Disorders of Potassium Homeostasis: Pathophysiology and Management

Sumedh S Hoskote*, Shashank R Joshi**, Amit K Ghosh***

Abstract
Disorders of potassium homeostasis are common electrolyte abnormalities encountered in hospitalized patients. Hypokalemia and hyperkalemia have been estimated to occur in about 21% and 3% of hospitalized patients, respectively; though the morbidity and mortality associated with the latter is significantly higher. Potassium is a predominantly intracellular ion and the understanding of its dynamics between intra- and extracellular fluid milieus, along with its handling by the kidneys, is important in the diagnosis and treatment of potassium disorders. This article aims to provide a clinically relevant update on management of potassium disorders for internists. ©

INTRODUCTION
Potassium is the main intracellular ion in the body and its levels are crucial to normal homeostasis. It is mainly contained within the intracellular fluid (ICF) compartment, with only about 2% of the total body potassium residing in the extracellular fluid (ECF).1 Nearly 80% of the cellular stores are present in muscle, with erythrocytes, liver and bone accounting for most of the remainder1 (Fig. 1). The normal ratio between extracellular and intracellular concentrations is important for maintenance of the resting membrane potential and neuromuscular functioning. Also, intracellularly, potassium participates in several vital functions, such as cell growth, maintenance of cell volume, DNA and protein synthesis, enzymatic function and acid-base balance. Disorders of potassium balance are important causes of ambulatory and in-hospital morbidity. In this review, we will discuss the pathophysiology of potassium transport, mechanisms and management of potassium disorders commonly encountered in clinical practice.

PATHOPHYSIOLOGY
Movement of Potassium Between ICF and ECF
Normal daily potassium intake is approximately 40-100 mEq, which is absorbed from the gut, enters the ECF and is rapidly redistributed into the intracellular compartment due to the action of post-prandial insulin. This is essential because an additional 100 mEq of K⁺ in plasma would increase plasma K⁺ concentration several fold, rapidly leading to death. The ECF acts as an intermediary between the intracellular stores and the input/output mechanisms. Potassium excretion matches the dietary intake, in the absence of disease, and is executed predominantly by the kidney, with about a 10% contribution from the large intestine.

Potassium transfer between the extra- and intracellular milieus is affected by a variety of other endogenous and exogenous factors (Fig. 1). Cellular potassium uptake is promoted by catecholamines and drugs activating β-adrenoceptors, and inhibited by α-antagonist drugs. States of acidosis and alkalosis affect potassium because it compensates for the movement of protons (hydrogen ions). In acidosis, H⁺ ions move into cells and, to maintain electrical balance, K⁺ ions move out into the ECF; and vice-versa in alkalosis. A hyperosmolar ECF environment can promote potassium efflux from the cells leading to depletion of intracellular potassium (and, hence, total body...
potassium). Finally, because potassium is predominantly contained intracellularly, even if 1% of the cellular K⁺ content were to be added to the ECF (due to lysis of cells, such as rhabdomyolysis or hemolysis), it could result in severe hyperkalemia.

Potassium Handling in the Nephron

Potassium handling by the nephron is unique, in that not only is it reabsorbed but it is also secreted by the tubule; and the amount excreted depends on the dietary intake.

Potassium is freely filtered at the glomerulus and approximately 65% of the filtered load is reabsorbed in the proximal convoluted tubule (PCT), which is tied to the reabsorption of sodium and water. This takes place isotonically and the K⁺ concentration of the fluid entering the loop of Henle almost equals that of plasma. In the descending part of the loop of Henle, the K⁺ concentration increases (greater than that accounted for by the reabsorption of water) owing to entry of K⁺ into the lumen, possibly driven by the high K⁺ concentration of the medullary collecting ducts. In the thick ascending part of the loop of Henle (TALH), the Na⁺/K⁺/2Cl⁻ cotransporter present on the luminal border is responsible for reabsorption of potassium. This is also the site of action of the loop diuretics, including furosemide. The next segment, the distal convoluted tubule (DCT), has been shown to be involved, to a small extent, in secretion of K⁺ into the luminal fluid.

The collecting duct (CD) is responsible for nearly all the K⁺ secretion into the urine. The principal cells express sodium and potassium ion channels on their luminal surface. Since the electrochemical force for Na⁺ entry into cells is much higher than that for K⁺, sodium reabsorption predominates, thus creating a negative charge in the lumen. This negative charge attracts K⁺ into the lumen and also repels chloride, via the paracellular pathway, into the peritubular capillaries. Aldosterone increases the activity of the luminal Na⁺ channels, while also enhancing the function of the basolateral Na⁺/K⁺/ATPase pump, thus amplifying the entire process. Also, any factor increasing distal Na⁺ flow, such as diuretic therapy or osmotic agents (e.g. mannitol, high glucose in uncontrolled diabetes; which prevent absorption of solutes due to increased toxicity of luminal fluid) can lead to greater K⁺ secretion.

Finally, the acid-base status of the body and the extracellular K⁺ affect each other via renal mechanisms. In metabolic alkalosis, excess HCO₃⁻ is filtered, which leads to increased distal HCO₃⁻ delivery and bicarbonaturia. Since HCO₃⁻ is a poorly reabsorbed anion, it makes the luminal charge more negative and draws out K⁺ from the collecting duct epithelium, leading to increased kaliuresis and hypokalemia. Hypokalemia increases renal tubular acid (ammonium ion) generation and, for each mole of acid generated and excreted in urine, one mole of base (HCO₃⁻) is added to blood. Thus, it contributes towards the metabolic alkalosis. In hyperkalemia, the converse occurs and renal ammoniagenesis is impaired, leading to metabolic acidosis.

Transtubular Potassium Gradient (TTKG)
The TTKG is a quick laboratory measure that gives information about renal K⁺ secretory function. The aim is to measure the K⁺ added into the tubular lumen as it passes through the cortical collecting duct (CCD). Assuming that the osmolality of the CCD luminal fluid is equal to that of plasma, a simple ratio of CCD K⁺ concentration to the plasma K⁺ concentration will yield the TTKG.

\[
\text{TTKG} = \frac{[K^+]_{\text{CCD}}}{[K^+]_{\text{Plasma}}}
\]

However, because it is clinically impractical to obtain CCD fluid, the parameters are derived using urinary measurements. TTKG is calculated as:

\[
\text{TTKG} = \frac{[K^+]_{\text{Urine}}/\text{OSM}_{\text{Urine}}}{[K^+]_{\text{Plasma}}/\text{OSM}_{\text{Plasma}}} = \frac{[K^+]_{\text{Urine}}}{[K^+]_{\text{Plasma}}} \times \frac{\text{OSM}_{\text{Plasma}}}{\text{OSM}_{\text{Urine}}}
\]

Normal TTKG is about 8-9, which may increase up to 11 if dietary potassium is increased. The TTKG is applied in the appropriate clinical setting to estimate renal K⁺ secretion. In the setting of hypokalemia, a TTKG greater than 3 implies renal K⁺ wastage, while in hyperkalemia, a TTKG lower than 7 implies impaired renal K⁺ secretion.

**Hypokalemia**

Hypokalemia is defined as a plasma K⁺ concentration lower than 3.5 mEq/L. It occurs in about 21% of all hospitalized patients and goes undertreated in nearly a fourth of all cases. Clinically, diuretic use is the commonest cause of hypokalemia. Manifestations of hypokalemia are consequences of the effects on the muscle resting membrane potential (RMP) and on the acid-base status (described above under “Pathophysiology”).

In muscles, low plasma K⁺ leads to a hyperpolarized myocyte that tends to be more refractory to excitation. This causes fatigue, myalgia and weakness, most pronounced in the large proximal skeletal muscles, like those of the hip and thigh. Worsening hypokalemia produces respiratory muscle weakness and, eventually, generalized muscle paralysis, including paralytic ileus.

In cardiac myocytes, potassium ion conductance is directly related to the plasma K⁺ concentration. Hence, hypokalemia reduces K⁺ conductance and leads to a prolonged repolarization phase of the cardiac action potential, reflected in the electrocardiogram (ECG) as a prolonged QT (or QU) interval. Other ECG changes include flattening or inversion of the T wave, a prominent U-wave (Fig. 2) and ST-segment depression. Patients receiving digitalis treatment are prone to increased toxicity in the setting of hypokalemia because digitalis and potassium inhibit each other’s binding at the Na⁺/K⁺/ATPase pump.

Causes

There are many disease processes that lead to or include hypokalemia (Table 1). Broadly, hypokalemia can be caused by a shift of K⁺ into the intracellular compartment, increased loss from the gut or integument, or from
also occurs due to K\(^+\) hypokalemia need special mention. of paralysis occur, beginning in adolescence, after rest autosomal-dominant inherited disorder involving mutations at cool ambient temperatures\(^1\_3\) and analyzed without much (pseudohypokalemia), blood samples should be maintained © JAPI • VOL. 56 • SEPTEMBER 2008 www.japi.org 687
\[ \text{Redistribution to ICF} \]
- Metabolic alkalosis
- Insulin
- Autonomic causes
  - Stress, catecholamines
  - \(\beta\)-agonists, \(\alpha\)-antagonists
- Anabolic states (Vitamin \(B\_\_2\), or GM-CSF therapy)
- Hypokalemic periodic paralysis
- Pseudohypokalemia

**Extra-renal Losses**
- Secretory diarrhea or laxative abuse
- Excessive sweating
- Intestinal neoplasms
  - VIPoma
  - Villous adenoma & McKittrick-Wheelock syndrome

**Renal Losses**
- Primary mineralocorticoid excess
  - Primary hyperaldosteronism (Conn syndrome)
  - Cushing syndrome
  - CAH (CYP 11B1 or CYP 17)
  - Glucocorticoid-remediable hyperaldosteronism
- Hyperaldosteronism due to hyperreninemia
  - Chronic low circulating volume
  - Renin secreting tumor
  - Renovascular and malignant hypertension
- Pseudohyperaldosteronism
  - Liddle syndrome
  - 11\(\beta\)-HSD2 deficiency or antagonism (licorice, \(Cd^{+}\))
- Increased distal Na\(^+\) delivery
  - Diuretics
  - Bartter syndromes
  - Gitelman syndrome
- Increased distal delivery of non-reabsorbed anions
  - Renal tubular acidosis – Type 2
  - Ketoacids (DKA), Penicillins
  - Bicarbonaturia from metabolic alkalosis
  - Renal Tubular Acidosis – Type 1

**Miscellaneous**
- Reduced dietary intake (<40 mEq/day)
- Barium toxicity, hypomagnesemia
- Hypothermia

Table 1 : Causes of hypokalemia

<table>
<thead>
<tr>
<th>Causes of Hypokalemia</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Redistribution to ICF</td>
<td>- Metabolic alkalosis</td>
</tr>
<tr>
<td></td>
<td>- Insulin</td>
</tr>
<tr>
<td></td>
<td>- Autonomic causes</td>
</tr>
<tr>
<td></td>
<td>- Stress, catecholamines</td>
</tr>
<tr>
<td></td>
<td>- (\beta)-agonists, (\alpha)-antagonists</td>
</tr>
<tr>
<td></td>
<td>- Anabolic states (Vitamin (B__2), or GM-CSF therapy)</td>
</tr>
<tr>
<td></td>
<td>- Hypokalemic periodic paralysis</td>
</tr>
<tr>
<td></td>
<td>- Pseudohypokalemia</td>
</tr>
<tr>
<td>Extra-renal Losses</td>
<td>- Secretory diarrhea or laxative abuse</td>
</tr>
<tr>
<td></td>
<td>- Excessive sweating</td>
</tr>
<tr>
<td></td>
<td>- Intestinal neoplasms</td>
</tr>
<tr>
<td></td>
<td>- VIPoma</td>
</tr>
<tr>
<td></td>
<td>- Villous adenoma &amp; McKittrick-Wheelock syndrome</td>
</tr>
<tr>
<td>Renal Losses</td>
<td>- Primary mineralocorticoid excess</td>
</tr>
<tr>
<td></td>
<td>- Primary hyperaldosteronism (Conn syndrome)</td>
</tr>
<tr>
<td></td>
<td>- Cushing syndrome</td>
</tr>
<tr>
<td></td>
<td>- CAH (CYP 11B1 or CYP 17)</td>
</tr>
<tr>
<td></td>
<td>- Glucocorticoid-remediable hyperaldosteronism</td>
</tr>
<tr>
<td></td>
<td>- Hyperaldosteronism due to hyperreninemia</td>
</tr>
<tr>
<td></td>
<td>- Chronic low circulating volume</td>
</tr>
<tr>
<td></td>
<td>- Renin secreting tumor</td>
</tr>
<tr>
<td></td>
<td>- Renovascular and malignant hypertension</td>
</tr>
<tr>
<td></td>
<td>- Pseudohyperaldosteronism</td>
</tr>
<tr>
<td></td>
<td>- Liddle syndrome</td>
</tr>
<tr>
<td></td>
<td>- 11(\beta)-HSD2 deficiency or antagonism (licorice, (Cd^{+}))</td>
</tr>
<tr>
<td></td>
<td>- Increased distal Na(^+) delivery</td>
</tr>
<tr>
<td></td>
<td>- Diuretics</td>
</tr>
<tr>
<td></td>
<td>- Bartter syndromes</td>
</tr>
<tr>
<td></td>
<td>- Gitelman syndrome</td>
</tr>
<tr>
<td></td>
<td>- Increased distal delivery of non-reabsorbed anions</td>
</tr>
<tr>
<td></td>
<td>- Renal tubular acidosis – Type 2</td>
</tr>
<tr>
<td></td>
<td>- Ketoacids (DKA), Penicillins</td>
</tr>
<tr>
<td></td>
<td>- Bicarbonaturia from metabolic alkalosis</td>
</tr>
<tr>
<td></td>
<td>- Renal Tubular Acidosis – Type 1</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>- Reduced dietary intake (&lt;40 mEq/day)</td>
</tr>
<tr>
<td></td>
<td>- Barium toxicity, hypomagnesemia</td>
</tr>
<tr>
<td></td>
<td>- Hypothermia</td>
</tr>
</tbody>
</table>

ICF, Intracellular fluid; GM-CSF, Granulocyte-Monocyte Colony Stimulating Factor; VIPoma, tumor secreting Vasoactive Intestinal Polypeptide; CAH, Congenital Adrenal Hyperplasia; CYP 11B1, 11\(\beta\)-hydroxylase; CYP 17, 17\(\alpha\)-hydroxylase; 11\(\beta\)-HSD2, 11\(\beta\)-hydroxysteroid dehydrogenase-2; DKA, Diabetic ketoacidosis

Dynamics of K\(^+\) exchange between ICF and ECF compartments have already been described (Fig.1). To prevent a spuriously low serum K\(^+\) reading (pseudohypokalemia), blood samples should be maintained at cool ambient temperatures\(^1\_3\) and analyzed without much delay to prevent cellular uptake of K\(^+\). A similar phenomenon also occurs due to K\(^+\) uptake by the abnormal white cells in myeloproliferative disorders.\(^1\_4\) Several unique causes of hypokalemia need special mention.

Hypokalemic periodic paralysis (HypoKPP) is an autosomal-dominant inherited disorder involving mutations of ion channels present on the muscle sarclemma. Attacks of paralysis occur, beginning in adolescence, after rest

following exercise or ingestion of a carbohydrate-rich meal.\(^1\_5\) Both these scenarios normally involve intracellular K\(^+\) uptake; but this process is abnormally increased in HypoKPP. Serum K\(^+\) levels are low during the attack. HypoKPP warrants K\(^+\) replacement despite being a disorder of transeellular K\(^+\) shift. Thyrotoxic periodic paralysis (TPP) is a disorder characterized by elevated thyroxine, hypokalemia and paralysis that most commonly occurs in patients of East and Southeast Asian extraction.\(^1\_6\) The importance of recognizing this condition is that it is self-limited and administration of K\(^+\) supplementation can result in rebound hyperkalemia in nearly half the patients.\(^1\_6\)

\(\beta\)-agonists are potent promoters of cellular K\(^+\) uptake and, for this reason, they are important in the management of hyperkalemia. Recently, a bizarre cause of hypokalemia was reported in heroin abusers. Clenbuterol (a drug used to treat airway obstruction in horses) was found to be an adulterant in heroin, and led to hypokalemia, in addition to the autonomic effects (tachycardia, palpitations).\(^1\_7\) This drug may also be abused by athletes for its propensity to increase lean muscle mass and reduce body fat.

Losses from the skin and gastrointestinal tract, if severe, can give rise to significant electrolyte depletion, resulting in hypokalemia. Infectious secretory diarrheas account for the vast majority of these. A pancreatic tumor secreting vasoactive intestinal polypeptide (VIPoma) is an exceedingly rare entity, while a villous adenoma only infrequently produces diarrhea sufficient to cause hypokalemia. Rectal neoplasms (commonly villous adenomas) producing electrolyte hypersecretion constitute the McKittrick-Wheelock syndrome.\(^1\_8\)

Diseases causing increased renal K\(^+\) loss can be grouped as: (1) those resulting from increased mineralocorticoid effect, (2) those producing increased delivery of Na\(^+\) to the distal nephron segments, and (3) those producing increased delivery of unabsorbed anions to the distal nephron segments. Some specific renal disorders have been discussed in detail.

Primary mineralocorticoid excess can result from primary hyperaldosteronism i.e., Conn syndrome (increased production of aldosterone from a benign or malignant adrenal neoplasm), or from generalized adrenal hyperfunction (Cushing syndrome). Increased mineralocorticoid action can occur due to mineralocorticoids produced in congenital adrenal hyperplasia. Inborn deficiencies of the 11
β-hydroxylase (CYP 11B1) and 17 α-hydroxylase (CYP 17) enzymes lead to increased levels of 11-deoxycorticosterone. Genetically male children with CYP 17 deficiency manifest as pseudohermaphroditism (female genitalia), while females present in later life with primary amenorrhea. Both deficiencies have adult-onset forms as well.

Liddle syndrome is a rare autosomal dominant genetic disorder manifested by a gain-of-function of the epithelial sodium channel (ENaC) of the principal cell in the collecting duct. Excessive Na⁺ is reabsorbed and, as a direct consequence, excessive K⁺ is secreted – leading to hypokalemia. Patients are volume overloaded, leading to hypertension in the setting of a suppressed renin-angiotensin-aldosterone (RAA) axis. A loss-of-function mutation of the ENaC produces aldosterone resistance, a syndrome exactly the opposite of Liddle syndrome, which is discussed later.

Another condition producing a similar picture to that of Liddle syndrome is the syndrome of apparent mineralocorticoid excess. Cortisol secreted by the adrenals possesses some mineralocorticoid action but, in aldosterone target tissues, the enzyme 11β-hydroxysteroid dehydrogenase-2 (11-βHSD2) converts cortisol to a non-mineralocorticoid, cortisolone. Symptoms of hyperaldosteronism develop if the activity of this enzyme is lacking, or in the presence of inhibitors (licorice or cadmium from tobacco smoke).

Glucocorticoid-remediable hyperaldosteronism is a genetic condition wherein the gene for 11 β-hydroxylase (the enzyme upregulated by corticotropin to synthesize cortisol) contains the correct promoter but carries the bases for aldosterone synthase in its coding region (chimeric gene duplication). Hence, aldosterone synthesis occurs in the region of the adrenal (zona fasciculata) responsible for cortisol secretion. Administration of dexamethasone can diagnose as well as manage this condition, because suppression of corticotropin takes away the stimulus for excessive aldosterone synthesis.

Bartter syndrome is a group of genetic conditions resulting from defective reabsorption of sodium from the TALH due to a variety of dysfunctional ion-transport proteins. These include the Na⁺/K⁺/2Cl⁻ cotransporter (Bartter I), the apical (luminal) potassium channel (Bartter II), and two defects in the basolateral chloride channel responsible for potassium-chloride flux through the tubular cell (Bartter III & IV). Recently, a milder variant of Bartter syndrome with hypocalcemia has also been described (Bartter V). All the Bartter syndrome genetic defects are inherited in an autosomal recessive fashion, except for Bartter syndrome V, which follows autosomal dominant inheritance.

Reabsorption of Na⁺ is impaired and the resultant excessive natriuresis has two important implications – there is increased distal Na⁺ load and the volume depletion causes activation of the RAA axis. Both factors are responsible for the excessive K⁺ excretion, leading to hypokalemia. In the TALH, K⁺ absorption is reduced and, consequently, its backflow into the lumen is also reduced. Since it is this luminal positive charge that drives transcellular reabsorption of other cations like Ca²⁺ and Mg²⁺, Bartter syndrome is associated with hypocalcemia (hypercalciuria) and hypomagnesemia. This fact is utilized in differentiating Bartter syndrome from Gitelman syndrome, of which hypocalciuria is a hallmark.

Gitelman syndrome is an autosomal recessive genetic defect resulting in dysfunction of Na⁺ absorption by the thiazide-sensitive Na⁺/Cl⁻ cotransporter (NCCT) located in the DCT. It is characterized by hypokalemia, metabolic alkalosis, hypomagnesemia, and hypocalciuria. Hypomagnesemia is considered the hallmark of NCCT dysfunction and is thought to occur due to reduced activity of epithelial Mg²⁺ receptors, while hypocalciuria occurs due to increased proximal tubular reabsorption of Ca²⁺.

Renal tubular acidosis (RTA) is an umbrella term for the common presentation of hyperchloremic metabolic acidosis with a normal anion gap, caused by a renal tubular dysfunction. There are four types of RTA and all, except type 4, produce hypokalemia.

RTA Type 1, also known as distal RTA, is caused by an impairment in acidification of urine due to dysfunctional acid secretion in the collecting ducts. There is also an associated defect of K⁺ conservation, the mechanism of which is uncertain. The urinary excretion of ammonium (NH₄⁺) is disproportionately low compared to the blood pH, which produces the characteristic finding of urine pH greater than 5.5 even in the setting of acidosis, aiding in the differentiation from RTA Type 2. Chronic acidosis is responsible for the renal calculi formed in Type 1 RTA by two synergistic mechanisms. Acidosis reduces calcium reabsorption, increasing the Ca²⁺ concentration in tubular fluid, while simultaneously enhancing citrate reabsorption, reducing its concentration. Usually, calcium binds citrate to form a soluble compound but, due to the imbalance in this ratio, calcium binds phosphate to produce a 50-times less soluble compound that precipitates in the alkaline urine to produce renal calculi.

RTA Type 2, also known as proximal RTA, can occur as a primary condition, with or without features of generalized proximal tubular dysfunction (Fanconi syndrome), or secondary to drugs such as carbonic anhydrase (CA) inhibitors. The result is impaired proximal reabsorption of HCO₃⁻. Distal sites in the nephron receive more than the usual HCO₃⁻ load and, since they are not as adept at its reabsorption, the HCO₃⁻ is lost. Bicarbonaturia is the characteristic of this condition. Eventually, the plasma HCO₃⁻ drops to a lower level, at which a new equilibrium is established and HCO₃⁻ is no longer lost in urine. Bicarbonate replacement therapy is difficult because a fractional HCO₃⁻ excretion of more than 15% is observed and HCO₃⁻ may be lost before the desired pH normalization is achieved. Interestingly, the defect in proximal tubular function protects these patients from renal calculi and...
nephrocalcinosis because of the normal/increased citrate in the tubular fluid. In RTA Type 2, relative to Type 1, a large quantity of HCO$_3^-$ needs to be replaced (5-15 mmol/kg/day vs. 1-2 mmol/kg/day). Since alkali replacement itself causes hypokalemia, the K$^+$ replacement required in RTA Type 2 is greater than that required in RTA Type 1.

RTA Type 3 is a rare condition caused by a mutation of the intracellular form of CA (CA-II). The deficiency of a functional CA-II enzyme gives rise to impaired proximal HCO$_3^-$ reabsorption as well as impaired distal acid secretion i.e. features of both RTA types 1 and 2. Other associated features are osteoporosis, cerebral calcifications and mental retardation.

Diagnosis

Hypokalemia should be suspected in any patient presenting with generalized or proximal muscle weakness or cardiac arrhythmias. History of gastrointestinal losses, use of any medications (especially diuretics), renal disease and history of familial conditions should be actively sought. Conditions leading to transcellular K$^+$ shift can be excluded with a good history and physical examination. Laboratory values for serum and urinary electrolytes, along with the blood pressure and plasma renin activity (PRA), are the main tools in narrowing down the causes of hypokalemia.

The headings listed in Table 1 (see "Renal losses") each represent a pathophysiologic mechanism in the process causing hypokalemia and each is a distinct endpoint in the diagnostic pathway (Fig. 3).

Once transcellular shift has been excluded, the first step is to find out if K$^+$ has been lost via renal or extrarenal mechanisms. A daily urinary K$^+$ excretion of > 20 mEq suggests renal K$^+$ wastage. If a renal cause has been found, the next factor to ascertain is the aldosterone status, since that is the main stimulus for K$^+$ loss. One of the reliable clinical manifestations of hyperaldosteronism is hypertension and, hence, the blood pressure (BP) guides the further diagnostic course. If the BP is low or normal, we can eliminate aldosterone as the cause for hypokalemia. The other reasons for increased K$^+$ loss are increased distal delivery of Na$^+$ or HCO$_3^-$. These causes are looked for using serum HCO$_3^-$ and urinary chloride. Increased distal Na$^+$ flow is the result of impaired Na$^+$ reabsorption due to an inherited defect of the transporters (Bartter and Gitelman syndromes) or due to their blockade by diuretics. These disorders secondarily cause metabolic alkalosis, producing elevated serum HCO$_3^-$. Because Cl$^-$ is simultaneously reabsorbed with Na$^+$, the above conditions lead to Cl$^-$ loss as well, causing a high daily Cl$^-$ excretion. On the other hand, an extra-renal cause of metabolic alkalosis (like vomiting or nasogastric suction) leads to increased serum HCO$_3^-$ with a resultant increased tubular HCO$_3^-$ whose negative charge repels chloride. The Cl$^-$ is driven out of the tubular lumen, leading to low urinary Cl$^-$ excretion. In case the serum HCO$_3^-$ is low, renal tubular acidosis is diagnosed.

Elevated BP implies excess mineralocorticoid action; however, this may be due to or independent of renin levels.

Hence, plasma renin activity should be tested prior to aldosterone. Conditions like Liddle syndrome give a clinical picture of hyperaldosteronism despite a suppressed RAA axis because their pathophysiology mimics aldosterone excess at the level of the target tissues.

Treatment

Hypokalemia caused due to true potassium deficit should be treated with K$^+$ replacement, though if serious complications are expected, hypokalemia resulting from transcellular shifts may also be treated similarly. Potassium chloride or acetate are used depending on coexistent alkalosis or acidosis, respectively. Other modalities can be employed depending on the specific underlying pathologic condition. If acidosis and hypokalemia coexist, the hypokalemia must be treated before the acidosis because alkali administration can further aggravate hypokalemia.

The 2005 American Heart Association (AHA) guidelines recommend K$^+$ replacement for serum levels below 2.5 mEq/L to avert risk of cardiac arrhythmias. Replacement should be carried out gradually, rather than rapidly, unless the patient’s severity so demands. It is difficult to estimate the K$^+$ requirement because the ECF concentration does not reflect body stores. Hence, it is important to frequently monitor serum K$^+$ while administering therapy. Response to treatment improves with co-administration of magnesium replacement, especially in hypokalemia that is refractory to therapy. Care must be taken to avoid overcorrection of the deficit, because rebound hyperkalemia is a serious complication of therapy.

Some authors recommend that replacement should be initiated with oral potassium chloride because a greater rise in ECF potassium can be achieved with this route at the expense of fewer adverse events and parenteral administration should be reserved for patients unable to take enteral doses. According to the AHA guidelines,
**HYPERKALEMIA**

Hyperkalemia is defined as a plasma K⁺ concentration greater than 5 mEq/L. It occurs in about 3.3% of all hospitalized patients, most commonly in patients of chronic renal insufficiency, and can carry a high rate of mortality. As for hypokalemia, the manifestations of hyperkalemia also relate to neuromuscular and acid-base effects. Increased ECF K⁺ concentration forces K⁺ into the cells through the always-open leaky potassium channels, leading to a slight depolarization. A constant state of depolarization affects excitability and, once again, the effect is fatigue and weakness. If severe, respiratory muscle weakness can be a life-threatening complication.

In cardiac myocytes, hyperkalemia causes increased K⁺ conductance. Since the K⁺ current is responsible for repolarization, the first manifestation of hyperkalemia is a rapid repolarization, reflected on the ECG as a sharp, peaked T wave. Increased K⁺ conductance also makes the RMP more negative, to a level at which Na⁺ channels start getting inactivated. Hyperkalemia can also induce an atrioventricular nodal block, reflected as a prolonged PR interval and a ventricular rhythm with wide QRS complexes. P wave amplitude decreases, and may not be detectable, due to an 'electrical paralysis' of the atria. With increasing severity of hyperkalemia, the widened QRS tends to merge with the peaked T wave (Fig. 4), producing a characteristic sine wave pattern. Eventually, the cardiac arrhythmia deteriorates into ventricular fibrillation or asystole, leading to death.

Causess

The various causes of hyperkalemia fall into two main pathophysiologic groups – movement of K⁺ from the ICF to the ECF and impaired renal excretion (Table 2). Factors causing transcellular shift of K⁺ have already been discussed (Fig. 1). Renal causes can, again, be either related to a defective mineralocorticoid action or due to an intrinsic tubular inability to secrete potassium. Oliguric renal failure can, by virtue of reduced renal perfusion and glomerular filtration rate (GFR), cause reduced K⁺ secretion. Additionally, the initiating pathologic process may entail catabolism and metabolic acidosis, both of which would increase serum K⁺. Thus, two separate mechanisms are responsible for hyperkalemia in oliguric renal failure. This may be compensated by RAA axis activation, but decompensation occurs if GFR falls below a critical value of about 10 mL/min.

Primary aldosterone deficiency can result from either a generalized adrenal cortex failure (Addison's disease) or from an inborn enzyme defect such as the 21-hydroxylase (CYP 21A2) deficiency. The CYP 21A2 deficiency, which may present in childhood or adulthood, causes congenital adrenal hyperplasia and presents with virilization and hypotension. Hyporeninemic hypoaldosteronism is a condition commonly seen in association with diabetic nephropathy and usually occurs in the presence of some underlying renal pathology causing volume expansion. The volume expansion secondarily causes suppression of the RAA axis, eventually manifesting as hyperkalemia.

Many drugs interact with the RAA axis. Non-steroidal anti-inflammatory drugs (NSAIDs) cause hyporeninemia by impairing prostaglandin synthesis in the juxtaglomerular apparatus, which are essential for renin release. Additionally, hypoaldosteronism can be caused by fluoride toxicity and heparin, which act as inhibitors of aldosterone synthesis, or by the angiotensin-converting enzyme inhibitors (ACEI) or angiotensin-receptor blockers, which antagonize angiotensin, the main stimulus for aldosterone release from the adrenals.

Impaired K⁺ secretion can result from receptor-antagonism of aldosterone (spironolactone) or from blockade of the principal cell Na⁺ channel (ENaC) by drugs like amiloride, triamterene, amantadine and trimethoprim. RTA Type 4, also known as hyperkalemic distal RTA, is usually the consequence of some other underlying renal pathology. There is reduced secretion of K⁺, leading to chronic hyperkalemia. And, as discussed earlier (see “Pathophysiology”), hyperkalemia impairs NH₄⁺ production in the collecting duct, leading to defective generation of acid for excretion, and metabolic acidosis. Type 4 RTA should be taken as a descriptive term rather than as a discreet pathology, because any condition in which the RAA axis is interrupted can potentially produce Type 4 RTA. Lastly, pseudohypoaldosteronism is a rare familial condition in which there is a defective gene coding for the ENaC.

---

**Fig. 4**: Electrocardiogram (ECG) of a patient with severe hyperkalemia. The ECG shows a wide QRS complex merging with the peaked T wave, producing a sine-wave pattern. Right axis deviation (I, aVF) can also be appreciated.
loss-of-function mutation produces aldosterone resistance and, in spite of elevated aldosterone levels, the kidneys continue to lose Na\(^{+}\) and retain K\(^{+}\).

**Diagnosis**

The initial presentation of hyperkalemia can be paralysis, cardiac arrhythmias or ileus. History of diabetes, medications and any familial disorders should be sought. Laboratory values of serum electrolytes, osmolality, blood urea nitrogen (BUN) and creatinine, along with urine electrolytes should be obtained. The diagnostic approach to hyperkalemia is detailed in Fig. 5.

**Treatment**

Treatment of hyperkalemia involves three major steps: (1) to reverse the cardiac effects, (2) to promote intracellular uptake, and (3) to remove excess potassium from the body. Later, on subsidence of the acute event, patients need to be put on a maintenance regimen to prevent episodes of hyperkalemia. Various treatment modalities and dosages are summarized in Table 3.

According to the 2005 AHA guidelines, management should be guided by the serum K\(^{+}\) level. In mild hyperkalemia (5-6 mEq/L), furosemide and sodium polystyrene sulfonate should be used. For moderate hyperkalemia (6-7 mEq/L), an intracellular shift of K\(^{+}\) should be achieved using an insulin-glucose drip, sodium bicarbonate and salbutamol. In severe hyperkalemia (>7 mEq/L with toxic ECG changes), the cardiac toxicity needs to be controlled at the earliest to prevent the advent of fatal arrhythmias. Calcium chloride (or gluconate) can be used as an infusion to achieve membrane stabilization. In addition to calcium, all the modalities mentioned above should be employed to lower serum K\(^{+}\) levels. In refractory cases, hemodialysis may be used as a last resort of treatment.

In summary, disorders of potassium metabolism are commonly encountered in clinical practice. Taking an excellent clinical history, along with a thorough understanding of potassium pathophysiology, will help the clinician to make an accurate diagnosis and initiate appropriate treatment. Additionally, anticipating potassium disorders in patients receiving medications like diuretics (hypokalemia) or ACEI (hyperkalemia), especially in patient with co-morbid illness and chronic kidney disease, will help in ensuring patient safety and optimizing patient care.

**REFERENCES**

8. Paice BJ, Paterson KR, Onyanga-Omara F, Donnelly T, Gray JM, Lawson...
<table>
<thead>
<tr>
<th>Therapeutic target and medications</th>
<th>Dose and route</th>
<th>Onset</th>
<th>Duration of action</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Membrane effects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>● Calcium chloride or gluconate</td>
<td>5-10 mL of 10% solution IV over 2-5 min.</td>
<td>Immediate</td>
<td>30 min.</td>
<td>Can worsen digitalis toxicity. Monitor ECG, stop if bradycardia develops.</td>
</tr>
<tr>
<td>Intracellular shift of K⁺</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>● Insulin-glucose drip</td>
<td>10 Units Regular insulin IV with 50 mL of 30% glucose</td>
<td>15-30 min.</td>
<td>2-6 h.</td>
<td>Glucose unnecessary if blood sugar &gt; 250 mg/dl</td>
</tr>
<tr>
<td>● Salbutamol</td>
<td>2-4 ml of 5% salbutamol by nebulizer over 15 min.</td>
<td>15-30 min.</td>
<td>2-3 h.</td>
<td>Synergistic with insulin. May cause a brief rise in plasma K⁺.</td>
</tr>
<tr>
<td>● Sodium bicarbonate</td>
<td>50 mEq IV over 5 min.</td>
<td>15-30 min.</td>
<td>1-2 h.</td>
<td>Should be used along with insulin and salbutamol; may be less effective in ESRD.</td>
</tr>
<tr>
<td><strong>Removal of excess K⁺</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>● Furosemide</td>
<td>40-80 mg furosemide IV, with saline if coexistent volume depletion</td>
<td>15-60 min.</td>
<td>4 h.</td>
<td>Causes kaliuresis. Only effective if adequate renal response to loop diuretics.</td>
</tr>
<tr>
<td>● Sodium polystyrene sulfonate</td>
<td>15-30 g in 50-100 mL of 20% sorbitol, either orally or as a retention enema</td>
<td>1-2 h.</td>
<td>4-6 h.</td>
<td>Sorbitol may be associated with bowel necrosis. May lead to Na⁺ retention. Rectal route acts faster. Avoid ultrafiltration in the first hour of dialysis.</td>
</tr>
<tr>
<td>● Hemodialysis</td>
<td></td>
<td>15-30 min.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Long-term maintenance therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>● Restriction of K⁺ intake to &lt; 2-3 g/day</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>● Discontinuation of drugs interfering with K⁺ homeostasis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>● Enhanced K⁺ excretion: furosemide, thiazides</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>● Fludrocortisone (in hypoaldosteronism)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>● Long-term sodium polystyrene sulfonate therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 3: Treatment of hyperkalemia


