

Approach to Hypokalemia

Salim Lim

ABSTRACT

Hypokalemia is frequently encountered in clinical practice. It can be due to either potassium deficiency (inadequate potassium intake or excessive potassium loss) or to net potassium shifts from the extracellular to the intracellular compartment. Inadequate dietary intake of potassium alone rarely causes hypokalemia since kidney is able to lower potassium excretion below 15 mmol per day. Hypokalemia due to excessive potassium loss can be due to renal or extrarenal losses. It is not necessary to wait for a timed urine collection for potassium to determine the etiology of hypokalemia. Measurement of spot urine for potassium and creatinine as well as evaluation of acid-base status can be used as an initial step in the diagnosis of hypokalemia. Subsequent evaluations such as measurement of spot urinary chloride, blood pressure, serum aldosterone, renin and cortisol levels may be needed in certain circumstances.

Key words: hypokalemia, potassium shift, potassium loss, metabolic acidosis, metabolic alkalosis.

INTRODUCTION

To a large extent, distribution of potassium in the body follows the distribution of water. Water comprises approximately 60% of body weight in men and 55% in women. Total body water is distributed in two major compartments: two-thirds is intracellular and one-third is extracellular. Potassium is the major intracellular cation. The normal serum K⁺ concentration is 3.5 to 5.0 mmol/l; whereas that inside cell is about 150 mmol/l. Total body K⁺ is about 3500 mmol. Approximately 98% of the total K⁺ is located intracellular, primarily in skeletal muscle and to a lesser extent in liver (60 x 0.58 x 2/3 x 150 = 3480 mmol). The remaining 1 to 2% is located extracellular (60 x 0.58 x 1/3 x 4.5 = 52 mmol). The ratio of intracellular to extracellular potassium (K_i/K_e) is the major determinant of resting membrane potential. It is regulated primarily by the Na⁺/K⁺-

ATPase pump located on the plasma membrane of most cells. Although only 2% of total body K⁺ is located extracellular, a small change in extracellular K⁺ has a major effect on the ratio of K_i/K_e and through that on the resting membrane potential. As a result, serum K⁺ concentration is normally regulated around the narrow range of 3.5–5.0 mmol/l.

CLINICAL MANIFESTATIONS OF HYPOKALEMIA

Hypokalemia is often asymptomatic, particularly when the disorder is mild. Hypokalemia appears to increase the risks of cardiac arrhythmias in patients with ischemic heart disease or patients taking digoxin. Patients with more severe hypokalemia (serum K⁺ less than 3 mmol/l) usually present with generalized weakness, fatigue and constipation. In some cases, life-threatening cardiac arrhythmias and weakness of the respiratory muscles can develop. In addition, severe hypokalemia can precipitate rhabdomyolysis and impair urinary concentrating mechanism. Moderate and severe hypokalemia can induce electrocardiographic changes, including a prominent U wave, a flattened T wave, and a widened QRS complex. The presence of a U wave is not specific for hypokalemia since it can also be a normal finding.

APPROACH TO HYPOKALEMIA

The kidney can avidly conserve K⁺, such that hypokalemia due to inadequate K⁺ intake is a rare event requiring prolonged starvation over several months (tea and toast diet). Therefore, hypokalemia is usually the result of K⁺ depletion induced by abnormal losses of K⁺ from the gut or the urine. Less frequently, hypokalemia occurs because of an abrupt transcellular shift of K⁺ from the extracellular to intracellular compartment. The most common causes of hypokalemia in clinical practice are due to drugs including diuretics and gastrointestinal loss secondary to diarrhea and/or vomiting. These etiologies should, therefore, be considered first before exhaustive work-up is initiated.

Several drugs and conditions can induce hypokalemia due to transcellular shift of K⁺ (Table

Department of Internal Medicine, Mobile Field Lingga Hospital, Province of Riau Archipelagos

Table 1. Condition or Drugs Causing Hypokalemia due to Transcellular Potassium Shift

Catecholamines: Epinephrine, Dopamine, Dobutamine
Stress-induced catecholamines release (e.g. coronary ischemia, delirium tremens, sepsis)
Bronchodilators : Albutero I, Salbutamol, Terbutaline
Exogenous Insulin
Phosphodiesterase inhibitors: Theophylline, Caffeine
Chloroquine intoxication
Verapamil intoxication
Barium poisoning
Cesium salts
Risperidone, Quetiapine
Hypothermia
Therapy of megaloblastic anemia
Transfusion of frozen red blood cells
Alkalosis
Familial and thyrotoxic hypokalemic periodic paralysis

1). Beta 2-adrenergic agonists (such as salbutamol, dobutamine, terbutaline) used to treat asthma, heart failure or to prevent premature labor can acutely lower serum K^+ concentration by more than 0.5 to 1 mmol/l.^{1,2} The release of epinephrine during a stress response such as coronary ischemia, delirium tremens, and sepsis can also acutely lower the serum K^+ concentration. In these settings of catecholamine surge, hypokalemia may be exacerbated by a rise in insulin levels. Acute insulin administration as encountered in the treatment of diabetes ketoacidosis, stimulates cellular K^+ uptake and can lead to hypokalemia. By increasing Na^+/K^+ -ATPase activity through inhibition of cellular phosphodiesterase and the degradation of cyclic AMP, theophylline and caffeine stimulates K^+ uptake, resulting in hypokalemia. Severe hypokalemia is an almost invariable feature of acute theophylline toxicity.³ Ingestion of large amounts of chloroquine can also cause hypokalemia, by inhibiting K^+ from exiting cells.⁴ Verapamil intoxication has also been described to cause severe hypokalemia.⁵ Barium poisoning from the ingestion of soluble barium salts results in severe hypokalemia by blocking channels for exit of K^+ from cells.⁶ Patients undergoing radiographic procedures are not at risk for this complication since the barium sulfate used in these studies does not enter the systemic circulation. Severe hypokalemia has also been described with the use of cesium salts prescribed as part of an alternative therapy regimen for malignancy.⁷ Its mechanism of action appears to be blockade of K^+ channels. Patients usually present with prolonged QT interval, hypokalemia and Torsade de Pointes. Toxic ingestion of risperidone or quetiapine have also been reported to cause hypokalemia, presumably as a result of cell shift.⁸ Accidental hypothermia can drive K^+ into the cells and cause hypokalemia. Therapy of

megaloblastic anemia is associated with K^+ uptake by newly formed cells, which is occasionally of sufficient magnitude to cause hypokalemia.⁹ Hypokalemia can also occur after the transfusion of previously frozen washed red blood cells, presumably because of the uptake of K^+ by these cells.¹⁰ Metabolic alkalosis can promote potassium entry into cells in exchange for hydrogen ions that leave the cells to minimize the change in extracellular pH. Extreme leukocytosis (white blood cells > 100,000 /ul) can take up K^+ when blood sample is stored for prolonged periods at room temperature. The most common underlying etiology is acute myelogenous leukemia. Patients with pseudohypokalemia do not have clinical manifestations of hypokalemia, as their in vivo serum K^+ values are normal. Differentiating between pseudohypokalemia and true hypokalemia requires rapid separation of the plasma from the cells or storing the blood sample on ice.

Before evaluating the etiology of hypokalemia, it is important first to address the potential emergency of moderate to severe hypokalemia (serum K^+ less than 3.0 mmol/l). Patients with moderate to severe hypokalemia are at increased risk of life-threatening cardiac arrhythmias and respiratory muscles weakness, especially if there is a need for increased ventilation (e.g., metabolic acidosis). This possible threat is best evaluated by examining the electrocardiogram (ECG) and arterial PCO_2 . If the ECG doesn't reveal life-threatening arrhythmias and arterial PCO_2 is not elevated, then further diagnostic evaluation can be performed without jeopardizing the safety of the patients.

Most commonly information obtained from history (vomiting or diarrhea) and review of patient's medications (especially diuretic use) is sufficient in making the diagnosis of hypokalemia. In some cases, however, the etiology of hypokalemia is not apparent and additional laboratory tests may be needed. The first step to evaluate the etiology of hypokalemia is to exclude pseudohypokalemia and conditions or drugs causing transcellular K^+ shift. (Figure 1) The next step is to assess renal K^+ excretion, which will allow us to determine whether hypokalemia is due to renal or extrarenal causes. Random measurement of the urinary K^+ concentration can be used, but may be less accurate since its value depends on the urine concentration. Despite this shortfall, in the absence of severe polyuria, a random urinary K^+ concentration of less than 20 mmol/l indicates renal K^+ conservation. A 24-hr urine collection for K^+ can be used to assess renal K^+ handling. A value of less than 20 mmol/24-hr urine specimen suggests appropriate renal conservation of K^+ , while values above that indicate some degree of renal wasting.

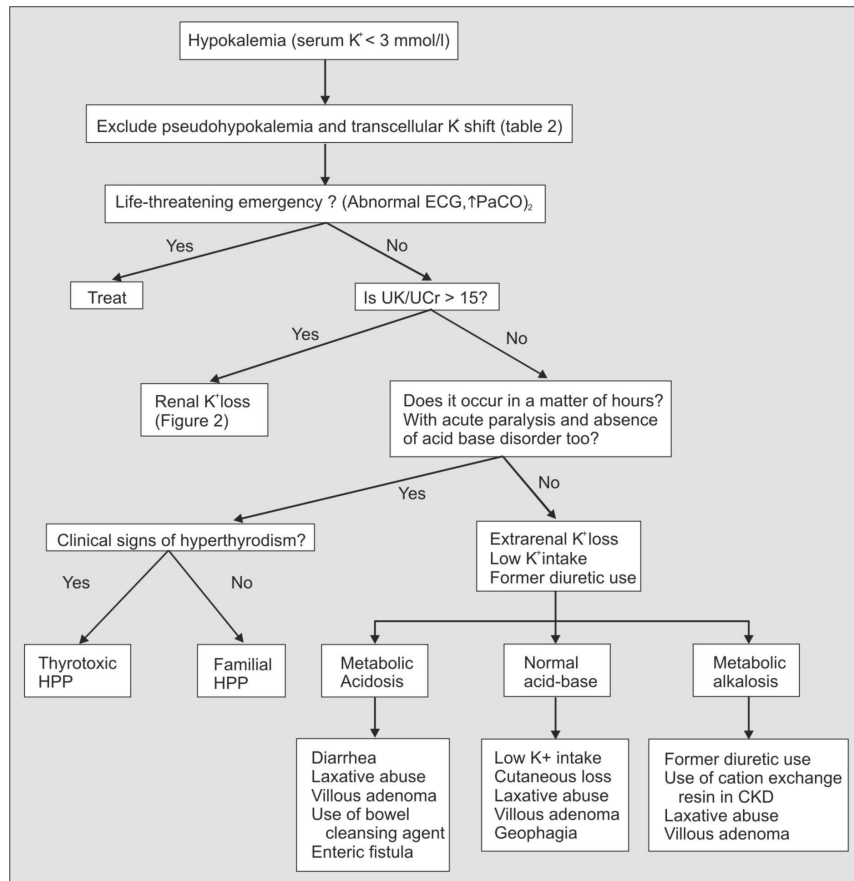


Figure 1. Diagnostic approach to hypokalemia

However, 24-hr urine collection is inconvenient and time consuming. It can also be subject to error if urine is collected incompletely. In addition, if 24-hr urine collection is performed while the patient is receiving large amount of K^+ , some of the administered K^+ will be excreted by the kidney causing urinary K^+ excretion to be deceptively high. Study has shown that the kidney can excrete approximately half of the administered K^+ in the first 6 hours.¹¹ Therefore, it is not necessary or desirable to wait for a timed urine collection for this purpose; the same information can be obtained by comparing the urinary K^+ concentration (UK) to the concentration of urinary creatinine (UCr), which is excreted at a constant rate.¹² A random UK/UCr ratio (mmol/g) > 15 suggests a renal cause, whereas a ratio < 15 suggests an extrarenal cause of hypokalemia.¹³

Hypokalemia with low rate of K^+ excretion (UK/UCr ratio < 15 mmol/g) can be due to transcellular K^+ shift into cells, extrarenal K^+ loss, low K^+ intake or former renal K^+ loss. If hypokalemia is accompanied with acute paralysis, which occurs in a matter of hours, rather than

days or weeks, hypokalemic periodic paralysis (HPP) should be suspected. The diagnosis is further supported if the attacks of paralysis are precipitated by rest after strenuous exercise, stress (β -adrenergic agonists activate Na^+/K^+ -ATPase), or high carbohydrate meals (high insulin levels).¹⁴ During an acute attack, serum K^+ can fall to as low as 1.5 to 2.5 mmol/l. The familial disorder is an autosomal dominant disease that is due to either mutations in the skeletal muscle dihydropyridine-sensitive calcium channel α_1 subunit gene (CACNA1S) or mutations in the skeletal muscle sodium channel SCN4A.¹⁵ The acquired form of periodic paralysis is typically seen in Asians, some of whom have hyperthyroidism.¹⁶ Thyroid hormone increases Na^+/K^+ -ATPase activity, which leads to influx of K^+ into cells. The activity of this pump is increased further by catecholamines, which are typically increased in this setting. Although the hypokalemia is caused by a shift of K^+ into cells, the administration of K^+ can be lifesaving and should be given to treat acute attacks. However, excess K^+ administration may lead to posttreatment rebound hyperkalemia as K^+ moves back out of the cells. In

addition, patients with periodic paralysis exhibit an exaggerated insulin response to carbohydrate loads and therefore, K^+ should not be given in dextrose-containing solutions.¹⁷ Administration of a large dose of a non-specific β -adrenergic receptor blocker (propranolol 3 mg/kg) has also been shown to quickly reverse both the paralysis and the hypokalaemia.¹⁸ Distal renal tubular acidosis (dRTA) needs to be considered when evaluating a patient with hypokalemia and paralysis. Muscle paralysis in this disorder can begin insidiously with weakness evolving gradually over a 24- to 48-hr time period to complete flaccid quadriplegia. It is quite common that clinical features alone are insufficient to differentiate among thyrotoxic HPP, familial HPP and dRTA.

HYPOKALEMIA DUE TO EXTRARENAL LOSS

If hypokalemia with low rate of K^+ excretion (UK/UCr ratio < 15 mmol/g) is not accompanied by acute paralysis, the hypokalemia is most likely due to extrarenal K^+ loss, low K^+ intake or former renal K^+ loss. Evaluation of acid-base status can help to differentiate among these disorders. Hypokalemia due to villous adenoma or laxative abuse may be associated with metabolic acidosis, alkalosis, or no acid-base disturbance. Stool has a relatively high K^+ (80-90 mmol/l) and HCO_3^- concentration. As a result, loss of these secretions (as in diarrhea) typically leads to metabolic acidosis and hypokalemia. However, some patients with a villous adenoma or factitious diarrhea due to laxative abuse develop metabolic alkalosis.¹⁹ Hypokalemia has also been described with the use of oral sodium phosphate solution as a bowel cleansing agent.²⁰ This most likely occurs among the elderly and those with bowel obstruction, poor gut motility and unrecognized renal disease. Since intestinal secretions contain a relative high HCO_3^- concentration, an enteric fistula typically leads to HCO_3^- loss and metabolic acidosis.

Patients with diuretic abuse can present with metabolic alkalosis and low rate of K^+ excretion if urinary collection is obtained after the diuretic effect has worn off. In this circumstance, urinary K^+ concentrations may be deceptively low despite renal K^+ losses. The diagnosis of diuretic induced-hypokalemia can be challenging if the drug is used surreptitiously. The diagnosis can be confirmed with urine diuretic screens.

Hypokalemia due to low K^+ intake, cutaneous K^+ loss and geophagia is usually associated with low renal K^+ excretion with normal acid-base status. Inadequate K^+ intake is a rare cause of hypokalemia. It requires prolonged starvation over several months (tea and toast diet). Significant loss of K^+ in sweat sufficient to

cause hypokalemia is uncommon since the volume of sweat is low and the K^+ concentration is only 5 mmol/l. However, hypokalemia may occur in the setting of intense exercise in a hot, humid environment. Habitual ingestion of clay (geophagia) can result in K^+ depletion by binding K^+ in the gut. Clay ingestion during pregnancy is occasionally found in the rural southeastern United States.²¹

HYPOKALEMIA DUE TO RENAL LOSS

Once high rate of K^+ excretion has been confirmed (UK/UCr ratio > 15), the next step of investigation is evaluation of acid base status. (Figure 2) Patients with hyperchloremic metabolic acidosis are divided in two groups based on the rate of ammonium (NH_4^+) excretion. Those with a low rate of NH_4^+ excretion have a renal acidification defect, whereas those with a high rate of NH_4^+ excretion has a normal renal acidification. There are two ways to assess NH_4^+ excretion rate: urine anion gap (UAG) and urine osmolal gap (UOG). The UAG is calculated as the sum of urine Na^+ plus K^+ minus urine Cl^- . The UAG represents an indirect estimate of urinary NH_4^+ excretion.²² In the face of metabolic acidosis, the kidney increases the amount of NH_3 synthesized to buffer the excess H^+ , and NH_4Cl excretion increases. The increased unmeasured NH_4^+ thus increases the measured anion Cl^- in the urine, and the net effect is a negative UAG, representing a normal response to systemic acidification. Thus, the finding of a positive UAG in the face of hyperchloremic metabolic acidosis points toward a renal acidification defect (e.g., dRTA). The reliability of the UAG is reduced when other unmeasured anions (e.g., ketones, hippurate) are present in the urine in increased amounts. The UAG will be positive or zero despite the fact that renal acidification and NH_4^+ are increased. The UOG is another method of indirect estimation of NH_4^+ excretion.²³ The UOG is the difference between the calculated and measured urine osmolality. The calculated urine osmolality equals $2(Na^+ + K^+) + urea + glucose$, with all constituents of urine expressed in mmol/l. Urine NH_4^+ concentration is equal to half of the UOG. If the UOG exceeds 100 mmol/l, urine NH_4^+ excretion is increased. The use of the UOG to estimate urine NH_4^+ concentration is less subject to error because it remains valid when the urine contains high concentrations of anions other than chloride (e.g., ketones, hippurate). Profound potassium wasting is a major side effect of treatment with amphotericin B.²⁴ Amphotericin B also causes magnesium depletion, which further contribute to renal K^+ wasting. Treatment with Amphotericin B has also been described to cause dRTA.²⁴

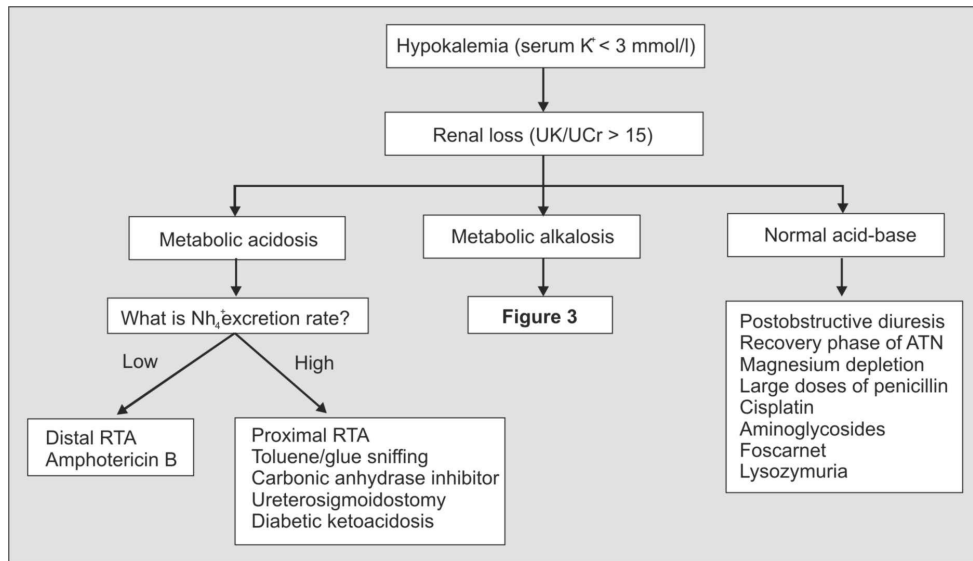


Figure 2. Diagnostic approach to hypokalemia due to renal loss

The probable causes of hypokalemic metabolic acidosis with a high NH_4^+ excretion rate include proximal RTA, toluene/glue sniffing, carbonic anhydrase inhibitor, ureterosigmoidostomy and diabetic ketoacidosis. Proximal RTA is caused by an impairment of proximal bicarbonate reabsorptive capacity and is characterized by a decreased renal HCO_3^- threshold to approximately 15 mmol/l. Once the serum HCO_3^- falls below this level, the fractional excretion of HCO_3^- falls off to normal levels and urinary pH usually drops below 5.5, as distal acidification is still intact. However, when serum HCO_3^- concentration is normalized by administration of alkali, the kidney can't absorb the increased load of filtered HCO_3^- above its proximal reabsorptive capacity. The ensuing marked delivery of sodium and water to distal tubules leads to K^+ wasting.²⁵ Toluene ingestion or glue sniffing can be confused with dRTA. Toluene ingestion also causes normal anion gap hypokalemic metabolic acidosis with positive UAG.²⁶ Ingested toluene is metabolized to hippuric acid, which then dissociates into H^+ and hippurate anion. H^+ is titrated by HCO_3^- . The hippurate anion is excreted in the urine, initially with NH_4^+ and then with Na^+ and K^+ when the capacity to excrete NH_4^+ is exceeded. The excretion of hippurate anions with Na^+ and K^+ (and not NH_4^+) is a major factor in the development of hypokalemia and metabolic acidosis. Carbonic anhydrase inhibitor such as acetazolamide results in an acquired form of proximal RTA by impeding hydrogen-linked Na^+ reabsorption in the proximal tubulus and thus causes a metabolic acidosis and hypokalemia. Ureterosigmoidostomy results in hypokalemia

in 10% to 35% of patients, owing to the sigmoid colon's capacity for net K^+ secretion. Diabetic ketoacidosis commonly increases urinary K^+ excretion due to osmotic diuresis with high urinary flow rate and high distal delivery of Na^+ . Despite renal K^+ wasting, patients may initially present with a normal serum K^+ value, owing to altered transcellular K^+ distribution.

Hypokalemia is occasionally observed after relief of acute obstructive uropathy or during the polyuric recovery phase of acute tubular necrosis (ATN), presumably secondary to increased delivery of sodium and water to the distal nephrons. Magnesium depletion can cause severe hypokalemia by increasing renal K^+ loss. The exact mechanism is, however, remains unclear. The ability to correct K^+ deficiency is impaired when magnesium deficiency is present. Magnesium repletion improves the coexistent potassium deficit.²⁷ Penicillin in large doses acts as a poorly reabsorbable anion, promotes renal K^+ wasting by increasing distal sodium delivery.²⁸ Aminoglycosides, cisplatin and foscarnet cause renal K^+ wasting by inducing magnesium depletion.²⁹ Patients with acute monocytic and myelomonocytic leukemias occasionally excrete large amounts of lysozyme in their urine. Lysozyme appears to have a direct kaliuretic effect on the kidneys (by an undefined mechanism).³⁰

HYPOKALEMIA DUE TO RENAL LOSS WITH METABOLIC ALKALOSIS

Determination of urinary chloride will be helpful in differentiating the causes of hypokalemia due to renal loss with metabolic alkalosis. (Figure 3) Patients with hypokalemia due to renal loss with metabolic alkalosis

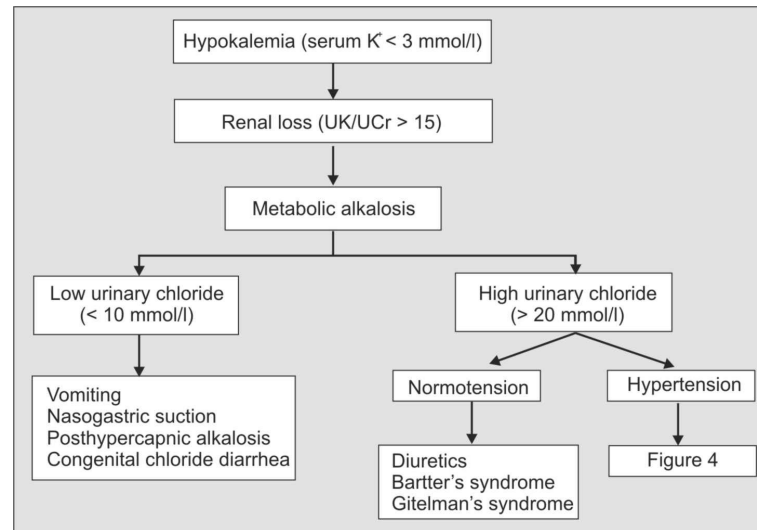


Figure 3. Diagnostic approach to hypokalemia due to renal loss with metabolic alkalosis

can be separated into two groups based on their urinary chloride excretion. The probable causes of low urinary chloride excretion (< 10 mmol/l) are vomiting, nasogastric suction, posthypercapnia and congenital chloride diarrhea. Loss of gastric contents, whether from vomiting or nasogastric suctioning can lead to hypokalemia and metabolic alkalosis. However, the hypokalemia is not due to gastrointestinal loss since the concentration of K^+ in gastric secretions is only 5 to 10 mmol/l. Rather, vomiting or nasogastric suction leads to the generation of new bicarbonate, thereby increasing delivery of $NaHCO_3$ and water to the distal and collecting tubules. The increase in distal Na^+ delivery coupled with hypovolemia-induced increase in aldosterone release, results in increased K^+ secretion. Chronic respiratory acidosis provokes a compensatory metabolic alkalosis. Posthypercapnic states are often associated with chloride depletion (from diuretics) and sodium avidity. If hypercapnia is corrected without replacing chloride, patients will develop chloride-depletion alkalosis and hypokalemia.³¹ Congenital chloride diarrhea is a rare autosomal recessive disorder due to loss of the normal ileal Cl^-/HCO_3^- anion exchanger so that Cl^- cannot be absorbed.³² A hypokalemic, hypochloremic, metabolic alkalosis develops with concomitant volume depletion and secondary hyperaldosteronism. Treatment generally consists of lifelong repletion of electrolyte and fluid losses.

Patients with high urinary chloride excretion (> 20 mmol/l) can be divided into two groups based on their blood pressure. Those with normal blood pressure are caused by diuretics, Bartter's syndrome and Gitelman's syndrome. Diuretic therapy is the most common cause

of hypokalemia. Thiazide and loop diuretics increase delivery of Na^+ to the CD, where it is reabsorbed via the amiloride-sensitive sodium channel (ENaC), therefore creating a favorable gradient for K^+ secretion. In addition, volume depletion that results from these diuretics increases aldosterone, further increasing K^+ secretion. Diuretic-induced hypokalemia is usually but not always associated with a mild-to-moderate metabolic alkalosis. Bartter's syndrome is an autosomal recessive disorder characterized by salt wasting, hypokalemia, metabolic alkalosis, hypercalciuria, normal blood pressure, high plasma renin and aldosterone levels. Mutations in at least 3 different renal tubular transporters have been discovered. They are the bumetanide-sensitive $Na^+-K^+-2Cl^-$ transporter, the apical potassium channel (ROMK channel), and the basolateral chloride channel (ClC-Kb and ClC-Ka) in the thick ascending limb of Henle's loop.³³ These patients act as if they are chronically ingesting loop diuretics. Most patients with Bartter's syndrome are usually detected in infancy with failure to thrive. In contrast, Gitelman's syndrome often presents in adults and is less severe than Bartter's syndrome. It is associated with hypomagnesemia and hypocalciuria and is due to a defect in the gene encoding for the thiazide-sensitive Na^+-Cl^- cotransporter.³³ These patients act as if they are chronically ingesting thiazide diuretics.

HYPOKALEMIA DUE TO RENAL LOSS WITH METABOLIC ALKALOSIS AND HYPERTENSION

The underlying mechanism for hypokalemia associated with metabolic alkalosis and hypertension increased reabsorption of Na^+ via ENaC in the CD. The

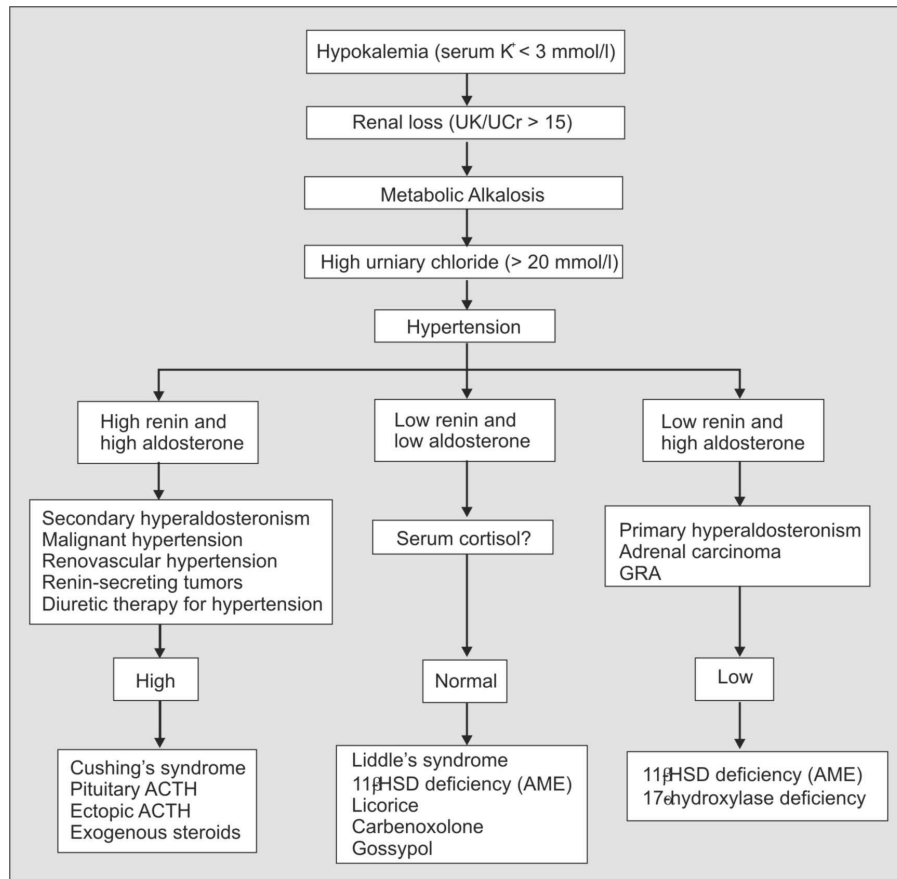


Figure 4. Diagnostic approach to hypokalemia due to renal loss with metabolic alkalosis and hypertension

cause includes gain-of-function mutation in the ENAC, higher aldosterone levels, increases in a non-aldosterone mineralocorticoid levels or increased mineralocorticoid like effect. Measurement of serum aldosterone levels, renin activity and serum cortisol levels can help subdivide these patients (Figure 4). The groups with high serum renin and aldosterone levels include secondary aldosteronism, malignant hypertension, renovascular hypertension, renin secreting tumor and diuretic therapy in patients with essential hypertension. The causes of hypokalemia associated with metabolic alkalosis and hypertension with low renin and high aldosterone levels include primary hyperaldosteronism, adrenal carcinoma and glucocorticoid-remediable aldosteronism (GRA). Primary hyperaldosteronism is caused by increased aldosterone excretion from the adrenal glands, which results primarily from either a unilateral aldosterone-producing adenoma (Conn's syndrome) or bilateral adrenal hyperplasia. Rarely primary hyperaldosteronism is due to adrenal carcinoma. GRA is a rare form of adrenal hyperplasia inherited as an autosomal dominant trait, in which there is fusion of the 11 β -hydroxylase (CYP11B1) and aldosterone synthetase (CYP11B2)

genes.³⁴ As a result, aldosterone secretion is stimulated by ACTH and can be suppressed by an exogenous glucocorticoids. Dexamethasone (0.25 mg mornings and 0.75 mg evenings) is the agent of choice to suppress ACTH production.³⁵ Patients with GRA have a very similar clinical presentation to those with primary hyperaldosteronism except that they are younger and have a family history of hypertension. The presence of a non-aldosterone mineralocorticoid or mineralocorticoid like substance should be suspected in any patients with hypokalemia, hypertension and metabolic alkalosis with low serum aldosterone and renin activity levels. Measurement of serum cortisol levels can help to subdivide these patients. Those who have high serum cortisol levels are due to Cushing's syndrome, ACTH-producing pituitary adenoma, ectopic ACTH syndrome (e.g, caused by small cell lung carcinoma) and exogenous steroids. Those who have normal serum cortisol levels are due to Liddle's syndrome, apparent mineralocorticoid excess (AME) syndrome, or drugs with mineralocorticoid or glucocorticoid effects such as licorice, carbenoxolone and gossypol. Liddle's syndrome, an autosomal dominant disorder, is characterized

by a structural defect in a subunit of the apical amiloride-sensitive sodium channel (ENaC) that leads to unregulated sodium reabsorption with increased potassium secretion.³⁶ The hypokalemia, hypertension, and metabolic alkalosis improve dramatically with inhibitors of ENaC channel such as amiloride or triamterene. AME syndrome is a rare autosomal recessive disorder that is due to a deficiency of 11 β -hydroxysteroid dehydrogenase enzyme type 2 (11 β -HSD2).³⁷ The mineralocorticoid receptor (MR) is capable of binding cortisol and aldosterone with equal affinity. However, cortisol circulates in the blood at a concentration that is >1000-fold higher than aldosterone. Under physiological conditions, the 11 β -HSD2 enzyme inactivates cortisol to cortisone in the CD, allowing aldosterone free access to its receptor. Deficiency of this enzyme leads to occupation and activation of the MR by cortisol, which like aldosterone, then causes hypertension, hypokalemia, metabolic alkalosis with a suppression serum renin and aldosterone levels. Several compounds such as licorice; found in chewing tobacco, confections and herbal preparations, as well as carbenoxolone; a drug used for the treatment of peptic ulcer, contain glycyrrhetic acid or its derivative, which inhibit 11 β -hydroxysteroid dehydrogenase, leading to hypokalemia, hypertension and metabolic alkalosis.³⁸ Patients who present with hypokalemia, hypertension, metabolic alkalosis with low serum renin, aldosterone and cortisol levels are due to 11 β -hydroxylase or 17 α -hydroxylase deficiency. Some patients with congenital adrenal hyperplasia (CAH) have 11 β -hydroxylase deficiency, an enzyme function in both mineralocorticoid and glucocorticoid synthesis.³⁹ In this disorder, cortisol synthesis remains impaired, but deoxycortisol accumulates. Deoxycortisol and its metabolites have mineralocorticoid properties and may cause hypertension, hypokalemia and metabolic alkalosis. These patients also have high levels of androgen, leading to early puberty in male and development of hirsutism and clitomegaly in female. This condition improves with exogenous steroids to suppress ACTH. Rarely, CAH is caused by 17 α -hydroxylase deficiency.

TREATMENT OF HYPOKALEMIA

The first step to treat hypokalemia is to identify the cause of hypokalemia and to stop the ongoing losses of K⁺ such as treating diarrhea, vomiting, hyperglycemia or discontinuing diuretics. The next step is to replete potassium and magnesium deficit. The ability to correct potassium deficiency is impaired when magnesium deficiency is present. Once hypomagnesemia is

corrected, serum K⁺ quickly normalized.²⁷ Potassium can be given orally or intravenously. There are four types of potassium preparations: potassium chloride, potassium phosphate, potassium bicarbonate and potassium citrate. Potassium phosphate is used to treat hypokalemia with hypophosphatemia. Potassium bicarbonate or citrate is preferred in patients with hypokalemia and metabolic acidosis. In all other settings, potassium chloride should be used. In the absence of stimuli that alter transcellular K⁺ shifts, a reduction of serum K⁺ by 0.3 mmol/l suggests a total body deficit of 100 mmol. A patient with a serum K⁺ concentration of 2 mmol/l may have a 500 mmol K⁺ deficit. Unless life-threatening cardiac arrhythmias or respiratory muscles weakness is present, potassium repletion is rarely an urgent undertaking.

CONCLUSION

Therefore, one should always err on the low end of this estimate to avoid inducing hyperkalemia. When given intravenously, the rate of K⁺ administration should not exceed 20 mmol/hour. When potassium is administered intravenously through a peripheral vein, the concentrations should not exceed 50 mmol/l. Higher K⁺ concentrations are often painful. Potassium should be diluted in saline rather than dextrose solution since the administration of dextrose can further lower potassium concentrations and in susceptible individuals can lead to life-threatening cardiac arrhythmias.

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