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# Management of hyperkalaemia

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**ABSTRACT** Hyperkalaemia, an elevated extracellular fluid potassium concentration, is a common electrolyte disorder and is present in 1–10% of hospitalised patients. Elevated serum potassium concentrations are usually asymptomatic but may be associated with electrocardiogram (ECG) changes. Hyperkalaemia occasionally leads to life-threatening cardiac arrhythmias. Prompt recognition of this disorder, patient risk management and administration of appropriate treatment can prevent serious cardiac complications of hyperkalaemia. Further assessment of the underlying basis for hyperkalaemia usually reveals a problem with renal potassium excretion (rather than transcellular shift of potassium or excess potassium intake).

Reduced potassium excretion is typically associated with decreased potassium secretion in the aldosterone-sensitive distal nephron of the kidney. Common causes for hyperkalaemia include kidney failure, limited delivery of sodium and water to the distal nephron and drugs that inhibit the renin-angiotensin-aldosterone system.

Treatment of life-threatening hyperkalaemia (particularly those patients with ECG changes) involves administration of intravenous calcium salts to stabilise the resting cardiac membrane potential. The potassium concentration can be lowered by administration of intravenous insulin combined with an infusion of glucose to stimulate intracellular uptake of potassium. Nebulised β-2 adrenoceptor agonists can augment the effects of intravenous insulin and glucose pending more definitive management of the recurrent hyperkalaemia risk. Additional management steps include stopping further potassium intake and careful review of prescribed drugs that may be adversely affecting potassium homeostasis. Changes to prescribing systems and an agreed institutional protocol for management of hyperkalaemia can improve patient safety for this frequently encountered electrolyte disorder.

**KEYWORDS** Hyperkalaemia, insulin and glucose infusion, intravenous calcium, salbutamol

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## INTRODUCTION

Hyperkalaemia is a potentially life-threatening electrolyte abnormality that is usually associated with renal impairment (acute or chronic).[1,2] There is no agreed definition of hyperkalaemia, but a serum potassium >5.5 mmol/L is typically quoted.[3] Both the absolute serum potassium value and the rate of rise of serum potassium are risk factors for electrocardiogram (ECG) changes and cardiac arrhythmias. The European Resuscitation Council recommends the stratification of hyperkalaemia into mild (5.5–5.9 mmol/L), moderate (6.0–6.4 mmol/L) and severe (>6.5 mmol/L) to aid clinical decision-making.[4] In practice, treatment of hyperkalaemia may be triggered by a combination of the absolute serum potassium level, the rate of change of serum potassium and the patient's clinical state.

### *Incidence*

Hyperkalaemia is present in 1–10% of hospitalised patients and is most often associated with renal failure, drugs that decrease renal potassium excretion and hyperglycaemia, or a combination of these factors.[1,2,5,6]

In primary care, drug prescribing contributes to the risk of hyperkalaemia, particularly in patients with heart failure, hypertension or chronic kidney disease (CKD).[6–9] Drugs that block the renin-angiotensin-aldosterone axis, especially when prescribed in combination (e.g. beta blockers, angiotensin, converting enzyme inhibitors, angiotensin receptor blockers, spironolactone and other potassium-sparing diuretics), increase the likelihood of developing hyperkalaemia.[6–9] An acute illness or prescription of non-steroidal anti-inflammatory drugs

(NSAIDs) may trigger an acute kidney injury (AKI),[10] in persons with heart failure or CKD, leading to a rapid increase in serum potassium concentration.

Hyperkalaemia is common in haemodialysis patients with the risk increased by prolonged intervals between dialysis and non-compliance with dietary potassium restriction. Hyperkalaemia is a frequent reason for emergency haemodialysis and is linked to the higher risk of sudden cardiac death in persons with end-stage renal disease.[11]

## ASSESSMENT OF HYPERKALAEMIA

Discovery of hyperkalaemia should prompt a rapid assessment of a patient's clinical status. This should include noting any relevant history (e.g. presence of CKD), their current drug prescriptions (Table 1) and an assessment of their clinical observations utilising an early warning score (EWS).[12] Clinical assessment of an acutely ill patient, using a structured airway, breathing, circulation, disability, exposure (ABCDE) approach, should trigger appropriate escalation of care and call for senior help.[13] Hyperkalaemia is not an isolated problem and may be present in a patient with hypoxia, sepsis, cardiac and/or renal failure. An urgent 12-lead ECG is recommended in patients with a serum potassium >6.0 mmol/L, although severe hyperkalaemia can still be present in patients without obvious ECG changes.[14,15] Typical ECG features, associated with increasing serum potassium levels, include tented T waves, prolonged PR interval, loss of P waves, broadening of QRS complexes, eventual merger of the QRS complex with the T wave and deterioration into cardiac arrhythmias such as ventricular fibrillation. Continuous ECG monitoring is recommended if severe hyperkalaemia and/or 12-lead ECG abnormalities are discovered in an ill patient (ideally in a high dependency bed).

The finding of severe hyperkalaemia (>6.5 mmol/L) should act as a trigger for appropriate management if the clinical situation is consistent with emergence of hyperkalaemia, e.g. the patient has renal failure. Ideally the presence of hyperkalaemia should be confirmed by either near patient testing (e.g. with a blood gas analyser) or repeat laboratory serum potassium measurement.

**TABLE 1** Drugs that may contribute to hyperkalaemia

- Drugs that limit renal potassium excretion, e.g. angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, spironolactone, amiloride, beta blockers, trimethroprim etc.)
- Nephrotoxic drugs, e.g. non-steroidal inflammatory drugs (naproxen, diclofenac, ibuprofen etc.)
- Potassium-containing drugs e.g. certain laxatives (Movicol®, Klean Prep®, Fybogel® etc.)
- Potassium supplements

There is evidence that using a lithium heparin anticoagulated specimen tube provides the most accurate potassium measurement in emergency situations.[16] Delay in the management of hyperkalaemia may be potentially life-threatening, particularly in the presence of typical ECG features, so confirmation of serum potassium value should be undertaken in parallel with emergency treatment of severe hyperkalaemia.

## EMERGENCY TREATMENT OF SEVERE HYPERKALAEMIA

A systematic clinical management strategy can provide effective treatment of hyperkalaemia with improved patient outcomes and reduced risks of adverse events. Unfortunately there is considerable variation in the algorithms and protocols for the management of hyperkalaemia in textbooks and guidelines. The absence of universally agreed guidelines has been compounded by the limited evidence for many of the commonly used treatments.[17] Immediate treatment principles include:

1. Providing calcium salts to reduce the risk of arrhythmia ('protect the heart');
2. Administering intravenous glucose and insulin ('shift potassium into cells');
3. Reducing intake and increasing output of potassium ('remove potassium from the body').

### *Intravenous calcium*

Hyperkalaemia decreases the resting membrane potential of myocardial cells, making them much more likely to spontaneously depolarise and thereby trigger cardiac arrhythmias. Intravenous calcium salts antagonise the depolarisation effect of hyperkalaemia and reduce cardiac membrane excitability. Intravenous calcium has no effect on the serum potassium level. Intravenous calcium 'buys time' for other treatment for hyperkalaemia to be administered. The rationale for use of intravenous calcium is well-established, although there have never been randomised trials of its efficacy in hyperkalaemia.[17]

Intravenous calcium has rapid effects, resulting in improvement of ECG abnormalities within minutes of administration. Intravenous calcium has a 30–60-minute duration of action. A dose may be repeated within 5–10 minutes if there has been no change in the ECG features of hyperkalaemia. Repeated doses may also be required if the hyperkalaemia remains uncontrolled or recurs.

Intravenous calcium salts may be administered as either calcium chloride or calcium gluconate with the choice dictated by local availability and clinical practice. It is important to recognise that volume for volume the calcium content is lower in calcium gluconate compared with calcium chloride (10 ml 10% calcium gluconate = 2.25 mmol calcium vs 10 ml 10% calcium chloride = 6.8

mmol calcium).[18] Extravasation of intravenous calcium salts can cause tissue necrosis which is one reason why calcium gluconate has been recommended in some guidelines. Secure venous access is essential for intravenous administration of calcium, glucose and insulin needed for the management of hyperkalaemia.

One caveat exists in relation to intravenous calcium administration. Patients with acute cardiac glycoside (e.g. digoxin) poisoning can develop hyperkalaemia. In such patients, however, intracellular hypercalcaemia may be present as a result of the poisoning, and treatment with intravenous calcium can result in severe cardiac dysfunction or death.[19] In these patients, the treatment priority is the administration of digoxin-specific antibody fragments, while potassium may be lowered using the methods described later. In practice, digoxin toxicity may be unrecognised at the time of treatment of hyperkalaemia. A recent study reported that there may be no increased risk of cardiac arrhythmia or death following intravenous calcium administration in patients with digoxin toxicity.[20]

### *Intravenous glucose and insulin*

Insulin is the most effective agent for reducing the serum potassium level. Insulin binds to cell membrane receptors stimulating increased sodium-potassium ATPase activity, resulting in a net shift of potassium into cells.[17,21] This action of insulin is independent of any hypoglycaemic effect. A dose of 10 units of soluble insulin has been used in the majority of published studies of insulin-glucose infusions for hyperglycaemia.[17] In patients with normal serum glucose levels the administration of intravenous insulin will potentially result in serious hypoglycaemia and for this reason the insulin is co-administered with hypertonic glucose. In hyperglycaemic patients (serum glucose >15 mmol/L) insulin may be given without additional intravenous glucose, provided the serum glucose level is monitored frequently thereafter.

The potassium-lowering effect of intravenous insulin and glucose typically begins within 15 minutes of administration and reaches peak effect 30–60 minutes after infusion. The serum potassium concentration may fall by up to 1 mmol/L.[22] The effectiveness of this insulin and glucose regimen is enhanced if nebulised salbutamol is also provided.[23,24] The reduction in serum potassium is sustained for several hours, but the potassium concentration will gradually rise again (rebound effect)[22] if the cause of hyperkalaemia cannot be rapidly ameliorated, e.g. kidney failure with recent use of drugs blocking the renin-angiotensin-aldosterone axis. Repeated administration of intravenous insulin and glucose may be necessary pending more effective measures to remove potassium from the body, e.g. haemodialysis.

Hypoglycaemia is the main risk of therapy with intravenous insulin and glucose.[25] Continued monitoring of blood glucose for up to six hours following administration of insulin and glucose is recommended.

### *Nebulised salbutamol*

Salbutamol is a β-2 adrenoceptor agonist that provides a dose-dependent stimulus to the sodium-potassium ATPase pump resulting in a shift of potassium into cells. Nebulised salbutamol is easier to administer and associated with fewer side-effects than intravenous salbutamol.[22] The potassium-lowering effect of nebulised salbutamol occurs within 30 minutes and lasts for up to two hours. The serum potassium level may fall by between 0.5–1.0 mmol/L when 10–20 mg of nebulised salbutamol is delivered.[17,24] The potassium-lowering effect of intravenous insulin and glucose is augmented by co-administration of nebulised salbutamol so that the peak lowering of serum potassium exceeds 1.0 mmol/L.[17,23]

Unfortunately, for unknown reasons, salbutamol may be ineffective in up to 40% of patients with end-stage renal disease.[26,27] Patients prescribed beta blockers may also be 'resistant' to the hypokalaemic effects of salbutamol. In view of these concerns, salbutamol is not recommended as monotherapy for hyperkalaemia[17] but is a useful adjunct to intravenous insulin and glucose.

### *Other therapies of limited or questionable efficacy*

Administration of sodium bicarbonate as monotherapy fails to lower serum potassium acutely.[17,28] Sodium bicarbonate therapy is also associated with the risks of sodium and fluid overload in ill patients and its use is not recommended in management of hyperkalaemia. There is limited evidence for the efficacy of cation exchange resins in the management of hyperkalaemia.[29,30] These resins are administered either orally or as an enema and they exchange bound sodium or calcium for potassium in the intestine. Cation exchange resins have no place in the emergency management of hyperkalaemia since these agents have not been convincingly shown to lower serum potassium within four hours of administration.[17,30]

## NEXT STEPS AFTER INITIAL TREATMENT OF HYPERKALAEMIA

The administration of an insulin-glucose infusion with nebulised salbutamol should effectively lower the serum potassium concentration within 30–60 minutes, with this beneficial effect lasting 4–6 hours. Repeated measurement of serum potassium is prudent to ensure there has been a fall in serum potassium at between one and two hours post-administration and again at between four and six hours to detect any 'rebound' in serum potassium level requiring further treatment.

Hypoglycaemia is arguably the most frequent complication of hyperkalaemia treatment. It can present with sweating, palpitations, hunger and, if severe, may lead to confusion, coma or even death.[25,31] The risk of hypoglycaemia is directly related to the dose of insulin given, and inversely related to the amount of hypertonic glucose infused. The incidence of hypoglycaemia has been reported to vary from 10–75% in persons receiving 25 g glucose by infusion (typically delivered as 50 mL 50% glucose intravenously).[23,32,33] Blood glucose levels should be monitored regularly and ideally every 30 minutes for two hours, then hourly until six hours following insulin administration. If hypoglycaemia does occur it can be managed by providing a further bolus of intravenous hypertonic glucose.

After initial successful therapy of severe hyperkalaemia it is important to re-evaluate the clinical state of the patient. Hyperkalaemia will usually have occurred in the setting of CKD or an AKI. Referral of the patient to a local renal unit or an Intensive Care Unit (ICU) team is appropriate if it seems likely that dialysis treatment for hyperkalaemia will be needed or further escalation of care is necessary.

To reduce the risk of persistent hyperkalaemia it is important to review prescribed drugs, intravenous fluids and the patient's diet. Nephrotoxic drugs and potassium-containing drugs should be discontinued. In addition, drugs that limit renal potassium excretion should at least be temporarily withheld. Potassium supplements in intravenous fluids or parenteral nutrition are to be avoided. A low potassium diet should be instituted, advising the patient to avoid foodstuffs with naturally high potassium content. Dietary supplements should also be reviewed since some of the commonly prescribed drinks are rich in potassium.

## GUIDELINES AND EDUCATION

The variation between different guidelines and treatment algorithms has contributed to uncertainty about the optimal management of severe hyperkalaemia. The Renal Association and Resuscitation Council (UK) have recently collaborated to develop clinical guidelines to improve the treatment of hyperkalaemia.[34] If such guidelines are widely adopted it will help to promote a standardised approach for the management of hyperkalaemia. Such guidance could be integrated into medical school curricula and postgraduate training and tested in knowledge-based exam and objective structured clinical evaluation (OSCE) formats.

Instances of maladministration of insulin have occurred during the management of hyperkalaemia, e.g. failure to use an insulin syringe to draw up or administer insulin. This can result in a 'never event' of accidental overdose of insulin. 'Never events' are defined by the Department of Health as 'very serious, largely preventable patient safety incidents that should not occur if the relevant preventative measures have been put in place'.[35]

Northern Ireland has adopted a system for management of severe hyperkalaemia in hospital following two 'never events' associated with accidental overdose of insulin. Local guidelines for the management of hyperkalaemia were published in 2009,[36] together with the development of a ward-based kit to aid management (Figure 1). A written step-by-step approach for the management of hyperkalaemia that particularly emphasises the dose of insulin to be administered, is included in the 'box'. This kit (Figure 2) contains:

- 10 x 10 ml calcium gluconate 10% ampoules
- 2 x 50 ml 50% glucose Minijet®
- 1 x 50 ml 50% glucose glass bottle
- 20 x 2.5 mg salbutamol nebules
- 2 x insulin syringes (labelled with the 10 unit dose of insulin to be administered) (Figure 3)

Short-acting insulin, e.g. Actrapid®, is available in the ward pharmaceutical fridge. A junior doctor, providing treatment for hyperkalaemia, must check with a senior nurse that an insulin syringe has been used and the correct dose of insulin drawn up before being

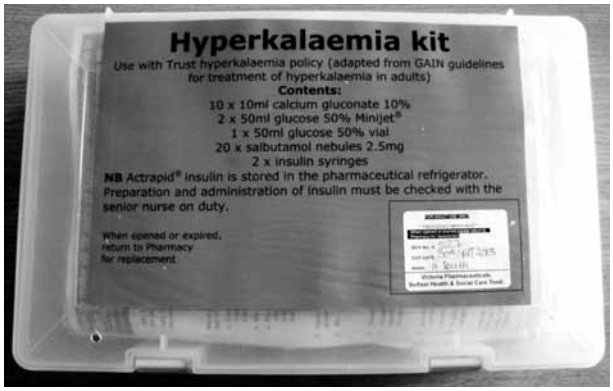


**FIGURE 1** Hospital ward-based box used in the management of hyperkalaemia.


**FIGURE 2** Contents of 'hyperkalaemia box'.

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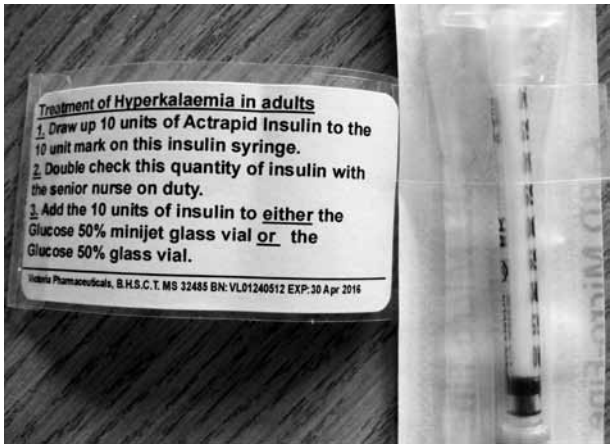


**FIGURE 3** Labelled insulin syringe to ensure correct insulin delivery device is used.

administered to a patient. Instructions on how to add 10 units of Actrapid® insulin to 50 ml 50% glucose Minijet® prior to administration are also provided in the 'hyperkalaemia box'. To the authors' knowledge, there have been no further 'never events' related to maladministration of insulin for hyperkalaemia in Northern Ireland since this 'hyperkalaemia box' was introduced into hospital practice. In addition, all medical students at Queens University Belfast must demonstrate safe practical knowledge of hyperkalaemia treatment in a clinical OSCE station.

## CONCLUSIONS

Hyperkalaemia is a serious electrolyte abnormality with non-specific or absent symptoms, even when severe, before causing cardiac arrest. The incidence of hyperkalaemia is increasing. The majority of cases relate to the prescription of drugs that block the renin-angiotensin-aldosterone axis which are commonly prescribed to treat patients with chronic heart failure, hypertension and CKD. Many of these patients are elderly and are often prescribed multiple medications, increasing the risk for adverse drug reactions. This group of patients are particularly susceptible to developing hyperkalaemia if they develop an acute illness or are prescribed drugs that compromise renal function. The implementation and use of protocols providing physicians with clear and concise information to enable safe and effective management of hyperkalaemia should improve the treatment of this serious electrolyte abnormality.

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