Hypokalaemia and hyperkalaemia

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Abstract

Disturbances in potassium homoeostasis presenting as low or high serum potassium are common, especially among hospitalised patients. Given the fact that untreated hypokalaemia or hyperkalaemia is associated with high morbidity and mortality, it is critical to recognise and treat these disorders promptly. In this article, normal potassium homoeostasis is reviewed initially and then a pathophysiological approach to work-up and management of hypokalaemia and hyperkalaemia is presented. Recent advances with respect to the role of kidney in handling of the potassium, the regulation of renal ion transporters in hypokalaemia, and treatment of hypokalaemia and hyperkalaemia will be discussed.

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Potassium homoeostasis

Potassium is the most abundant cation in the body. It is predominantly restricted to the intracellular space, such that only 2% is located extracellularly and the remaining 98% is in the intracellular compartment. The ratio of intracellular to extracellular potassium (Ki/Ke) is the major determinant of resting membrane potential, and is regulated primarily by the sodium-potassium ATPase pump located on the plasma membrane of most cells. Although extracellular potassium accounts for only 2% of total body potassium, it has a major effect on the ratio of Ki/Ke and through that on the resting membrane potential. As a result, serum potassium is normally regulated around the narrow range of 3.5–5.0 mmol/l.

The daily intake of potassium in the western diet is between 80–120 mmol. The kidney is the major route of potassium excretion, accounting for 90% of potassium loss daily. The remaining 10% is excreted through the gastrointestinal tract. The kidney is, therefore, responsible for long term potassium homoeostasis, as well as the serum potassium concentration. On short term basis, serum potassium is also regulated by the shift of potassium between the intracellular and extracellular compartments. Humans, as carnivorous animals, consume large amount of potassium intermittently. Dietary potassium, which is rapidly absorbed by the gut, could increase serum potassium dramatically. However, several physiological mechanisms quickly shift the potassium intracellularly, allowing slow excretion of potassium by the kidney, and maintenance of normal potassium homoeostasis.[1]

Normal physiological regulators, insulin and catecholamines, are stimulated by ingestion of food containing glucose and potassium. These hormones are essential in shift of potassium intracellularly, depositing it primarily in the liver and striated muscle cells.[2] Catecholamines, by acting through different receptors, have different effect on potassium deposition. β_2-stimulation results in a shift of potassium into the cell, while α-stimulation has the opposite effect.[3] The effect of mineralocorticoids and parathyroid hormone in internal potassium homoeostasis is minimal at best. In addition to these physiological regulators, internal potassium homoeostasis is also affected by changes in acid-base and osmolarity. Sudden changes in osmolarity, by shifting the water out of cell, creates a solvent drag phenomenon, and helps push potassium out of the cell, resulting in a rise in serum potassium (table 1). The effect of acid-base status is much more complicated and depends on the nature of the disorder (box 1). Although, the rule of thumb has been that for each 0.1 unit change in pH, there is a 0.6 mmol/l change in serum potassium, this is a very crude approximation and varies greatly by the nature of acid-base disorders. For example organic acidosis as seen in diabetic ketoacidosis or lactic acidosis result in little or no change in serum potassium while non-organic (mineral) acidosis, such as acidosis of renal failure, has the greatest effect. Other acid-base disorders shift potassium minimally.[4 5]

Table 1 Regulators of potassium distribution between intracellular and extracellular compartment

Regulators	*Mechanism of action*	*Potassium shift into cells*
Insulin	Activation of sodium-potassium ATPase	Increase
Catecholamines	Activation of β_2 receptors	Increase
	Activation of α receptors	Decrease
Mineralocorticoids	Unknown	Mild increase
Parathormone	Unknown	Mild decrease
Acid-base changes	Exchange of H+ for K+	See table 2
Hyperosmolality	Solvent drags	Shifts potassium extracellularly

Box 1: Effect of acid-base disorders on serum potassium

- For any pH change the effect of acidaemia is greater than alkalaemia.
- Non-organic (mineral acidosis) results in a shift of 0.24–1.7 mmol/l per 0.1 unit pH change.
- Organic acidosis has little to no effect on potassium shift.
- Respiratory and metabolic alkalosis and respiratory acidosis result in similar small shift of potassium into and out of cell respectively (0.1–0.4 mmol/l on average).
- In chronic acid-base disorders the final potassium reflects primarily the effect on renal handling of potassium and to lesser extent of transcellular shift.

Renal handling of potassium

The filtered potassium (around 700–800 mmol/day) is largely reabsorbed by proximal nephron segments, including proximal convoluted tubules and thick limb of Henle. The potassium that is excreted is, therefore, a result of secretion by distal segments, predominantly distal convoluted tubule and the collecting duct. Transport studies in these latter tubule segments have demonstrated that potassium secretion is accomplished via apical potassium channels. The secretion of potassium in these nephron segments is indirectly but tightly coupled to sodium reabsorption via the amiloride-sensitive sodium channel; increased sodium reabsorption increases whereas decreased sodium reabsorption decreases potassium secretion. It is this secretory ability of the potassium channels in the distal segments which regulates the excretion of potassium. As a result, any condition that decreases the activity of renal potassium channels results in hyperkalaemia (for example, amiloride intake or aldosterone deficiency) whereas their increased activity results in hypokalaemia (for example, primary aldosteronism or Liddle's syndrome).

In summary, kidney is the major regulator of long term potassium homoeostasis and serum potassium. However, on short term basis, insulin and catecholamines, among others, regulate serum potassium through changes in transcellular distribution of potassium.

Hyperkalaemia

Hyperkalaemia is defined as serum potassium greater than 5.0 mmol/l. True hyperkalaemia should however be distinguished from pseudohyperkalaemia, a rise in serum potassium secondary to release of intracellular potassium during phlebotomy or storage of blood sample. During phlebotomy the combination of venous occlusions and hand clinching could result in potassium release locally. If this is suspected, a blood sample should be drawn from a free flowing vein without fist clinching. Potassium can also be released in test tube by haemolysis, severe thrombocytosis (usually $>900 \times 10^{10}$/l platelets) or leucocytosis (leucocytes $>70 \times 10^{9}$/l). If this is suspected the measurement should be repeated using fresh heparinised blood drawn carefully to prevent haemolysis.

The incidence of hyperkalaemia in hospitalised patients varies depending on the level of potassium used from 1.4% to 10%. In the largest study in a single hospital overall incidence of hyperkalaemia (defined as serum potassium >6.0 mmol/l) was 1.4%. Potassium supplementation and potassium-sparing diuretics account for about one third of the cases. Severe hyperkalaemia is more common in older patients with underlying renal insufficiency treated with potassium supplementation. Hyperkalaemia accounts for approximately 1:1000 deaths in hospitalised patients (reviewed by Ponce *et al*[6]).

CLASSIFICATION OF HYPERKALAEMIA

Hyperkalaemia could be due to transcellular shift, increase in intake, and/or decrease in output (box 2). Transcellular shift is often due to metabolic acidosis; however, a sudden rise in osmolality, especially in association with insulin deficiency, could result in significant hyperkalaemia. β-blockers alone are rarely associated with significant hyperkalaemia, however, they could play a contributory part.

Given the renal ability to excrete large amount of potassium, increase in intake could result in hyperkalaemia, only if associated with subtle or overt defect in potassium excretion. Salt substitutes, which may contains as much as 200 mmol of potassium per tablespoon, are major hidden sources of ingested potassium. Hyperkalaemia can also occur by infusion of potassium containing solution at a rate that can not be handled by transcellular shift and/or renal excretion (see below under treatment of hypokalaemia). The most important cause of hyperkalaemia is, however, decrease in renal potassium excretion. This is seen in many disorders including mineralocorticoid deficiency, such as Addison's disease or resistance to the effect of aldosterone such as seen in patients on aldosterone antagonist drugs (box 2). Trimethoprim, a commonly used antimicrobial drug, is an important cause of hyperkalaemia in patients with mild renal failure.[7] Although this side effect is more common on high dose intravenous therapy, it does occur on regular oral dose. Patients with renal failure can often maintain near normal serum potassium unless glomerular filtration rate decreases below 15

Box 2: Classification of hyperkalaemia

(1) Spurious hyperkalaemia
- Due to high platelet and/or leucocyte count.
- Due to muscular activity during venepuncture.

(2) Transcellular shift of potassium
- Acidaemia (for example, acute renal failure).
- Hyperosmolality (for example, severe hyperglycaemia).
- β_2-blockers (for example, propranolol).
- Insulin deficiency (for example, type I diabetes mellitus).

(3) Increase intake
- Infusion of potassium containing solutions.
- Increase potassium intake in patients with defect in potassium excretion.

(4) Decrease renal excretion
- Mineralocorticoid deficiency: (a) Addison's disease, (b) isolated aldosterone deficiency, (c) renin deficiency (for example, diabetic nephropathy), (d) angiotensin II receptor blockers, (e) angiotensin converting enzyme inhibitors, (f) use of non-steroidal anti-inflammatory drugs.
- Resistance to mineralocorticoids effect: (a) tubulointerstitial disease, (b) high dose mineralocorticoids antagonists (for example, spironolactone, trimethoprim).
- Severe renal failure.

ml/min. However, a significant number of patients with renal disease have low aldosterone levels with or without low renin level, or have resistance to aldosterone effect. This group presents with mild to moderate renal failure and hyperkalaemia, often in association with renal tubular acidosis (type IV).[8]

CLINICAL PRESENTATION

Hyperkalaemia is often asymptomatic and is discovered on routine laboratory tests. Patients with severe hyperkalaemia (potassium >6.5 mmol/l) may, however, present with generalised weakness, paralysis, and cardiac arrhythmia, including cardiac stand still and sudden death. In general, the severity of clinical presentation does correlate with the severity of hyperkalaemia. Changes in the electrocardiogram (ECG) also reflect the severity of hyperkalaemia. In mild to moderate hyperkalaemia, changes in the ECG are subtle and often limited to peaking of the T-wave. If hyperkalaemia is more severe, prolongation of PR and QRS interval followed by loss of P wave and marked widening of QRS is seen. In extreme hyperkalaemia, the ECG shows sine wave, often followed by ventricular fibrillation. Although some patients show a gradual progression of ECG findings, many progress rapidly without warning. Therefore, hyperkalaemia in association with ECG changes is a true medical emergency.

WORK-UP OF HYPERKALAEMIA

It is important to stress that in severe hyperkalaemia diagnostic work-up should be postponed until hyperkalaemia is treated. In other patients, if the cause of hyperkalaemia is not evident from the initial work-up, a stepwise approach is recommended. The first step should be to evaluate the adequacy of the renal response to hyperkalaemia. Potassium excretion is primarily through potassium secretion in the cortical collecting duct. Urinary potassium concentration is however greatly affected by the amount of water reabsorbed in the collecting duct. To evaluate adequacy of renal response it is therefore important that urinary potassium to serum potassium ratio be corrected for urinary concentration. This is simply done by dividing the ratio of urinary potassium to serum potassium by the ratio of urinary osmolality to serum osmolality (urinary potassium:serum potassium/urinary osmolality:serum osmolality). This ratio, referred to as transtubular potassium gradient or TTKG, is >5 and often 7 in hyperkalaemia and <1 in hypokalaemia.[9 10] It is worth mentioning that the cut off values of >5 or <1 are indicative of a non-renal cause for high or low potassium, respectively. This formula, however, can not be used if urine is more dilute than the serum or contains very little sodium.[9 10]

The next step is to establish if low urinary potassium *excretion* is due to low aldosterone or to resistance to aldosterone effect by measuring serum aldosterone level. In patients with underlying renal disease hyperkalaemic renal tubular acidosis is a very common finding and is often due to hypoaldosteronism with or without a low renin level. In these patients we commonly do not embark on a costly and detailed evaluation and focus on long term treatment. However in patients with normal renal function, and especially in patients suspected of primary adrenal failure, a complete work-up including measurement of aldosterone and cortisol level is mandatory.

One of the more overlooked and less well understood causes of hyperkalaemia is the use of prostaglandin inhibitors or non-steroidal anti-inflamatory drugs (NSAIDS). Studies have shown that the use of NSAIDS, specifically in conditions associated with raised basal renal prostaglandins such as liver cirrhosis or mild renal insufficiency, can cause hyperkalaemia by causing hypoaldosteronism. Two independent mechanisms are responsible for this hyperkalaemia; first is the direct inhibition of renin synthesis by prostaglandin inhibition.[11] The second mechanism is indirect and is via enhanced reabsorption of sodium and chloride in the thick ascending limb which can result in volume expansion and as a result suppress renin and aldosterone.[11]

If renal response to hyperkalaemia is appropriate (TTKG >5), increase in potassium intake, or transcellular shift of potassium should be suspected. As indicated above, transcellular shift most commonly occurs in the setting of metabolic acidosis, hyperosmolality, and/or insulin deficiency. If transcellular shift is ruled out, hyperkalaemia is probably due to an increase in potassium intake, which should be established by a careful dietary (including food supplements) and drug history.

MANAGEMENT OF HYPERKALAEMIA

The initial management should be dictated by the changes in ECG. In the presence of ECG changes, hyperkalaemia should be considered an emergency and treatment should begin immediately with calcium gluconate infusion. This should be followed by use of insulin and glucose or albuterol to help shift potassium into the cell before a more definitive treatment, cation exchange resin (sodium or calcium polysteryene sulphone resin) and/or dialysis, is used to remove potassium from the body. Insulin and albuterol have an additive effect in lowering serum potassium.[12] Table 2 summarises emergency treatment for severe hyperkalaemia. Although sodium bicarbonate use has fallen out of favour in patients on dialysis, it should be considered in patients with significant acidaemia where it is expected that infusion of bicarbonate would increase serum pH significantly.[13] *Cation exchange resin* mixed with sorbitol should be used orally if hyperkalaemia is not life threatening, however resin mixed with water (and not sorbitol) can be repeated hourly for rapid removal of potassium. It should be remembered that each gram of *sodium polystyrene resin* (Kayexalate) removes 0.5–1.0 mmol of potassium in exchange for 2–3 mmol of sodium. Therefore Kayexalate use is associated with significant sodium infusion and can result in volume overload. In addition several cases of colonic perforation have been reported in

Table 2 Treatment of hyperkalaemia

Mechanism of action	*Therapy*	*Onset/duration*	*Dose*
I. Membrane stabilisation	Calcium	1–3 min/30–60 min	Calcium gluconate 10% 10 ml iv
II. Shift of potassium intracellularly	Insulin	20 min/4–6 hours	10 U regular insulin iv with 50 ml 50% dextrose
	β_2-adrenergic agonist	20 min/2–4 hours	Dose depending on the type of agonist used
III. Removal of potassium	Sodium or calcium polystyrene sulphone	1–2 hours/4–6 hours	15 g every six hours orally or 30–60 g by retention enema
	Dialysis	Immediate/duration of dialysis	2–3 hours haemodialysis

iv = intravenous.

patients treated with Kayexalate mixed with sorbitol.[14]

After the acute treatment of hyperkalaemia, a long term plan should be devised to prevent recurrence of hyperkalaemia. Initially the treatment should be directed toward correction of the underlying cause of hyperkalaemia (such as replacement therapy in patients with Addison's disease). If hyperkalaemia is due to use of drug (such as aldosterone antagonists or potassium supplements), these should be discontinued. If hyperkalaemia is due to tubular defect in potassium secretion in association with renal failure, several therapeutic manoeuvres should be considered including:

- Hydration and volume expansion to increase urine flow rate and sodium delivery to exchange site.
- Use of loop diuretics to increase sodium delivery and stimulate potassium excretion.
- Restriction of dietary potassium intake to approximately 60 mmol/day.
- Use of oral mineralocorticoids such as fludrocortisone in supraphysiological doses. Most patients can be managed without use of fludrocortisone, however in some patients use of this drug in doses of 0.4–1.0 mg maybe needed. Hypertension and/or oedema formation maybe a limiting side effects in use of this drug.

Hypokalaemia

Hypokalaemia is probably the most common electrolyte abnormality in hospitalised patients. It is usually defined as a serum potassium of less than 3.5 mmol/l. Patients with mild hypokalaemia (serum potassium 3.0–3.5 mmol/l) usually have no symptoms. However, with more severe hypokalaemia (serum potassium of less than 2.5 mmol/l), generalised weakness can occur. In addition, patients with severe hypokalaemia can develop muscle necrosis (rhabdomyolysis) and paralysis. Both mild and severe hypokalaemia can increase the incidence of cardiac arrhythmias.

CLASSIFICATION OF HYPOKALAEMIA

Hypokalaemia can result from increased loss, transcellular shift, or decreased intake of potassium.[3 4 8] Increased potassium loss (through the kidney or gastrointestinal tract) is the most common cause of hypokalaemia. Less frequently, hypokalaemia can occur as a result of shift of potassium from the extracellular space into cells. Rarely, hypokalaemia can result from decreased intake of potassium.

Increased potassium loss, which is the most common cause of hypokalaemia, occurs mostly in patients who are on diuretics (thiazide or loop diuretics) or in patients with gastrointestinal diseases (diarrhoea). Thiazide and loop diuretics increase delivery of sodium to the collecting ducts, where it is reabsorbed via the amiloride-sensitive sodium channel, therefore creating a favourable gradient for potassium secretion via potassium channels. In addition, volume depletion that results from these diuretics increases aldosterone (by activation of renin-angiotensin-aldosterone pathway), further increasing potassium secretion via the secretory potassium channels in the collecting ducts. Increased aldosterone, in addition, can cause metabolic alkalosis by increasing hydrogen mediated bicarbonate reabsorption in the collecting duct. This latter phenomenon can worsen the diuretic-induced hypokalaemia by increasing potssium shift into cells. The diuretic acetazolamide, which causes metabolic acidosis by decreasing bicarbonate reabsorption in the proximal tubule, increases potassium excretion by increasing the delivery of sodium and bicarbonate to the distal nephrons. Hypokalaemia can also be due by increased loss in the stool in patients taking large doses of laxatives or having diarrhoea.

Hypokalaemia due to potassium shift into cells is caused by medications, hormonal dysregulation, or raised blood pH.[3 4 8 15] These medications include β_2-sympathomimetics (that is brochodilators such as albuterol) or phosphodiesterase inhibitors (that is theophylline and caffeine), exogenous insulin and rarely calcium channel blockers. Decreased potassium intake (less than 1 g/day), while rare, can lead to hypokalaemia. This is due to obligatory potassium loss of 10–15 mmol/day by the kidney despite a low potassium intake.

Among other disorders causing hypokalaemia magnesium depletion needs special emphasis.[14] Magnesium depletion, which is caused by either decreased dietary intake or increased loss, is a common electrolyte disorder in hospitalised patients. It can cause severe hypokalaemia by increasing renal potassium loss. The exact mechanism is, however, remains unclear. Hypokalaemia is also a common finding in patients with raised serum aldosterone either secondary to the activation of the renin-angiotensin system (Bartter's syndrome or Gitelman's syndrome) or due to overproduction by aldosterone-producing tumours (primary aldosteronism).

CLINICAL PRESENTATION OF HYPOKALAEMIA

Similar to hyperkalaemia, hypokalaemia is often asymptomatic. This is specifically true in patients with mild hypokalaemia (serum potassium 3.0–3.5 mmol/l). Patients with more severe hypokalaemia (serum potassium of less

than 2.5 mmol/l) usually present with generalised weakness and, in some cases, ascending paralysis. In addition, severe hypokalaemia can precipitate rhabdomyolysis which manifests as muscle tenderness and swelling. Cardiac arrhythmias are common in hypokalaemia, specifically in patients with underlying heart disease or on digoxin. In moderate to severe hypokalaemia changes in ECG are minimal and is often limited to the presence of a U wave.

RENAL SYNDROMES ASSOCIATED WITH HYPOKALAEMIA

In addition to the above clinical symptoms, hypokalaemia can cause several distinct renal syndromes as will be discussed below.

Nephrogenic diabetes insipidus

Hypokalaemia can impair urinary concentrating mechanism and result in nephrogenic diabetes insipidus. Patients with nephrogenic diabetes insipidus due to hypokalaemia present with polyuria and polydipsia. Molecular studies have demonstrated that potassium depletion causes downregulation of the water channel aquaporin 2 in the collecting duct, therefore impairing the renal concentrating mechanism and resulting in polyuria.[16]

Metabolic alkalosis

Hypokalaemia can contribute to the maintenance of metabolic alkalosis in several disease states (such as vomiting) by enhancing bicarbonate absorbing ability of renal tubules.[17–20] This in turn decreases the ability of the kidney to excrete the excess bicarbonate and as a result maintains the plasma bicarbonate at a raised level.[17] Functional and molecular studies in luminal and basolateral membranes of kidney proximal tubules and in microperfused kidney nephrons have demonstrated that hypokalaemia upregulates the expression of bicarbonate absorbing transporters in proximal tubules and cortical and medullary collecting ducts.[17–20] There is also evidence in support of hypokalaemia being involved in the generation of metabolic alkalosis in human by increasing ammoniagenesis.[17]

Enhanced renal chloride excretion

Hypokalaemia increases urinary chloride excretion.[19 20] Functional and molecular studies in the kidney have demonstrated that renal chloride wasting in hypokalaemia is due to suppression of the apical sodium-potassium-chloride cotransporter in the thick limb of Henle and the apical sodium-chloride cotransporter in the distal convoluted tubule.[21] It is possible that by increasing renal chloride excretion, hypokalaemia can result in hypochloraemia, which in turn can contribute to the maintenance of metabolic alkalosis in pathophysiological states.[17]

WORK-UP OF HYPOKALAEMIA

In working up patients with hypokalaemia a combination of common sense as well as pathophysiology should be used (box 3). Transient short term hypokalaemia is usually caused by a potassium shift due to medication or alkalaemia, however prolonged hypokalaemia is commonly due to renal or gastrointestinal loss of potassium. The most common causes of hypokalaemia in clinical practice are due to diuretics and gastrointestinal loss secondary to diarrhoea and/or vomiting. These aetiologies should therefore be considered first before exhaustive and sophisticated work-up is initiated. In other patients the initial step is to see if hypokalaemia is in association with systemic hypertension or not. In the former group hypokalaemia is associated with a high mineralocorticoid effect due to high aldosterone (as in primary aldosteronoma or renal artery stenosis) or cortisol as in Cushing's disease or hyperactive sodium channel as in Liddle's syndrome. Measurement of the renin, aldosterone, and cortisol concentrations under appropriate conditions would help in differentiating among these aetiologies. In normotensive patients, hypokalaemia could be secondary to overt or occult gastrointestinal loss or due to renal potassium wasting. Although low urinary potassium (less than 15 mmol/l) would favour gastrointestinal loss, high urinary potassium is seen in patients with vomiting or diarrhoea due to secondary elevation in the aldosterone level and is therefore not very helpful. In normotensive patients with renal potassium wasting, a low serum bicarbonate would favour the diagnosis of renal tubular acidosis, while a high serum bicarbonate is compatible with the high mineralocorticoid effect seen in patients with Bartter's or Gitelman's syndromes. Magnesium deficiency can result in renal potassium wasting and is often seen in alcoholics who are also nutritionally depleted. Diuretic and/or laxative abuse often mimics these rare syndromes and should be considered in any adult patient with hypokalaemia of unknown aetiology and ruled out by urinary test for specific diuretics and stool test for phenolphthalein.

MANAGEMENT OF HYPOKALAEMIA

The management of hypokalaemia is almost always by potassium replacement, with the amount of potassium supplement depending on the severity of hypokalaemia (box 4). The potassium can be given orally (in mild to moerate hypokalaemia) or intravenously (in severe hypokalaemia). When given intravenously, the rate of potassium administration should not exceed 20 mmol/hour. To calculate the amount of potassium supplement, one should have an estimate of the potassium deficit. On average, a reduction of serum potassium by 0.3 mmol/l suggests a total body deficit of 100 mmol. Based on this formula, a patient with a serum potassium of 2.6 mmol/l needs at least 300 mmol of potassium for the correction of the deficit. In calculating the total body potassium deficit one has to consider factors that can independently affect serum potassium. A patient with a serum potassium of 2.6 mmol/l has less total body deficit at blood pH of 7.5 than 7.3. The reason is that alkaline serum pH (that is, 7.5) can independently lower the serum potassium by intracellular shift.

Box 3: Work-up of hypokalaemia

(1) Acute hypokalaemia (less than 12 hours of onset)
- Alkalosis (metabolic or respiratory).
- Insulin therapy (for example, in severe hyperglycaemia).
- β_2-stimulant (for example, albuterol).

(2) Chronic hypokalaemia (more than 24 hours of onset)
- With normal blood pressure.

(A) Increased potassium loss through gastrointestinal tract: (i) diarrhoea, (ii) laxatives.
(B) Increased potassium loss through kidney: (i) diuretics, (ii) hypomagnesaemia, (iii) renal tubular acidosis (proximal and distal), (iv) genetic defects (for example, Bartter's syndrome, Gitelman's syndrome).
- With high blood pressure.

(A) Increased aldosterone: (i) primary aldosteronism (low renin), (ii) renal artery stenosis (high renin), (iii) Cushing's disease (high renin).
(B) Normal or low aldosterone: (i) hyperactive sodium channel (Liddle's syndrome), (ii) increased liquorice intake.

Box 4: Treatment of hypokalaemia

(1) Intravenous potassium (as potassium chloride)
- Usually reserved for severe hypokalaemia (serum potassium of <2.6 mmol/l).
- The rate of should not exceed 20 mmol/hour.

(2) Oral potassium
- Potassium chloride: 40–100 mmol/day in divided doses.
- Potassium phosphate (in patients with hypokalaemia and hypophsphataemia).
- Potassium bicarbonate (in patients with acidosis).

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In addition to potassium chloride, which is commonly used in treating hypokalaemias, potassium phosphate and potassium bicarbonate can be used in certain conditions. Potassium phosphate can be used in patients with combined potassium and phosphate depletion (for example in patients with liver cirrhosis or diabetic ketoacidosis). Potassium bicarbonate can be used in patients with potassium depletion and metabolic acidosis (for example in distal renal tubular acidosis). Aside from intravenous potassium chloride for severe hypokalaemia, mild or moderate hypokalaemia (see above) can be treated with oral potassium chloride. Usually, 50 to 100 mmol of potassium chloride is required per day to maintain serum potassium concentration within the normal range in patients with increased potassium loss (that is, in patients receiving a diuretic).

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