen the symptoms, of hepatic encephalopathy. One toxin that causes hepatic encephalopathy is ammonia, and hypokalemia increases proximal tubule ammoniagenesis (19). Approximately 50% of proximal tubule ammonia production is returned to the systemic circulation via the renal veins. In hepatic insufficiency, the increased systemic burden of ammonia resulting from increased renal ammoniagenesis can be sufficient to cause the development or worsen the symptoms of hepatic encephalopathy (27).

**Physiology of Potassium Homeostasis**

Serum potassium concentration is a balance between intake, excretion, and distribution between the intra- and extracellular space. The average daily potassium intake in a typical Western diet is 70 mEq. Under normal conditions, excretion equals intake, with approximately 90% of potassium excreted in the urine and the vast majority of the remainder in the stool. Distribution of potassium between the intra- and extracellular space plays an important role in potassium homeostasis.

Most potassium is present in the intracellular space. Intracellular potassium averages 120 to 140 mEq/liter, largely as a result of active potassium uptake by Na$^+$.K$^+$-ATPase. Approximately 98% of total body potassium is present in the intracellular space. Consequently, small changes in the distribution of potassium between the intra- and extracellular fluid spaces result in proportionally large changes in extracellular potassium concentration. The large intracellular potassium store functions to minimize changes in extracellular potassium in states of potassium deficiency. Under these conditions, potassium shifts from the intra- to the extracellular fluid, apparently to reduce changes in the transmembrane potassium.
gradient. With potassium depletion, certain tissues, notably muscle, exhibit a more rapid reduction in intracellular potassium than do others, such as the brain. As a result, small potassium losses minimally affect the serum potassium level. Conversely, the potassium deficit in hypokalemic states that result from potassium loss (excluding pseudohypokalemia and redistribution, as will be discussed below) is very large. For example, a decrease in serum potassium from 3.5 to 3.0 mEq/liter typically indicates a total body potassium deficit of 100 to 300 mEq, and a decrease to 2.0 mEq/liter can indicate a total body deficit of 600 to 800 mEq.

Potassium is present in most foods in varying amounts. Although the typical dietary intake averages 70 mEq/d, there is considerable variation, depending on the dietary preferences of the individual. In the absence of other factors, the body can adapt to a wide range of potassium intake without development of marked hypokalemia. Notably, African Americans commonly eat diets containing less potassium, which may induce a state of physiologic potassium deficiency and contribute to the incidence and severity of hypertension in this population (28,29).

The primary mechanism of potassium excretion is the urine. Potassium is freely filtered at the glomerulus, followed by reabsorption of approximately 85% by the proximal tubule and the loop of Henle (30). Relatively little regulation of potassium reabsorption occurs in these segments, however (30). Instead, the primary site for renal potassium regulation is the collecting duct (31). The CCD both secretes and reabsors potassium, whereas the outer and inner medullary collecting ducts (OMCD and IMCD, respectively) reabsorb potassium (30,31).

At least three cell types are present in the CCD, all of which may contribute to potassium homeostasis. Figure 1 summarizes the transporters involved in CCD potassium transports. The principal cell is the most numerous cell, comprising 60 to 70% of the CCD, and is believed to be responsible for potassium secretion. Potassium is actively taken up into the cell via a basolateral Na\(^+\)-K\(^+\)-ATPase and secreted down its electrochemical gradient into the luminal fluid (urine) via an apical potassium channel. Additional evidence indicates that potassium secretion is codependent on Cl secretion. Electrogenic sodium reabsorption generates a lumen-negative charge or voltage. Because this negative charge increases the electrochemical gradient for potassium secretion, the rate of sodium reabsorption also regulates the rate of potassium secretion.

In contrast to the principal cell, the CCD A- and B-type intercalated cells (A cell and B cell, respectively), which comprise the remainder of the CCD, are modeled to reabsorb luminal potassium. Potassium reabsorption occurs through processes different from those of principal cell potassium secretion. An apical H\(^+\)-K\(^+\)-ATPase secretes protons and reabsorbs luminal potassium, contributing to urinary acidification and potassium reabsorption (31). In the presence of normal potassium, most reabsorbed potassium is recycled across the apical membrane, resulting in little net potassium transport. In response to potassium deprivation, potassium can exit the cell via a basolateral barium-sensitive transporter, presumably a potassium channel (20). This provides a sensitive mechanism that allows active potassium reabsorption when necessary.

Recent studies show that the B cell, generally believed to mediate bicarbonate secretion and recovery from metabolic alkalosis, may also contribute to potassium homeostasis. Results from our laboratories and those of others provide strong functional evidence for an apical H\(^+\)-K\(^+\)-ATPase in this cell (32,33). We have also shown that there is coupling of chloride reabsorption by the apical Cl\(^-\)/HCO\(_3\)\(^-\) exchanger to the apical H\(^+\)-K\(^+\)-ATPase (31). Parallel operation of apical H\(^+\)-K\(^+\)-ATPase and apical Cl\(^-\)/HCO\(_3\)\(^-\) exchange provide a new model for active KCl reabsorption. Additionally, inhibition of H\(^+\)-K\(^+\)-ATPase reduces CCD amiloride-insensitive sodium reabsorption, suggesting that sodium can substitute for potassium on the CCD H\(^+\)-K\(^+\)-ATPase (31). In hypokalemia, the increased CCD H\(^+\)-K\(^+\)-ATPase activity, in combination with sodium substituting for potassium on the H\(^+\)-K\(^+\)-ATPase, could lead to net NaCl reabsorption, volume expansion, and the increased blood pressure that is observed clinically.

The OMCD and IMCD do not transport potassium under normal conditions, but in response to hypokalemia or potassium deficiency can reabsorb potassium. This appears to occur via mechanisms similar to the CCD A cell, e.g., luminal potassium uptake by an apical H\(^+\)-K\(^+\)-ATPase and basolateral potassium exit via a basolateral potassium channel (20). As noted previously, at least two isoforms of H\(^+\)-K\(^+\)-ATPase are present in the collecting duct: HK\(_{α1}\) and HK\(_{α2}\) (20). HK\(_{α1}\) may be regulated to a greater extent by hypokalemia than HK\(_{α2}\) in the CCD, whereas the opposite appears to be true in the OMCD (34,35).

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**Figure 1.** Model of potassium transport in the cortical collecting duct.
Despite the presence of active potassium reabsorptive transporters in the CCD, OMCD, and IMCD, the urinary potassium level is generally not lower than 15 to 20 mEq/liter. This may reflect both water reabsorption, which exceeds potassium reabsorption, and persistent potassium secretion in the CCD.

Little potassium is excreted in the stool under normal conditions because of a low stool volume and a low stool potassium concentration. Conditions that increase stool potassium concentration, such as chronic renal failure and hyperkalemia, or stool volume, such as diarrhea, increase fecal potassium excretion. Chronic renal failure can cause adaptive changes in stool potassium content, such that as much as 20 to 30 mEq/d can be excreted by this route. Decreases in stool potassium content do not materially affect the response to hypokalemia because the basal level of stool potassium excretion is normally small.

Causes

The accurate treatment of hypokalemia requires correct identification of the cause. Hypokalemia can be associated either with normal or decreased total body potassium content. Normal total body potassium with hypokalemia is a result of potassium redistribution from the extracellular to the intracellular space. Total body potassium depletion can result from either renal or extrarenal potassium losses. We suggest that the clinician evaluating a patient with hypokalemia consider four broad groups of etiologies: pseudohypokalemia, redistribution, extrarenal potassium loss, and renal potassium loss.

Pseudohypokalemia

Abnormal white blood cells, if present in large enough numbers, can take up extracellular potassium when stored for prolonged periods at room temperature, resulting in a low measured plasma potassium level. The apparent hypokalemia is an artifact of the storage procedure and is referred to as "pseudohypokalemia" (36). The most common underlying disease state is acute myelogenous leukemia. Rapid separation of the plasma or storing the sample at 4°C confirms the diagnosis, avoids this artifact, and prevents inappropriate treatment.

Redistribution

More than 98% of total body potassium is present in the intracellular fluid, predominantly in skeletal muscle cells, enabling small changes in the distribution of potassium to alter the extracellular concentration markedly. Certain hormones, particularly insulin, aldosterone, and sympathomimetics, are the most common cause of redistribution-induced hypokalemia. Insulin activates Na+-K+-ATPase, which results in active potassium uptake (37). Acute insulin administration produces rapid potassium shifts from the extra- to intracellular space, resulting in hypokalemia. This problem is most frequently encountered in the treatment of diabetic ketoacidosis. Insulin-induced redistribution of potassium is the physiologic principle underlying the administration of insulin with glucose to patients with hyperkalemia. In contrast to acute insulin administration, chronically high insulin levels, as occur in insulinomas, do not typically cause hypokalemia; the mechanism of this "escape" is unknown. The decreased end-organ responsiveness to insulin in adult-onset diabetes may contribute to the hyperkalemia frequently seen by altering the distribution of potassium between the intracellular and extracellular space.

A second, clinically common cause of potassium redistribution is aldosterone. Aldosterone induces cellular uptake of potassium through a variety of effects, but much more slowly than insulin. Aldosterone stimulates the production of Na+-K+-ATPase, which results in increased enzyme activity and the transport of potassium from the intracellular to extracellular space (37-39). In addition, as will be discussed below, aldosterone also regulates renal potassium transport. Thus hyperaldosteronism causes hypokalemia as a result of the combined effects of redistribution and stimulation of renal potassium clearance.

The final major hormonal cause of potassium redistribution includes sympathomimetic agents, β1-adrenergic agonists, dopamine, dobutamine, and theophylline. The first three agents directly stimulate the cellular uptake of potassium and also stimulate insulin release, whereas theophylline indirectly stimulates potassium uptake (36,37). Sympathomimetic-induced redistribution leading to hypokalemia is important in acute myocardial ischemia and acute asthma therapy. Myocardial ischemia commonly increases sympathetic tone, whether as a direct result of the ischemia, decreased cardiac output, or from either the pain or the anxiety related to the ischemia. Cellular potassium redistribution leading to hypokalemia can then increase the risk of ventricular arrhythmia and sudden death. Treatment of the asthma patient with β-adrenergic agonists or theophylline can lead to potassium redistribution, hypokalemia, and impairment of respiratory muscle contractile ability. Patients may develop CO2 retention, or, even more seriously, decreased wheezing, as a result of decreased air movement, which might be misinterpreted as an overall improvement in the patient's condition. Another clinical concern is premature labor therapy involving β-agonists. These patients frequently do not have oral intake for prolonged periods, providing a setting for the development of severe hypokalemia.

Hypokalemia as a result of potassium redistribution can also occur from acute anabolic states. Cells contain approximately 130 mEq/liter of potassium; consequently, stimulation of either cell hypertrophy or cell production can cause rapid movement of potassium from the extracellular to the intracellular space. Rapid cell production can occur in acute leukemia and high-grade lymphomas. Acute stimulation of cell production can result from granulocyte macrophage colony-stimulating factor treatment of refractory anemia or the initial treatment of pernicious anemia with vitamin B12 (40). The resultant cell production can cause acute hypokalemia and in some individuals has resulted in arrhythmias and sudden death (41).

Rarely, hypokalemia secondary to redistribution with enhanced cellular uptake can be a result of hypokalemic periodic paralysis (16,36). Both familial and sporadic cases have been reported. Most hereditary cases follow an autosomal dominant distribution, although an X-linked recessive form has been documented. In Asians there is a high frequency of this condition associated with thyrotoxicosis (16). Attacks frequently
commence during the night or the early morning and are characterized by flaccid paralysis of all extremities, which may persist from 6 to 24 h (36). A genetic defect in a dihydropyridine-sensitive calcium channel has been determined to cause certain cases of this disorder (42). Carbonic anhydrase inhibitors (acetazolamide 250 mg four times daily), beta blockers, or spironolactone may prevent attacks.

Finally, hypokalemia has been reported in connection with chloroquine and barium intoxication. The latter effect can be explained by the known action of barium to block potassium channels and, hence, cellular potassium exit (16).

Non-Renal Potassium Loss

Both the skin and the gastrointestinal tract can transport significant amounts of potassium. Under normal conditions, net fluid loss from these organs is small, limiting net potassium loss. Occasionally, in cases such as prolonged exertion in hot, dry environments or chronic diarrhea, severe potassium loss can occur, leading to hypokalemia (43). In most of these cases, intravascular volume depletion is present also, leading to secondary hyperaldosteronism, stimulation of renal potassium excretion, and further worsening of the potassium deficit (43).

Prolonged loss of gastric contents, whether from vomiting or nasogastric suctioning, can lead to hypokalemia. A small part of this potassium loss is direct because these body fluids contain 5 to 8 mEq/liter potassium. More importantly, concomitant alkalosis and intravascular volume depletion contribute to renal potassium loss. Metabolic alkalosis results in bicarbonaturia, which increases potassium excretion both directly, as a cation to balance the negative charge of bicarbonate ions, and indirectly, through stimulation of urinary sodium excretion, leading to worsening of intravascular volume depletion and stimulation of the renin-angiotensin-aldosterone system. In addition, potassium reabsorption by the collecting duct is affected by acid-base status. Thus metabolic alkalosis increases renal potassium excretion by increasing potassium secretion and probably by direct suppression of potassium reabsorption.

Diarrhea, whether secretory or as a result of laxative abuse, can cause profound gastrointestinal potassium loss. Patients with laxative abuse may deny the condition because of overconcern about body image and may also abuse diuretics (44). Sigmoidoscopy and urine screening for diuretics may be needed to confirm the diagnosis. The former will reveal melanosis coli in patients who have been using anthracene laxatives, such as senna, cascara and aloe, for more than 4 months (45). If phenolphthalein laxatives are being used, alkalinization of the stool to pH 9 will produce a pink color. If magnesium or phosphate-containing cathartics, such as magnesium citrate or sodium phosphate, are suspected, direct measurement of these compounds in the stool can confirm the diagnosis.

Renal Potassium Loss

The most common cause of hypokalemia is excess renal potassium loss. This can occur either because of medications, endogenous hormone production or, in rare conditions, intrinsic renal defects. Table 1 summarizes these causes.

Table 1. Causes of renal potassium loss

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Drugs. Many medications can cause renal potassium wasting, including diuretics and some antibiotics. Both thiazide and loop diuretics increase urinary potassium excretion; when factored for their natriuretic effect, thiazide diuretics are more potent kaliuretic agents (46). In part this is because loop diuretics have a shorter pharmacologic half-life, enabling renal potassium conservation during periods between drug administration, but may also reflect their site of action in the distal convoluted tubule with secondary effects on flow to the primary site of potassium secretion in the CCD. All diuretics, except the potassium-sparing diuretics, induce potassium-wasting by increasing CCD luminal flow rate, luminal sodium delivery, and luminal electronegativity, which are the primary determinants of potassium secretion by the CCD. They may also induce intravascular volume contraction, resulting in secondary hyperaldosteronism and further stimulation of renal potassium secretion. The incidence of diuretic-induced hypokalemia is both dose- and treatment duration–related.

Antibiotics can increase urinary potassium excretion by a variety of mechanisms. High-dose penicillin and some penicillin analogues, such as carbenicillin, oxacillin, and ampicillin, increase distal tubular delivery of a non-reabsorbable anion, thereby increasing urinary potassium excretion (47). Cisplatin is another drug that may induce hypokalemia via an increase in renal potassium excretion. Polyene antibiotics, such as ampho-
tericin B, create cation channels in the apical membrane of collecting duct cells, which increases potassium secretion and results in potassium wasting (36). Toluene exposure, which can result from sniffing certain glues, can also cause hypokalemia, presumably by renal potassium wasting (2). Aminoglycosides can cause hypokalemia either in the presence or absence of overt nephrotoxicity. The mechanism is not completely understood but may relate to stimulation of magnesium depletion (see below) (36) or direct inhibition of potassium reabsorption. However, most antibiotics do not cause hypokalemia, and some, such as trimethoprim and pentamidine, can cause hyperkalemia by inhibition of apical sodium channels in the CCD.

**Endogenous hormones.** Endogenous hormones are very important causes of hypokalemia. Aldosterone is perhaps the most important hormone regulating total body potassium homeostasis, and excess aldosterone production or effect frequently leads to hypokalemia. The CCD is the primary site in the kidney where aldosterone regulates potassium transport, and the CCD principal cell is the CCD cell responsible for potassium secretion (30,31). Aldosterone increases principal cell apical sodium conductance, basolateral Na⁺-K⁺-ATPase activity, and electrogenic sodium absorption in the CCD. These effects increase the net luminal-negative charge or transepithelial voltage, which increases the electrochemical gradient for potassium movement from the principal cell cytoplasm to the luminal fluid. Thus aldosterone, via actions on apical Na⁺ channels and basolateral Na⁺-K⁺-ATPase, increases CCD principal cell potassium secretion. Although potassium reabsorption is absent in the OMCD and IMCD (31), the reabsorptive capacity of these segments, particularly with normal Na intake, is less than the rate of potassium secretion by the CCD. Thus the net effect of aldosterone is to enhance renal potassium clearance.

Hyperaldosteronism can be either primary or secondary. Primary hyperaldosteronism results in cases of hypertension (48), predominantly because of the sodium-retaining effects of aldosterone, but the associated hypokalemia may also contribute by sensitizing the vasculature to neurohumoral regulators of blood pressure. Because angiotensin II regulates adrenal gland aldosterone synthesis, conditions involving elevated angiotensin II levels will typically involve hyperaldosteronism. This may occur in a variety of conditions, such as decreased oral intake, diuretic use, vomiting, or diarrhea. Activation of the renin-angiotensin-aldosterone system, as may occur in malignant hypertension (49), renovascular hypertension (50), and renin-secreting tumors (51), can also lead to secondary hyperaldosteronism with subsequent hypokalemia. The secondary activation of the renin-angiotensin-aldosterone system suggests that potassium redistribution significantly contributes to the hypokalemia.

Rarely, genomic defects lead to excessive aldosterone production. In glucocorticoid-remediable aldosteronism, an adrenocorticotropic (ACTH)-regulated gene is linked to the coding sequence of the aldosterone synthase gene, the rate-limiting enzyme for aldosterone synthesis (52). Aldosterone synthase is no longer regulated by the renin-angiotensin system, and excessive aldosterone production ensures. In congenital adrenal hyperplasia, there is the congenital absence of either 11β-hydroxylase or 17α-hydroxylase, resulting in excess hypothalamic corticotropin-releasing hormone (CRH) secretion and persistent adrenal synthesis of 11-deoxycorticosterone, a potent mineralocorticoid (53). This condition can be recognized by the associated effects on sex steroid production. 11β-hydroxydylase deficiency results in increased androgen production, leading to early virilization of men and women. In contrast, 17α-hydroxylase deficiency inhibits sex hormone metabolism, leading to incomplete development of sexual characteristics.

Under rare conditions, glucocorticoids function as mineralocorticoids, causing hypokalemia and hypertension. Glucocorticoids, such as cortisol, have a high affinity for the mineralocorticoid receptor but are normally prevented from binding to it because the enzyme 11β-hydroxysteroid dehydrogenase (11β-HSDH) converts cortisol to cortisone, which does not bind to the mineralocorticoid receptor (54). Some drugs, such as glycercethinic acid (found in carbeneplone, chewing tobacco, and licorice), inhibit 11β-HSDH, allowing cortisol to exert mineralocorticoid-like effects in the distal nephron (55). Infrequently, circulating cortisol can exceed the metabolic capacity of 11β-HSDH and cause hypokalemia. This can occur either in severe cases of Cushing’s disease or in the ectopic ACTH syndrome (56).

**Magnesium depletion.** Concomitant magnesium deficiency may prevent correction of hypokalemia (36). This is particularly true with diuretic-induced hypokalemia and in certain cases of aminoglycoside- and cisplatin-induced potassium wasting, hypokalemia associated with lysozymuria in acute leukemia, and in individuals with Gitelman’s syndrome (see below). Supplementation with magnesium oxide, 250 to 500 mg by mouth four times daily, may serve to correct both the magnesium and potassium deficiency.

**Intrinsic renal defects.** Intrinsic renal defects leading to hypokalemia are rare but have led to important advances in our understanding of renal solute transport. In 1962, Bartter described the association of hypokalemia, hypomagnesemia, hyperreninemia, and metabolic alkalosis (57). Recent studies show that these patients can be divided into two groups now known as either Bartter’s syndrome or Gitelman’s syndrome. Patients with Bartter’s syndrome are hypercalciciuric and present at an early age with severe volume depletion. This condition appears to be a result of defects in either the renal Na-K-2Cl cotransporter gene, NKCC2 (58), or the ATP-sensitive potassium channel, ROMK, both of which are necessary for loop of Henle sodium reabsorption (59). Gitelman’s syndrome features hypocalciuria, hypomagnesemia, and milder clinical manifestations and presents at a later age. This syndrome appears to be a result of mutations in the thiazide-sensitive NaCl cotransporter (60). Both Bartter’s syndrome and Gitelman’s syndrome are associated with hypotension and intravenous volume depletion due to renal sodium-wasting. In contrast, Liddle’s syndrome is associated with hypertension, hypokalemia, metabolic alkalosis, and suppressed renin and aldosterone levels (61). This condition appears to be a result of defects in the CCD principal cell apical sodium channel, ENaC, leading to an
increased open probability, excessive sodium reabsorption, and subsequent volume expansion, hypertension, and suppression of renin and aldosterone (62). Renal potassium wasting occurs because increased CCD sodium reabsorption leads to increased luminal electronegativity and an increased electrochemical gradient for potassium secretion.

Bicarbonaturia. The last major cause of renal potassium wasting is bicarbonaturia. Bicarbonaturia can result from either metabolic alkalosis, distal renal tubular acidosis, or treatment of proximal renal tubular acidosis. In each case, distal tubular bicarbonate delivery increases potassium secretion. Certain cases of distal renal tubular acidosis may reflect primary defects in potassium reabsorption.

Diagnostic Approach
In approaching the patient with hypokalemia, we recommend using the approach outlined above. Figure 2 summarizes our diagnostic algorithm. First, ensure that pseudohypokalemia, due to potassium uptake by abnormal leukocytes, is not responsible for the reported reduction in serum potassium. Second, consider whether redistribution of potassium from the extracellular to the intracellular space accounts for the hypokalemia. If neither of these possibilities is present, the hypokalemia probably represents total body potassium depletion resulting from either skin, gastrointestinal (GI) tract, or renal potassium loss. Excessive potassium loss from the skin results from prolonged exertion in hot, dry environments where sweat loss is high. This diagnosis can be readily made from the history under most conditions. GI tract potassium loss occurs from either diarrhea, vomiting, nasogastric suction, or a GI fistula. Occasionally, patients may be reluctant to admit to self-induced diarrhea from cathartic use, and the diagnosis may need to be confirmed by sigmoidoscopy or direct testing of the stool. Renal potassium loss is most frequently a result of diuretic use. Secondary hyperaldosteronism from cardiac or hepatic disease or a nephrotic syndrome is a common cause of renal potassium loss. Hypomagnesemia-induced hypokalemia causes renal potassium wasting and is frequently a complication of diuretic useage. Rarer causes of renal potassium loss include renal tubular acidosis (RTA), diabetic ketoacidosis, and ureterosigmoidostomy. Finally, primary aldosteronism, surreptitious diuretic use, and either Bartter’s or Gitelman’s syndrome may need to be considered.

Correction
The risks associated with hypokalemia must be balanced against the risks of therapy when the appropriate approach to the patient is determined. Usually, the primary short-term risks are cardiovascular, and the most important is the proarrhythmogenic effect of hypokalemia. In contrast, the primary risk of overaggressive replacement is the development of hyperkalemia with resultant ventricular fibrillation. Occasionally, incorrect therapy of hypokalemia can lead to paradoxical worsening of the hypokalemia.

Conditions requiring emergent therapy are rare. The classic causes include severe hypokalemia in a patient preparing to undergo emergent surgery, particularly in patients with known coronary artery disease or on digitalis treatment, and the patient with an acute myocardial infarction and significant ventricular ectopy. In such cases, administration of 5 to 10 mEq of KCl over 15 to 20 min may be used to increase serum potassium to a level above 3.0 mEq/liter. This dose can be repeated as needed. Close, continuous monitoring of the serum level and the electrocardiogram (ECG) are necessary to reduce the risk of hyperkalemia.

In most other conditions, the choice of parenteral versus oral therapy is dependent on the ability of the patient to take oral medication and the ability of the GI tract to function appropriately. In many cases, such as myocardial infarction, paralysis, and hepatic encephalopathy, the patient may be unable to take oral potassium safely or questions may exist about the speed of GI tract absorption. In these cases, KCl can be given intravenously. When given via the intravenous (IV) route, replacement can be given safely at a rate of 10 mEq KCl per hour. One study has found that 20 mEq KCl per hour causes the serum potassium level to increase by an average of 0.25 mEq/L per hour (63). If more rapid replacement is necessary, then 40 mEq per hour can be administered through a central catheter with continuous ECG monitoring. However, replacement therapy should be administered orally if possible.

The parenteral fluids used for potassium administration can affect the response. In nondiabetic patients, IV dextrose increases serum insulin levels, which can cause redistribution of potassium from the extra- to the intracellular space. As a result, providing KCl in glucose solutions such as D3W can paradoxically lower serum potassium levels (64). In most cases, parenteral KCl should be provided in normal saline. If large concentrations of KCl are added to the parenteral fluid, then KCl might be administered in half normal saline to avoid administration of a hypertonic solution.

Usually hypokalemia can be treated successfully with oral therapy. Patients with diuretic-induced hypokalemia should be re-evaluated to reconsider the need for diuretics. If continual use is required, assessment of sodium intake should be performed. Excessive sodium intake accentuates diuretic-induced hypokalemia. If this is not the case concomitant use of the potassium-sparing diuretics amiloride, triamterene, and spironolactone may be considered. When oral replacement therapy is required, KCl is the preferred drug in all patients except those with metabolic acidosis. In the latter condition, either potassium bicarbonate or potassium citrate should be used. The chloride salt of potassium minimizes renal potassium losses. If indicated for other reasons, beta blockers or angiotensin-converting enzyme inhibitors can assist in maintaining potassium levels.

Finally, hypomagnesemia can lead to renal potassium wasting and refractoriness to potassium replacement (36). In these patients, correction of the hypokalemia does not occur until the hypomagnesemia is corrected (65). Patients with diuretic-induced hypokalemia, unexplained hypokalemia, or diuretic-induced hypokalemia should have their serum magnesium levels checked and magnesium replacement therapy begun if indicated.
Figure 2. Diagnostic evaluation of hypokalemia.

**Diagnostic evaluation of hypokalemia**

\( K < 3.5 \text{ mEq/L} \)

- **Pseudohypokalemia**
  - K after rapid separation of plasma and storage at 4 degrees
  - WBC count
    - \( > 50,000 \)
    - \( < 50,000 \)
  - Normal
    - No
  - Low
    - Yes

- **Redistribution or hypokalemic periodic paralysis**
  - Skin, GI or Renal K loss
    - Skin vs GI tract K loss
      - Prolonged exertion in hot environment?
        - Yes
          - Skin Loss
        - No
          - Diarrhea or GI fistula?
            - Yes
              - GI K Loss
            - No
              - Inadequate dietary potassium intake or diuretic use recently discontinued
                - Yes
                  - Hypomagnesemia-induced hypokalemia
                - No
                  - NG suction, surreptitious vomiting or diuretic use, and, more rarely, Bartter's or Gitelman's syndromes

- **Probable diuretic-induced hypokalemia**
  - Recent diuretic use?
    - Yes
      - CHF, hepatic insufficiency, nephrotic syndrome or renal artery stenosis?
        - Yes
          - Probable secondary hyperaldosteronism
        - No
          - Hypomagnesemia?
            - Yes
              - Serum bicarbonate?
                - Normal or high
                  - RTA, DKA or ureterosigmoidostomy
                - Low
                  - Possible primary hyperaldosteronism
            - No
              - Blood pressure?
                - Low
                  - NG suction, surreptitious vomiting or diuretic use, and, more rarely, Bartter's or Gitelman's syndromes
                - High
                  - Probable secondary hyperaldosteronism

References