Hyperkalaemia

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Hyperkalaemia is defined as serum potassium concentration greater than 5.5 mmol/l. Its prevalence in the general population is unknown, but it is thought to occur in 1–10% of patients admitted to hospital.1 The rate of morbidity and mortality associated with hyperkalaemia has risen greatly with the use of drugs that target the renin-angiotensin system, and since publication 10 years ago of a randomised trial that showed that adding an aldosterone receptor antagonist to usual treatment for congestive failure improved outcomes,2,5

Potassium is the most abundant cation in the human body and has key roles in the excitatory properties needed for conduction of nerve impulses and muscle contraction. Ninety eight per cent of the body’s potassium is in the intracellular fluid (concentration about 140 mmol/l), with only 2% in extracellular fluid (3.8–5.0 mmol/l). A complex interplay of regulatory mechanisms is needed to maintain normal potassium balance, which involves the transfer of potassium between the extracellular and intracellular compartments (fig 1). In the long term potassium homeostasis is mainly governed by regulation of renal potassium excretion, notably by the actions of aldosterone (fig 2). These mechanisms ensure that although total daily potassium intake could range from 40 mmol to 200 mmol per day, potassium levels in serum remain within the relatively narrow normal range. Derangements in potassium regulation, and resultant changes in serum potassium concentration, may alter membrane excitability. Disorders of plasma potassium can therefore have profound effects on nerve, muscle, and cardiac function.

What are the common causes of hyperkalaemia?

Multiple factors are often involved in the pathogenesis of hyperkalaemia, which commonly results from decreased potassium excretion or increased release of potassium from cells.5 Hyperkalaemia can be spurious, and this possibility should be excluded first, except in severe cases when immediate treatment is needed.

Spurious hyperkalaemia

Spurious hyperkalaemia (also called pseudohyperkalaemia) occurs when the reported laboratory potassium values do not reflect actual in vivo concentrations—usually because platelets, leucocytes, or erythrocytes have released intracellular potassium in vitro. It can be excluded by sending a new sample for analysis or by simultaneously measuring potassium in plasma and serum; serum potassium concentration is usually 0.2–0.4 mmol/l higher than that in plasma, owing to release during normal clotting. Box 1 lists common causes of spurious hyperkalaemia.

Hyperkalaemia due to increased potassium intake

Excessive dietary intake of potassium is an uncommon cause of hyperkalaemia, unless concurrent decreased excretion is a factor. High potassium intake should be avoided in patients with compromised renal function. Box 2 lists foods rich in potassium. Hyperkalaemia can also occur with blood transfusion (due to release

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**Fig 1** Schematic representation of regulation of transcellular potassium movement. Cellular potassium concentration is controlled by an active uptake mechanism regulated by Na-K-ATPase and a passive leak mechanism driven by the electrochemical gradient favouring potassium exit from the cell. The rate of leak is dependent on the permeability of the potassium channels in the cell membrane. Insulin and β- adrenergic agonists (acting via cyclic AMP) promote potassium uptake into cells by stimulating the Na-K-ATPase pump. Insulin deficiency and β-blockers increase potassium movement out of cells leading to hyperkalaemia. Acidosis, hyperosmolarity, or cell lysis also cause potassium to leave cells and can cause hyperkalaemia. ECF=extracellular fluid; ICF=intracellular fluid.

**SUMMARY POINTS**

Hyperkalaemia is usually caused by a combination of factors, but renal failure and drugs are often implicated. Increased use of drugs that interact with the renin-angiotensin-aldosterone system has caused the prevalence of hyperkalaemia to rise. Hyperkalaemia can cause life threatening cardiac arrhythmias and should be urgently managed. ECG changes correlate poorly with the degree of potassium disturbance.

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Hyperkalaemia caused by shift of potassium out of cells
Several endogenous and exogenous factors can affect transfer of potassium between the extracellular and intracellular fluid to raise the concentration in serum. However, this mechanism is rarely the sole cause of severe hyperkalaemia, except when excessive release of intracellular potassium occurs with tissue injury or necrosis—for example, in rhabdomyolysis, tumour lysis, and severe burns. Box 3 shows causes of hyperkalaemia due to potassium redistribution.

Hyperkalaemia caused by reduced excretion of potassium
The kidneys are the main route of potassium elimination, and renal failure is the major cause of hyperkalaemia, accounting for up to 75% of cases of severe hyperkalaemia.1 In patients with chronic kidney disease, the capacity to excrete potassium is reasonably well maintained until renal failure is advanced (glomerular filtration rate <15–20 ml/min); until then hyperkalaemia is not usually seen unless intake of potassium is high or the patient is taking a drug that promotes hyperkalaemia.

Damage to the juxtaglomerular apparatus with resulting deficit in renin production can cause hyporeninaemic hypoaldosteronism, which can also cause hyperkalaemia in the absence of severe renal failure. Hyporeninaemic hypoaldosteronism is also known as type 4 renal tubular acidosis because it is often, but not always, associated with mild to moderate metabolic acidosis with a normal anion gap. Diabetic nephropathy is the most common underlying cause. Hypoaldosteronism can also be caused by primary disorders of the adrenal gland (such as Addison’s disease or congenital steroidogenic enzyme defects, most commonly 21 hydroxylase deficiency) or by reduced mineralocorticoid activity due to resistance to the action of aldosterone action in the kidney. The latter problem is often seen in sickle cell anaemia, systemic lupus erythematosus, amyloidosis, and obstructive nephropathy or with use of potassium sparing diuretics. In rare cases, it is caused by mutations of the gene encoding the mineralocorticoid receptor or its major downstream targets, including the epithelial sodium channel ENaC.

In general, an abnormality in mineralocorticoid level by itself does not produce hyperkalaemia if sufficient amount of sodium is delivered to the distal nephron. Thus, patients with Addison’s disease do not usually exhibit hyperkalaemia if they have adequate salt intake; it is only when sodium intake is restricted or they otherwise become volume depleted that hyperkalaemia develops. Disturbances of urinary flow rate or delivery of sodium to the distal nephron are therefore also important in the pathogenesis of hyperkalaemia. These defects can be intrinsic or (more commonly) caused by drugs (box 3, box 4).

Which drugs cause hyperkalaemia?
Drugs can interfere with potassium homoeostasis by promoting transcellular potassium shift or by impairing renal potassium excretion (for example, through effects on aldosterone action, sodium delivery to the distal nephron, or function of collecting tubules).136 In a prospective study of 242 consecutive patients admitted
Box 3 Causes of hyperkalaemia

Potassium redistribution (intracellular to extracellular fluid)
- Exercise
- Tissue necrosis or lysis (rhabdomyolysis, tumour lysis syndrome, severe burns)
- Insulin deficiency
- Metabolic acidosis (especially with mineral acids)
- Hyperosmolality (hyperglycaemia, mannitol infusion)
- Drugs (for example, succinylcholine, β-blockers, digoxin toxicity)
- Hyperkalaemic periodic paralysis

Decreased excretion of potassium
- Renal failure (glomerular filtration rate <20 ml/min)
- Decreased mineralocorticoid activity
- Hyporeninaemic hypoaldosteronism (chronic renal failure, diabetic nephropathy, NSAIDs)
- Adrenal insufficiency (Addison’s disease, congenital enzyme defects)
- Aldosterone blocking drugs (see box 4)
- End organ unresponsiveness to aldosterone (sickle cell anaemia, systemic lupus erythematosus, amyloidosis, and obstructive nephropathy)

Decreased urine flow rate or sodium delivery to distal nephron
- Severe volume contraction
- Rare genetic disorders, such as Gordon’s syndrome

Box 4 Drug induced hyperkalaemia

Drugs that alter transmembrane potassium movement
- β-blockers
- Digoxin
- Hyperosmolar solutions (mannitol, glucose)
- Suxamethonium
- Intravenous cationic amino acids

Potassium containing agents
- Potassium supplements
- Salt substitutes
- Herbal medicines (such as alfalfa, dandelion, horsetail, milkweed, and nettle)
- Stored red blood cells (haemolysis releases potassium)

Drugs that reduce aldosterone secretion
- ACE inhibitors
- Angiotensin II receptor blockers
- NSAIDs
- Heparins
- Antifungals (ketoconazole, fluconazole, itraconazole)
- Ciclosporin
- Tacrolimus

Drugs that block aldosterone binding to mineralocorticoid receptor
- Spironolactone
- Eplerenone
- Drospirenone

Drugs that inhibit activity of epithelial sodium channel
- Potassium sparing diuretics (amiloride, triamterene)
- Trimethoprim
- Pentamidine

with hyperkalaemia, 63% were taking drugs that interfere with potassium balance. The risk of hyperkalaemia is particularly great when such drugs are given to patients with underlying renal insufficiency. The elderly and patients with diabetes are especially susceptible. Doctors should therefore prescribe such drugs with caution in these populations; it is best to start with low doses and to recheck serum potassium within a week of starting the drug, and with each increase in dose. There are no consensus guidelines as to what constitutes timely follow-up, but the frequency with which serum potassium is monitored will depend on the level of renal impairment, the presence of diabetes, and concurrent use of other hyperkalaemia inducing medications. Particular caution should be exercised in patients with underlying cardiac conduction defects, in whom even minor increases in serum potassium can precipitate severe arrhythmias. A comprehensive list of drugs associated with hyperkalaemia is given in box 4. We will briefly discuss some of the most commonly prescribed ones.

Angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) are increasingly used for renoprotection and to reduce cardiovascular mortality in patients at high risk, particularly those with diabetes. They also are standard treatment in the management of patients with chronic heart failure. ACE inhibitors and ARBs predispose to hyperkalaemia because they impair aldosterone secretion and reduce renal perfusion (and thus glomerular filtration rate), both of which decrease excretion of potassium by the kidneys. However, in general, they do not cause hyperkalaemia in patients with normal renal function; indeed, the degree of aldosterone suppression is usually not sufficient to substantially impair potassium excretion unless pre-existing hypoaldosteronism from other causes (disease state or from other drugs) is present. Unfortunately, most patients targeted for renovascular benefits of these drugs (such as those with diabetes, renal failure, or heart failure) are at high risk of developing hyperkalaemia. About 10% of outpatients develop hyperkalaemia within a year of starting treatment with ACE inhibitors or ARBs. Moreover, these drugs contribute to hyperkalaemia in 10-38% of patients admitted to hospital with the condition, with the risk increasing substantially when higher doses are used or when they are used in combination or with other hyperkalaemia inducing drugs.

Aldosterone (mineralocorticoid) receptor antagonists are also commonly prescribed to treat patients with congestive cardiac failure since the Randomized Aldactone Evaluation Study showed that the addition of spironolactone to standard treatment is associated with significant reduction in morbidity and mortality. Serious hyperkalaemia occurred in only 2% of patients in the study, where the average serum creatinine concentration was 106 µmol/l and the dose of spironolactone did not exceed 25 mg daily. By contrast, population based time-series analyses have demonstrated significant increases in rates of hospitalisation and mortality from hyperkalaemia. This is probably because these studies included patients with more severe renal dysfunction who were given higher doses of
spironolactone. These patients were also more likely than those in the clinical trial to be taking potassium supplements or other drugs that impair potassium excretion. The risk was highest in patients who took spironolactone in combination with ACE inhibitors or ARBs, particularly in elderly patients with renal failure. Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit renin secretion (leading to hypoaldosteronism and reduced potassium excretion) and can impair renal function. These agents should be prescribed judiciously in patients with diabetes or renal insufficiency, particularly if they are concurrently receiving ACE inhibitors or ARBs.

**How is hyperkalaemia diagnosed?**

Hyperkalaemia is often asymptomatic and discovered on routine laboratory tests. When symptoms are present, they are non-specific and predominantly related to muscular function (paresthesiae, muscle weakness, fatigue) or cardiac function (palpitations). Hyperkalaemia may produce progressive abnormalities on the electrocardiogram (ECG), including peaked T waves, flattening or absence of P waves, widening of QRS complexes, and sine waves (fig 3). However, electrocardiography is not a sensitive method for detecting hyperkalaemia. In a study by Acer and colleagues nearly half the patients with serum potassium concentration greater than 6.5 mmol/l did not have ECG changes. Moreover, whereas some patients show gradual progression in changes, others progress from benign to potentially fatal ventricular arrhythmias without warning.

Assessment of a patient with hyperkalaemia should include a thorough review of the medical history to identify potential contributing factors such as renal failure, diabetes, adrenal insufficiency, and use of drugs that cause hyperkalaemia. Laboratory blood tests should be directed towards causes suggested by the history and physical examination, and should include urea, creatinine, electrolytes, and serum osmolarity (acute increase in osmolarity can cause potassium to exit from cells). Analysis of urine potassium concentrations could help to ascertain whether renal potassium elimination is appropriate. In selected patients, additional specialised tests such as measurement of the fractional excretion of potassium or transtubular potassium gradient may be useful in distinguishing between renal and non-renal causes of hyperkalaemia.

**How is severe hyperkalaemia managed?**

Guidelines for treatment of hyperkalaemia are based on consensus or expert opinion because of a lack of controlled clinical trials. Treatment should be aimed at restoring normal potassium balance, preventing serious complications, and treating the underlying causes. Figure 4 shows a general approach in management of patients with hyperkalaemia. Mild to moderate hyperkalaemia can be treated with a loop diuretic to increase urinary potassium excretion. Dietary potassium is restricted and hyperkalaemic drugs should be minimised or withdrawn. If a patient has renal failure a diuretic may not be effective and other measures, including dialysis, may be needed.

Severe hyperkalaemia is a life threatening state because it can cause catastrophic cardiac and neuromuscular effects, such as cardiac arrest and paralysis of the respiratory muscles. Therefore prompt and aggressive treatment is necessary. Most authorities consider that serum potassium concentration of greater than 6.0 mmol/l with ECG changes, or greater than 6.5 mmol/l regardless of the ECG, represents severe hyperkalaemia that warrants urgent treatment. If the patient's ECG suggests hyperkalaemia, or in a clinical scenario such as cardiac arrest in a patient having chronic dialysis, for example, therapy is frequently started without waiting for laboratory confirmation. Other factors that might necessitate pre-emptive treatment of hyperkalaemia include a rapid rise of serum potassium, the presence of significant acidosis, and rapid deterioration in renal function.

Most guidelines and experts advise that severe hyperkalaemia should be treated in an inpatient setting to allow continuous cardiac monitoring, because even patients without symptoms or ECG changes can swiftly develop life threatening arrhythmias. Although urgent

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**Fig 3** ECG changes in patients with hyperkalaemia

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**Sources and Selection Criteria**

We searched PubMed for articles whose titles included the terms “hyperkalaemia” or “potassium homoeostasis” and restricted the search to articles published in English in the past 15 years. We also searched contemporary textbooks.
Raised potassium level

Is the increase genuine? (see box 1 for causes of spurious hyperkalaemia)

Yes

Is potassium >6.5 mmol/l or are ECG changes present?

Yes

Emergency treatment*

Give IV calcium gluconate

Give IV insulin with glucose and/or nebulised salbutamol

Give furosemide and/or calcium resonium

Consider dialysis

No

No treatment needed

Dietary restriction

Stop any potassium sparing diuretic

Use of diuretic depending on underlying cause

Long term measures to prevent recurrence

*Management of severe hyperkalaemia should be undertaken in an inpatient setting with continuous cardiac monitoring
†Patients with moderate hyperkalaemia (serum potassium 6.0-6.5 mmol/l) should probably be admitted to hospital for supervised lowering of serum potassium

Fig 4 | Algorithm for diagnosis of hyperkalaemia. IV=intravenous

dialysis to remove potassium from the body would be the definitive treatment, delays in starting this treatment are inevitable. A 2005 Cochrane systematic review of emergency interventions for hyperkalaemia recommended that immediate temporising treatment incorporates three key measures.19

The first step is to stabilise the myocardium to reduce its susceptibility to ventricular arrhythmias. Intravenous calcium is used to directly antagonise the membrane effects of hyperkalaemia, stabilising cardiac conduction. Calcium gluconate in a volume of 10 ml of 10% solution is infused over 3–5 minutes with cardiac monitoring. Calcium infusion does not affect serum potassium level, but beneficial ECG changes can be seen after 1-3 minutes of administration and the effect can last for 30-60 minutes. The infusion can be repeated if no effect is seen within 5-10 minutes. Caution should be exercised when replacing calcium in patients taking digoxin because calcium potentiates myocardial toxicity to digoxin.20

The second step is to shift potassium from the extracellular to the intracellular fluid compartment so as to rapidly decrease serum potassium. This shift is achieved by administration of insulin or β2 agonist, both of which stimulate the Na+/K+ pump. Insulin is given as an intravenous bolus along with sufficient glucose to prevent development of hypoglycaemia (usually 10 units of insulin with 50 ml of 50% dextrose given over 5 minutes). The hypokalaemic effect of this treatment can be seen within 20 minutes, peaking between 30 and 60 minutes, and it may last for 6 hours. Salbutamol is the most commonly used selective β2 agonist. It is usually given through a nebuliser (10-20 mg in 4 ml of saline). An effect may be seen in 30 minutes, with maximum effect at 90–120 minutes. Salbutamol can be used alone or to augment the effect of insulin. Patients with acidosis may also be treated with intravenous sodium bicarbonate (500 ml of a 1.26% solution [75 mmol] over 60 minutes) although the benefit is uncertain and routine bicarbonate treatment for hyperkalaemia remains controversial.19,21

Thirdly, further interventions are undertaken to remove potassium from the body. Potent loop diuretics (for example, 40-80 mg of intravenous furosemide) enhance renal potassium excretion by increasing urine flow and sodium delivery to the distal nephron. However, diuretics only work if the patient has adequate renal function, and many patients with hyperkalaemia have acute or chronic renal failure. Cation exchange resins, which remove potassium from extracellular fluid via the gut in exchange for sodium, are also commonly used, although their effectiveness is debatable.22 They act more quickly when given as enemas (for example, calcium resonium 30 mg) than when given orally (15 mg four time a day); it may take 6 hours to achieve a full effect. Dialysis is the definitive treatment for patients with severe hyperkalaemia and advanced chronic kidney disease.

**Long term management of hyperkalaemia**

After acute treatment, measures should be established to prevent recurrence of hyperkalaemia. The first step is to carefully review the patient’s medication and to avoid or minimise drugs that increase potassium retention. Because ACE inhibitors and ARBs slow the progression of chronic

**TIPS FOR NON-SPECIALISTS**

- In patients without predisposition to hyperkalaemia, recheck serum potassium to rule out spurious hyperkalaemia, unless ECG changes suggest that emergency treatment is warranted
- Do not overlook hidden causes of hyperkalaemia, such as herbs, salt substitutes, and over the counter drugs (such as NSAIDs)
- ACE inhibitors and ARBs should be started at low doses and potassium checked a week after starting treatment or after increasing dose
- All patients with hyperkalaemia should undergo 12 lead electrocardiography
- ECG changes and cardiac arrhythmias associated with hyperkalaemia are true medical emergencies

**QUESTIONS FOR ONGOING AND FUTURE RESEARCH**

- How important are the different risk factors for hyperkalaemia, and how does the clinician define them quantitatively in an individual?
- With increasing use of cardioprotective or renoprotective treatments that promote potassium retention, what is the best way to monitor potassium levels?
- Do patients with chronic hyperkalaemia actually achieve balance for potassium—if so, how is this balance achieved?
- Further understanding of the molecular pathways responsible for maintaining potassium concentration in extracellular fluid, to develop novel therapeutic strategies to treat life threatening hyperkalaemia.
Additional educational resources

Resources for clinicians

• Rose BD. Clinical manifestations and treatment of hyperkalemia. UpToDate (online). Version 15.1. 2007 (www.uptodateonline.com).


Resources for patients

• National Kidney Foundation (www.kidney.org/atoz/content/potassium.cfm)—information on potassium content of foods.

Renal disease, use of other measures to control the hyperkalaemia or dose reduction are preferable to discontinuing these drugs. Dietary advice to restrict potassium intake to 40-60 mmol a day is prudent. Diuretics may be effective in promoting renal potassium loss to prevent recurrence of hyperkalaemia. Thiazide diuretics may be used in patients with preserved renal function, but are usually ineffective when the glomerular filtration rate is less than 40 ml/min, when a loop diuretic such as furosemide is preferable. Fludrocortisone may be used in patients with hyporeninaemic hypoaldosteronism. However, this drug can cause fluid retention and hypertension, and should be used with caution—particularly in patients with type 2 diabetes, who often have co-existing hypertension.

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Corrections and clarifications

Potential causes and health effects of rising global food prices

In this Analysis article by Karen Lock and colleagues (BMJ 2009;339:b2403, print publication 1 Aug, pp 269-72), the graphs for figure 1 and figure 2 were wrongly switched at page proof stage. The captions to the graphs were correctly placed and numbered, but the graph that was with the figure 1 caption should have been with the figure 2 caption, and vice versa.

Rosiglitazone and pioglitazone: Beware macular oedema

The second author of this letter by Rosemary G Lambley and colleagues (BMJ 2009;339:b3856, print publication 26 Sep, p 709) is Kaveh Vahdani [not Kaveh Vahdani, as published].

Sarcoidosis: Technique to enable diagnosis

During the editing of this Letter by Andrew R L Medford and colleagues (BMJ 2009;339:b3962, print publication 3 Oct, pp 766-7) we managed to transpose the authors’ addresses. Thus, Dr Medford is at North Bristol Lung Centre, Southmead Hospital, Bristol, whereas Sanjay Agrawal and Jonathan Bennett are at the Department of Respiratory Medicine, Glenfield Hospital, Leicester.

Picture of the week

The Picture of the week in the print publication of 19 September 2009 showed an example of the “lying down game,” and the caption gave a link to a doc2doc discussion about certain hospital staff who got into trouble for playing the game. The correct link is http://ow.ly/oI2I.