Clinical Practice Guidelines
Treatment of Acute Hyperkalaemia in Adults

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Endorsements

The National Institute for Health and Care Excellence (NICE) has accredited the process used by the Renal Association to produce its Clinical Practice Guidelines. Accreditation is valid for 5 years from January 2017. More information on accreditation can be viewed at www.nice.org.uk/accreditation

Method used to arrive at a recommendation

The recommendations for the first draft of this guideline resulted from a collective decision reached by informal discussion by the authors and, whenever necessary, with input from the Chair of the Clinical Practice Guidelines Committee. If no agreement had been reached on the appropriate grading of a recommendation, a vote would have been held and the majority opinion carried. However this was not necessary for this guideline.

Conflicts of Interest Statement

All authors made declarations of interest in line with the policy in the Renal Association Clinical Practice Guidelines Development Manual. Further details can be obtained on request from the Renal Association.
Summary of the changes since 2014 Hyperkalaemia Guideline

Format of the Guideline

The scope of the guideline has been extended to include the management of hyperkalaemia in the community.

The current guideline has been written in 3 sections:

- Section I: Management of Hyperkalaemia in the Community
- Section II: Management of Hyperkalaemia in Hospital
- Section III: Management of Hyperkalaemia in Resuscitation

This format allows clinicians to navigate the guideline to find areas of interest more easily.

New therapies for treating hyperkalaemia

Over the past 5 years, there has been some progress with new treatments for hyperkalaemia.

Sodium zirconium cyclosilicate

This oral potassium binder has recently been approved by NICE (September 2019) for the treatment of hyperkalaemia in restricted circumstances:

- SZC is recommended for life-threatening hyperkalaemia (K⁺ ≥ 6.5 mmol/l) alongside standard treatment with insulin-glucose and salbutamol.
- SZC is recommended for persistent hyperkalaemia with a confirmed serum K⁺ ≥ 6.0 mmol/l in outpatients with CKD Stage 3b-5 (not on dialysis) or heart failure receiving a sub-optimal dose of RAASi therapy.

NICE has recommended that SZC is initiated in secondary care only and the drug should be discontinued if RAASi therapy is stopped.

Patiromer

This oral potassium binder is currently being assessed by NICE, therefore a formal recommendation is not feasible at present.

New recommendations for therapies in treating hyperkalaemia

Insulin-glucose infusion

The 2014 Hyperkalaemia Guideline recommended the use of 10 units of soluble insulin with 25g glucose. In recent years, there have been multiple published reports of a high incidence of iatrogenic hypoglycaemia. This has prompted review of this treatment regimen.

The most consistent risk factor for iatrogenic hypoglycaemia is a low pre-treatment blood glucose. Reducing the dose of insulin alone did not consistently reduce hypoglycaemic episodes. There is more evidence to support increasing the total glucose load to 50g. The lowest risk of severe hypoglycaemia was associated with continuous delivering of glucose.

Preserving efficacy is essential in treating hyperkalaemia. One study reported that low dose insulin (5 units) may not be as effective as conventional dose insulin (10 units) in treating patients with a serum K⁺ > 6.0 mmol/l. Studies using 10 units insulin also show a trend towards greater efficacy with worsening
hyperkalaemia. These observations require confirmation before a reduction in insulin dose can be recommended.

**2019 Hyperkalaemia Guideline for moderate or severe hyperkalaemia recommends:**

- Give 10 units soluble insulin with 25g glucose
- Give 10% glucose by infusion @ 50ml/hr for 5 hours (25g) for patients with a pre-treatment blood glucose < 7.0 mmol/l to avoid hypoglycaemia in the patients most at risk.
- Blood glucose monitoring is required for up to 12 hours after glucose-insulin infusion.

**Hyperkalaemic Cardiac Arrest**

This is the most serious consequence of hyperkalaemia and yet the most effective treatment, dialysis, is rarely used. This is largely because nephrologists have received no training to initiate dialysis during CPR and technical failure is anticipated. The largest study of hyperkalaemic cardiac arrest demonstrated that survival in patients with extreme hyperkalaemia (K > 9.0 mmol/l) treated without dialysis was very poor. Over the past three decades, successful outcomes with all dialysis modalities have been reported during CPR.

The 2019 Hyperkalaemia Guideline recommends dialysis for refractory cardiac arrest and provides a protocol for the initiation of dialysis during resuscitation.

**Methods**

**Purpose**

This guideline provides an updated version of the original Hyperkalaemia guideline (2014). The main aims are to provide evidence-based recommendations for the treatment of chronic hyperkalaemia in the community, acute hyperkalaemia in the hospital setting and to reduce the risk of complications associated with hyperkalaemia itself and its treatment.

**Guideline development**

This guideline was written by a multidisciplinary writing group consists of three consultant nephrologists (one with an interest in Intensive Care Medicine), a renal registrar and renal pharmacist. In November 2018, each contributor was nominated by the Renal Association Guidelines Committee after a call for expressions of interest to participate in updating the existing guideline. A lay representative, who has experienced recurrent hyperkalaemia, provided a patient’s perspective and additional insight.

The group communicated frequently via video conference calls and email to agree the scope of the guideline and critically assess the available evidence. Each author was assigned sections of the guideline, although the lead author undertook editing and revision.

This guideline has been reviewed by the Renal Association Clinical Practice Guideline Committee and wider consultation has also been sought via the Renal Association.

**Review of Evidence**

hyperkalaemia in adults. Websites searches included National Institute for Health and Care Excellence (NICE), Scottish Medicines Consortium (SMC), Healthcare Improvement Scotland, Medicines and Healthcare products Regulatory Agency (MHRA) and European Medicines Agency (EMA).

The keywords used for literature search were – hyperkalaemia, potassium, treatment, pseudohyperkalaemia, spurious hyperkalaemia, ECG, point or care, near patient testing, insulin, hypoglycaemia, salbutamol, calcium, bicarbonate, diet, resonium, Patiromer, sodium zirconium cyclosilicate, dialysis, arrhythmias, resuscitation, and cardiac arrest.

The hyperkalaemia guideline comprises of a series of guideline statements accompanied by supporting evidence and audit measures. The recommendations in each guideline statement have been graded using the GRADE system (www.gradeworkinggroup.org) in evaluating the strength of each recommendation (1 = strong, 2 = weak) and quality of evidence (A= high, B = moderate, C= low, D = very low). Each guideline statement begins with a recommendation (Grade 1 evidence) or a suggestion (Grade 2 evidence).

Limitations

- Most treatments for hyperkalaemia, including intravenous calcium salts, have a limited evidence-base.
- The studies conducted on the novel K\(^+\)-lowering drugs, Patiromer and sodium zirconium cyclosilicate, were all undertaken in stable out-patients and the treatment threshold was lower than standard practice.
- Recent studies assessing the risk of hypoglycaemia in patients treated with insulin-glucose for hyperkalaemia have a retrospective design, variable dosing regimens and variable timing for assessing efficacy.
- Adverse events, including hypoglycaemia, are not consistently reported.

Scope


Format of the Hyperkalaemia Guideline 2019

This guideline will be presented in three sections:

I Hyperkalaemia in the Community

II Hyperkalaemia in Hospitalised Patients

III Hyperkalaemia in Resuscitation

Each section will include an introduction, guidance on treatment, prevention and treatment algorithm.
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Figure 6: K+-lowering efficacy in studies using 10 units insulin over a range of baseline serum K+ levels (5.48 – 6.9 mmol/l) showing a trend towards greater efficacy with increasing severity of hyperkalaemia.
Introduction

Potassium (K\(^+\)) is the most abundant cation in the body and normal homeostasis is crucial to maintaining health. The total estimated reserve in an adult is 3000-4000 mmol, of which only 2% is extracellular.\(^1\) This large concentration gradient between cellular compartments enables the establishment of transmembrane voltage gradients and action potentials of ‘excitable membranes’ in cardiac muscle, skeletal muscle, smooth muscle and nerve cells.\(^2\)\(^-\)\(^4\) Hyperkalaemia occurs when there is a rise in the extracellular K\(^+\) level. Potassium regulation is predominantly via the kidneys; therefore the most common cause of hyperkalaemia is renal failure, either acute or chronic.

Prompt recognition and treatment of hyperkalaemia can avoid arrhythmias and cardiac arrest. Changes in K\(^+\) concentration at the cellular level often correlates with ECG manifestations of hyperkalaemia,\(^5\) therefore hyperkalaemia may be suspected before biochemistry is available. In addition to the absolute serum K\(^+\) level, the rate of rise of serum K\(^+\) is also important. Co-existing metabolic disturbances can ameliorate (e.g. hypernatraemia, hypercalcaemia, and alkalaemia) or exacerbate (e.g. hyponatraemia, hypocalcaemia or acidosis) the effects of hyperkalaemia.\(^6\)

Definition of Hyperkalaemia

There is no universally accepted definition of hyperkalaemia. This guideline has adopted the European Resuscitation Council (ERC) Guideline definition of hyperkalaemia with a threshold serum K\(^+\) level of \(\geq 5.5\) mmol/l, established in 2005\(^7\) and maintained to current date.\(^8\)\(^-\)\(^9\) It is further classified by severity into mild (5.5-5.9 mmol/l), moderate (6.0-6.4 mmol/l) or severe (\(\geq 6.5\) mmol/l).\(^9\) This classification provides a guide to clinical decision-making although in practice, the precise values that trigger treatment decisions will depend on the patient’s clinical condition and rate of change in the serum K\(^+\) concentration.

The threshold for defining ‘severe’ hyperkalaemia is important as this is the level where emergency treatment is initiated. Early guidelines and review articles provided either no guidance\(^10\), no specific K\(^+\) level\(^11\) or defined severe hyperkalaemia at a level of > 7.0 mmol/l.\(^12\)\(^-\)\(^14\) The ERC Guidelines (2005)\(^7\) adopted a lower threshold (i.e. \(\geq 6.5\) mmol/l) for several reasons:

1. The threshold used to define ‘severe’ hyperkalaemia is likely to influence speed and intensity of treatment.
2. Treatment for hyperkalaemia is frequently delayed. Acker et al demonstrated that the mean time to first treatment in hospitalised patients was 2.1 hours for patients with a serum K\(^+\) \(\geq 6.5\) mmol/l and was significantly longer for patients with a serum K\(^+\) of 6.0-6.4 mmol/l at 2.8 hours.\(^15\) Similarly, Freeman et al reported the median time to treatment of hyperkalaemia was 117 minutes (IQR 59-196 minutes) in patients presenting to an Emergency Department.\(^16\)
3. There is usually a time delay in obtaining laboratory results by which time the serum K\(^+\) may have risen further.
4. Most patients manifest ECG changes of hyperkalaemia at a serum K\(^+\) level \(\geq 6.7\) mmol/l.\(^6\)\(^,\)\(^17\)
5. Definitive treatment with dialysis, if indicated, will take time to arrange.
Incidence of hyperkalaemia

The incidence of hyperkalaemia in hospital patients ranges from 1.1% and 10%.\textsuperscript{15,18-22} The incidence in the community varies dependent on the case mix of the population studied. Studies in the general population report an incidence of hyperkalaemia (K$^+$ > 5.5 mmol/l) ranging from 2.3 - 7.2% in patients with an eGFR > 60 ml/min\textsuperscript{23,24} and 2.9 - 40% in patients with an eGFR < 30 ml/min.\textsuperscript{25-27}

The USRDS (2018) reported the proportion of patients with hyperkalaemia (K$^+$ ≥ 5.5 mmol/l) over the transition period around dialysis initiation.\textsuperscript{28} The proportion of patients with hyperkalaemia in the pre-dialysis initiation period rose from 3.2% to 4.8% just prior to starting HD. After dialysis initiation, the prevalence of hyperkalaemia initially fell to 2%, but then rose to 4% by the end of the first year and 5% thereafter. This compares to earlier studies demonstrating hyperkalaemia in 10% of pre-dialysis samples\textsuperscript{29} and a 3-month averaged serum K$^+$ > 5.5 mmol/l in 12.5% of HD patients.\textsuperscript{30} Historically, hyperkalaemia has been reported as the reason for emergency dialysis in 24% of HD patients.\textsuperscript{31}

Acute kidney injury (AKI) is a common complication of acute intercurrent illness and hyperkalaemia is common in this setting.\textsuperscript{32} In clinical practice, there may be a combination of factors, particularly drugs, contributing to hyperkalaemia. Patients with heart failure are at risk and recent guidance has been published.\textsuperscript{33}

Drugs are an important cause of hyperkalaemia, especially following the widespread use of renin-angiotensin-aldosterone system inhibitor (RAASi) drugs.\textsuperscript{34} RAASi drugs have been implicated in hyperkalaemia in approximately 10% of outpatients within a year of starting treatment\textsuperscript{35,36} and in 10-38% of patients admitted to hospital with hyperkalaemia.\textsuperscript{37,38} Drugs have been identified as the primary cause or a contributing factor of hyperkalaemia in 35-75% of hospitalised patients.\textsuperscript{35}

Outcome of hyperkalaemia

Hyperkalaemia is the most common electrolyte abnormalities associated with arrhythmias, cardiac arrest and sudden death. Hyperkalaemia is unpredictable and arrhythmias or cardiac arrest can occur at any time. Hyperkalaemia is usually fatal at K$^+$ levels > 10 mmol/l, but survival has been reported in patients with extreme hyperkalaemia.\textsuperscript{39,40} In one of these reports, the patient recovered completely despite a serum K$^+$ of 14 mmol/L.\textsuperscript{39}

In-hospital mortality is significantly higher in patients with hyperkalaemia (18.1%) compared to those with hypokalaemia (5.0%) or normokalaemia (3.9%).\textsuperscript{21} A U-shaped association between serum potassium and mortality has been shown in patients with ischaemic heart disease\textsuperscript{41}, CKD\textsuperscript{25,42,43} and in patients receiving longterm haemodialysis (HD).\textsuperscript{30} Patients with severe hyperkalaemia (K$^+$ > 6.5 mmol/l) are most at risk and in one report, the hospital mortality was 30.7%.\textsuperscript{44} In patients with CKD, hyperkalaemia increases the odds of mortality within 1 day of the event.\textsuperscript{20} Among HD patients, hyperkalaemia and is responsible for 3-5% of deaths.\textsuperscript{45}

References


Summary of Clinical Practice Guideline for Hyperkalaemia

Section I: Community

Guideline 1.1 – Monitoring of patients at risk of Hyperkalaemia in the community.
We recommend that patients known to have CKD, heart failure and/or diabetes, who are at risk of hyperkalaemia, undergo regular blood monitoring at a frequency (2-4 times per year) dependent on level of renal function and degree of proteinuria. (1B)

Guideline 1.2.1 – Monitoring of patients after an episode of mild hyperkalaemia detected in the community.
We recommend that the serum K⁺ is repeated within 3 days of an episode of mild hyperkalaemia (K⁺ 5.5 – 5.9 mmol/l) if detected unexpectedly in the community. (1C)

Guideline 1.2.2 – Monitoring of patients after an episode of moderate hyperkalaemia detected in the community.
We recommend that the serum K⁺ is repeated within 1 day of an episode of moderate hyperkalaemia (K⁺ 6.0 – 6.4 mmol/l) when detected in the community. (1C)

Guideline 1.2.3 – Monitoring of patients after an episode of severe hyperkalaemia detected in the community.
We recommend that patients with severe hyperkalaemia (K⁺ ≥ 6.5 mmol/l) detected in the community are admitted for immediate assessment and treatment. (1B)

Guideline 2.1 – Assessment of patients prior to initiation of ACE-I or ARB.
We recommend that renal function should be assessed prior to initiation of ACE-I or ARB and these drugs should be used with caution if the serum K⁺ is > 5.0 mmol. (1A)

Guideline 2.2 – Assessment of patients prior to initiation of Mineralocorticoid Receptor Antagonists (MRA).
We suggest that initiation of MRAs should be avoided in patients with a baseline serum K⁺ > 5.0mmol/l, serum creatinine > 221 μmol/l or eGFR < 30 ml/min. (1B)

Guideline 2.3 – Monitoring of patients after initiation of ACE-I and ARB. We recommend that renal function should be assessed at 1 – 2 weeks after initiation of ACE-I or ARB and after every dose titration. (1A)

Guideline 2.4 – Monitoring of patients after initiation of MRAs.
We recommend that renal function should be assessed at 1 week after initiation of MRA or after dose up-titration, then monthly for the first 3 months, 3-monthly for the first year, and 4-monthly thereafter. (1A)

Guideline 2.5 – Management of hyperkalaemia in patients treated with RAASi drugs.
We suggest increased frequency of monitoring in patients with a serum K⁺ between 5.5-5.9 mmol/l and consideration of dose reduction of RAASi drugs (ACE-I, ARB, MRA). (1B)

Guideline 2.6 – Management of hyperkalaemia in patients treated with RAASi drugs during acute illness.
We recommend that RAASi drugs be withheld during acute intercurrent illness (e.g. sepsis, hypovolaemia and/or AKI) at all severities of hyperkalaemia. (1D)
Guideline 2.7 – Cessation of RAASI drugs in patients with moderate or severe hyperkalaemia.

We recommend cessation of RAASI drugs in patients with serum K ≥ 6 mmol/l who do not meet the criteria for treatment with sodium zirconium cyclosilicate. (1B)

Guideline 3.1 – Threshold for treating Hyperkalaemia in the community.

We recommend that interventions to lower serum potassium be instituted in patients with a serum K⁺ ≥ 5.5 mmol/l. (1B)

Guideline 4.1 – Indication for hospital admission for patients with severe hyperkalaemia detected in the community.

We recommend admission to hospital for urgent assessment and treatment for all patients with severe hyperkalaemia (serum K⁺ ≥ 6.5 mmol/l) detected in the community. (1A)

Guideline 4.2 – Indication for hospital admission for patients with mild-moderate hyperkalaemia detected in the community.

We suggest hospital admission for assessment and treatment for acutely unwell patients with mild (serum K⁺ 5.5 – 5.9 mmol/l) or moderate hyperkalaemia (serum K⁺ 6.0 - 6.4 mmol/l), particularly in the presence of an acute kidney injury. (1B)

Guideline 5.1 – Dietary Intervention for managing Hyperkalaemia in the community.

We recommend that a low potassium diet is instituted for patients with a serum K⁺ > 5.5 mmol/l. (1B)

Guideline 6.1 – Sodium bicarbonate for management of Hyperkalaemia in the community.

We recommend that sodium bicarbonate is used in CKD patients with a serum bicarbonate level < 22 mmol/l with or without hyperkalaemia. (1B)

Guideline 7.1 – Use of diuretics for managing Hyperkalaemia in the community.

We suggest that loop diuretics may be a useful adjunct for the treatment of chronic hyperkalaemia in patients who are non-oliguric and volume replete. (2C)

Guideline 8.1 – Calcium resonium for the management of Hyperkalaemia in the community.

We suggest that calcium resonium may be used as a short-term measure to lower serum potassium to a level of ≤ 5 mmol/l in patients with mild to moderate hyperkalaemia. (2C)

Guideline 9.1 – Patiromer for the management of Hyperkalaemia in the community.

We recommend that Patiromer is not used routinely for the management of hyperkalaemia. (1B)

Guideline 10.1 – Sodium Zirconium Cyclosilicate for the management of Hyperkalaemia.

We recommend that Sodium Zirconium Cyclosilicate (SZC) is used in out-patients for the management of persistent hyperkalaemia with a confirmed serum K⁺ ≥ 6.0 mmol/l in patients with CKD Stage 3b-5 (not on dialysis) or heart failure receiving a sub-optimal dose of RAASI therapy. (1A)

Guideline 10.2 – Sodium Zirconium Cyclosilicate for the management of Hyperkalaemia.

We recommend that treatment with Sodium Zirconium Cyclosilicate (SZC) in out-patients is discontinued if RAASI therapy is stopped. (1A)

Guideline 10.3 – Sodium Zirconium Cyclosilicate for the management of Hyperkalaemia.

We recommend that Sodium Zirconium Cyclosilicate (SZC) is initiated in secondary care only. (1A)


We recommend monitoring of renal function in patients at risk of hyperkalaemia with known CKD, heart failure, diabetes and in any patient taking RAASI medication. (1A)
Guideline 11.2 – Prevention of Hyperkalaemia in the community: prescribing
We recommend caution in prescribing trimethoprim to patients with renal impairment or those taking RAASi drugs. (1A)

Guideline 11.3 – Prevention of Hyperkalaemia in the community: sick day rules
We recommend that healthcare professionals provide advice to patients regarding the risks of AKI and hyperkalaemia during acute illness and measures to avoid these complications. (1B)

Guideline 12.1 – Algorithm for treatment of Hyperkalaemia in the community.
We recommend that the treatment of hyperkalaemia in patients in the community and out-patient setting is guided by its severity and clinical condition of the patient as summarised in the treatment algorithm. (1A)

Section II: Hospital

Guideline 13.1 – Hyperkalaemia: Clinical Assessment; ABCDE and Early Warning Scoring (EWS) Systems.
We recommend that all patients with known or suspected hyperkalaemia undergo urgent clinical assessment using an early warning scoring system. (1C)

Guideline 13.2 – Hyperkalaemia: Clinical Assessment; History and examination
We recommend that all patients presenting with hyperkalaemia undergo a comprehensive medical and drug history and clinical examination to determine the cause of hyperkalaemia. (1B)

Guideline 14.1 – Hyperkalaemia: ECG
We recommend that all patients with a serum K⁺ level ≥ 6.0 mmol/L have an urgent 12-lead ECG (electrocardiogram) performed and assessed for changes of hyperkalaemia. (1B)

Guideline 14.2 – Hyperkalaemia: Cardiac monitoring
We recommend a minimum of continuous 3-lead ECG monitoring for all patients with a serum K⁺ ≥ 6.5 mmol/L, patients with features of hyperkalaemia on 12-lead ECG, and in patients with a serum K⁺ 6.0-6.4 mmol/L who are clinically unwell or in whom a rapid rise in serum K⁺ is anticipated, ideally in a higher-dependency setting. (1C)

Guideline 15.1 – Hyperkalaemia: Laboratory tests
We recommend that lithium heparin anti-coagulated specimens are the sample type of choice when rapid turnaround of urea and electrolytes results is required. (1B)

Guideline 15.2 – Hyperkalaemia: Blood gas analysis
We recommend that in emergencies, K⁺ level is measured from an arterial or venous blood sample using a point-of-care blood gas analyser whilst awaiting the results from a formal laboratory measurement. (1B)

Guideline 15.3 – Hyperkalaemia: Pseudo-hyperkalaemia
We recommend that urea and electrolytes are measured using paired lithium heparin and clotted serum samples from a large vein using gentle traction with prompt laboratory analysis if pseudo-hyperkalaemia is suspected. (1A)

Guideline 16.1 – Hyperkalaemia: Summary of treatment strategy
We recommend that the treatment of hyperkalaemia in hospital follows a logical 5-step approach. (1B)
Guideline 16.2 – Hyperkalaemia: STEP 1 - Protect the heart; intravenous calcium salts
We recommend that intravenous calcium chloride or calcium gluconate, at an equivalent dose (6.8mmol), is given to patients with hyperkalaemia in the presence of ECG evidence of hyperkalaemia. (1A)

Guideline 16.3.1 – Hyperkalaemia: STEP 2 - Shift K⁺ into cells; insulin-glucose infusion
We recommend that insulin-glucose (10 units soluble insulin in 25g glucose) by intravenous infusion is used to treat severe hyperkalaemia (K⁺ ≥ 6.5 mmol/l). (1B)

Guideline 16.3.2 – Hyperkalaemia: STEP 2 - Shift K⁺ into cells; insulin-glucose infusion
We suggest that insulin-glucose (10 units soluble insulin in 25g glucose) by intravenous infusion is used to treat moderate hyperkalaemia (K⁺ 6.0 – 6.4 mmol/l). (2C)

Guideline 16.3.3 – Hyperkalaemia: STEP 2 - Shift K⁺ into cells; avoiding hypoglycaemia
We suggest pre-emptive initiation of an infusion of 10% glucose at 50ml/hour for 5 hours (25g) following insulin-glucose treatment in patients with a pre-treatment blood glucose < 7.0 mmol/l to avoid hypoglycaemia (target blood glucose 4-7 mmol/l). (2D)

Guideline 16.4.1 – Hyperkalaemia: STEP 2 – Shift K⁺ into cells; Salbutamol
We recommend nebulised salbutamol 10-20mg is used as adjuvant therapy for severe (K⁺ ≥ 6.5 mmol/L) hyperkalaemia. (1B)

Guideline 16.4.2 – Hyperkalaemia: STEP 2 – Shift K⁺ into cells; Salbutamol
We suggest that nebulised salbutamol 10-20mg may be used as adjuvant therapy for moderate (K⁺ 6.0-6.4 mmol/L) hyperkalaemia. (2C)

Guideline 16.4.3 – Hyperkalaemia: STEP 2 – Shift K⁺ into cells; Salbutamol
We recommend that salbutamol is not used as monotherapy in the treatment of severe hyperkalaemia. (1A)

Guideline 16.5 Hyperkalaemia: STEP2 –Shift K into cells; Sodium bicarbonate
We recommend that Sodium Zirconium Cyclosilicate is used in the emergency management of acute life-threatening hyperkalaemia (serum K⁺ ≥ 6.5 mmol/l). (1A)

Guideline 16.6.1 – Hyperkalaemia: STEP 3 – Remove K⁺ from body; Potassium binders
We recommend that Sodium Zirconium Cyclosilicate is used in the emergency management of acute life-threatening hyperkalaemia, but may be considered in patients with moderate hyperkalaemia. (2B)

Guideline 16.6.2 – Hyperkalaemia: STEP 3 – Remove K⁺ from body; Cation-exchange resin
We suggest that calcium resonium is not used in the emergency management of severe hyperkalaemia, but may be considered in patients with moderate hyperkalaemia. (2B)

Guideline 17.1.1 – Hyperkalaemia: STEP 4 - Blood monitoring; serum K⁺
We recommend that the serum K⁺ is monitored closely in all patients with hyperkalaemia to assess efficacy of treatment and monitor for rebound hyperkalaemia after the initial response to treatment wanes. (1B)

Guideline 17.1.2 – Hyperkalaemia: STEP 4 - Blood monitoring; serum potassium
We suggest that serum K⁺ is assessed at least 1, 2, 4, 6 and 24 hours after identification and treatment of hyperkalaemia. (2C)
Guideline 17.2 – Hyperkalaemia: STEP 4 - Blood monitoring; blood glucose
We recommend that the blood glucose concentration is monitored at regular intervals (0, 30, 60, 90, 120, 180, 240, 300, 360 minutes) for a minimum of 6 hours after administration of insulin-glucose infusion in all patients with hyperkalaemia. (1C)

Guideline 18.1 - Hyperkalaemia: Specialist Referral
We suggest that patients with severe hyperkalaemia (serum potassium ≥ 6.5 mmol/L) be referred to their local renal or critical care team for an urgent opinion, guided by the clinical scenario and its persistence after initial medical treatment. (2C)

Guideline 18.2 - Hyperkalaemia: Referral to critical care services
We recommend that for patients with severe hyperkalaemia, and where there is no provision of renal services on site, referral is made to the local critical care team in the first instance, guided by the clinical scenario and established local policies. (1C)

Guideline 18.3 - Hyperkalaemia: Escalation of care
We recommend that patients are referred to the critical care team by a senior member of the referring team if escalation of care is required from the outset or if the patient fails to respond to initial treatment. (1B)

Guideline 18.4 - Hyperkalaemia: Treatment facilities - Critical care
We recommend that patients with severe hyperkalaemia and problems with airway, breathing, circulation and/or conscious level, be referred to the local critical care team in the first instance. (1C)

Guideline 18.5 – Hyperkalaemia: Treatment facilities – Ward or High dependency area
We recommend that stable patients with severe hyperkalaemia be admitted to an area with facilities for continuous cardiac monitoring which are sufficiently staffed to support clinical monitoring and treatment, including an acute medical unit, renal unit, coronary care unit, HDU or ICU depending on local facilities or practice. (1C)

Guideline 18.6 – Hyperkalaemia: RRT in treatment of hyperkalaemia
We recommend that the decision on timing, suitability and modality for initiation of RRT in patients with life-threatening hyperkalaemia, either from the outset or resistant to initial medical therapy, is taken urgently by a nephrologist or critical care specialist. (1C)

Guideline 19.1 - Hyperkalaemia: Transfer to renal services
We suggest that transfer to renal services be considered in clinically stable patients in whom hyperkalaemia cannot be controlled (i.e. serum K <6.5 mmol/L) using medical measures, particularly in the presence of advanced or oliguric renal failure (either AKI or CKD). (2C)

Guideline 19.2 - Hyperkalaemia: Minimum standards for safe patient transfer
We suggest that any inter- or intra-hospital patient transfer is coordinated by senior clinicians and follows national guidelines. (2B)

Guideline 20.1 – Hyperkalaemia: Prevention of hyperkalaemia in hospitalised patients
We recommend that the need for prescribed medication which can cause hyperkalaemia are reviewed in the context of the current illness and level of renal function both on and during hospital admission. (1B)
**Guideline 20.2 – Hyperkalaemia: Prevention of hyperkalaemia in hospitalised patients**

We recommend that community blood monitoring is arranged on discharge for all patients who have required treatment for hyperkalaemia during hospital admission. (1B)

**Guideline 20.3 – Hyperkalaemia: Prevention of hyperkalaemia in hospitalised patients**

We recommend that the risk of recurrence of hyperkalaemia is considered before reinstating previous medication that may have contributed to the episode. (1B)

**Guideline 20.1 – Hyperkalaemia: Prevention of hyperkalaemia in hospitalised patients**

We recommend that the need for prescribed medication which can cause hyperkalaemia are reviewed in the context of the current illness and level of renal function both on and during hospital admission. (1B)

**Guideline 20.2 – Hyperkalaemia: Prevention of hyperkalaemia in hospitalised patients**

We recommend that community blood monitoring is arranged on discharge for all patients who have required treatment for hyperkalaemia during hospital admission. (1B)

**Guideline 21.1 – Algorithm for the treatment of Hyperkalaemia in hospital**

We recommend that the treatment of hyperkalaemia is undertaken using the 5-step approach in the treatment algorithm and is guided by its severity, ECG findings and clinical condition of the patient. (1B)

**Section III: Resuscitation**

**Guideline 22.1 – Hyperkalaemia; Cardiac Arrest - special circumstance**

We recommend that hyperkalaemia be considered in all patients who have a cardiac arrest, as part of identifying and treating a reversible cause using the ‘4 Hs and 4 Ts’ approach. (1A)

**Guideline 23.1 – Hyperkalaemia; Cardiac Arrest – Resuscitation strategy in haemodialysis patients**

We recommend that renal wards and dialysis units follow standard ALS practice in cardiac arrest. (1A)

**Guideline 23.2 – Hyperkalaemia; Cardiac Arrest – Resuscitation training for staff in renal services**

We recommend that staff working within out-patient dialysis units and renal wards receive resuscitation training. (1A)

**Guideline 23.3 – Hyperkalaemia; Cardiac Arrest – Defibrillation practice in haemodialysis patients**

We recommend disconnection from dialysis equipment prior to defibrillation unless the dialysis machine is defibrillator-proof. (1C)

**Guideline 24.1 – Cardiac Arrest: Treatment - Intravenous calcium**

We recommend that intravenous calcium chloride is administered if hyperkalaemia is known or suspected to be the cause of cardiac arrest. (1A)

**Guideline 24.2 – Cardiac Arrest: Treatment – Insulin-glucose**

We suggest that 10 units soluble insulin and 50g glucose is administered if hyperkalaemia is known or suspected to be the cause of cardiac arrest. (2C)

**Guideline 24.3 – Hyperkalaemia; Cardiac Arrest – Sodium bicarbonate**

We suggest that sodium bicarbonate is administered if hyperkalaemia is known or suspected to be the cause of cardiac arrest. (2C)
Guideline 24.4 – Hyperkalaemia; Cardiac Arrest – Initiation of dialysis during CPR
We suggest that renal replacement therapy with ongoing CPR is considered for hyperkalaemic cardiac arrest, if hyperkalaemia is resistant to medical therapy. (2C)

Guideline 25.1 – Hyperkalaemia; Prevention of Cardiac Arrest in Hyperkalaemia
We recommend that hyperkalaemia is treated urgently in patients with severe hyperkalaemia ($K^+ \geq 6.5$ mmol/l) and in those with ECG changes suggestive of severe hyperkalaemia. (1C)

Guideline 25.2 – Hyperkalaemia; Prevention of Cardiac Arrest in Hyperkalaemia
We recommend continuous cardiac monitoring for patients with severe hyperkalaemia ($K^+ \geq 6.5$ mmol/l) in a setting appropriate for the level of care required. (1C)

Guideline 26.1 – Algorithm for treatment of Cardiac Arrest in Hyperkalaemia
We recommend that the 5-step approach to treatment of hyperkalaemia is applied if hyperkalaemia is identified as a potential reversible cause of cardiac arrest and dialysis initiation considered if cardiac arrest is refractory to medical treatment. (1C)
Summary of Audit Measures

The Renal Association encourages non-renal specialties to record audit measures for all patients diagnosed with hyperkalaemia irrespective of whether or not they are referred to renal services. Hospital laboratories should be capable of providing data to help audit compliance with these guidelines. It is recommended that the following audit measures be recorded for patients with hyperkalaemia.

1. Incidence of hyperkalaemia detected on routine blood tests in the community.
2. Frequency of hospital admission for severe hyperkalaemia (serum K⁺ > 6.5 mmol/l) detected on routine blood test in the community.
3. Frequency of blood monitoring of patients receiving RAASi drugs in the community.
4. Proportion of patients achieving optimal dosing of RAASi drugs with and without use of SZC.
5. Frequency of severe hyperkalaemia in patients receiving combination of RAASi drugs.
6. Proportion of patients with a serum K⁺ ≥ 5.5 mmol/l in whom an intervention for lowering serum potassium was instituted.
7. Number of patients admitted from Primary Care with severe hyperkalaemia (serum K⁺ ≥ 6.5 mmol/l) annually.
8. Proportion of patients admitted from Primary Care with severe hyperkalaemia who subsequently did not warrant emergency treatment on repeat testing.
9. Proportion of patients with mild hyperkalaemia who have received dietary potassium advice.
10. Proportion of patients with moderate hyperkalaemia who have received dietary potassium advice.
11. The proportion of patients attending renal clinics with serum bicarbonate < 22 mmol/l.
12. The frequency of hyperkalaemia in CKD patients with a serum bicarbonate < 22 mmol/l.
13. The frequency of persistent hyperkalaemia (serum K⁺ ≥ 5.5 mmol/l) despite correction of metabolic acidosis with sodium bicarbonate.
14. The proportion of patients with persistent hyperkalaemia (K⁺ ≥ 5.5 mmol/l) treated with RAASi and loop diuretic.
15. Duration of treatment with calcium resonium required to lower serum potassium to a level of ≤ 5 mmol/l.
16. The proportion of out-patients with moderate hyperkalaemia (serum K⁺ 6.0 - 6.4 mmol/l) treated with SZC who achieved a serum K⁺ ≤ 5.0 mmol/l within 48 hours.
17. The number of patients who achieve maximal dose RAASi therapy whilst taking SZC.
18. The number of patients treated with trimethoprim who develop moderate-severe hyperkalaemia (serum K⁺ ≥ 6.0 mmol/l) in hospital or community setting.
19. Proportion of patients with severe hyperkalaemia (Serum K⁺ ≥ 6.5 mmol/l) on admission to hospital who had been provided with 'Sick Day Rules' advice compared with those who had not received this advice.
20. Length of hospital stay of patients admitted with hyperkalaemia.
21. In-hospital mortality of patients admitted with hyperkalaemia.
22. Proportion of patients with a serum K⁺ level ≥ 6.0 mmol/L who had a 12-lead ECG recorded before treatment [Audit Standard 100%].
23. Proportion of patients with a serum K⁺ level ≥ 6.0 mmol/L and an ECG showing features of hyperkalaemia who had their 12-lead ECG repeated following treatment [Audit Standard 100%].
24. Proportion of patients with a serum K⁺ value ≥ 6.5 mmol/L who have documented evidence of continuous ECG monitoring [Audit standard: 100%].

25. The average laboratory analysis time for K⁺ concentration using clotted (serum) and lithium heparin (plasma) samples [Audit standard: within 60 minutes].

26. The frequency of ECG changes in patients treated with intravenous calcium salts.

27. Adverse events as a result of treatment with intravenous calcium salts.

28. The proportion of patients with severe hyperkalaemia (K⁺ ≥ 6.5 mmol/L) treated with insulin-glucose infusion [Audit Standard: 100%].

29. The proportion of patients who develop adverse effects of salbutamol (e.g. tachycardia, arrhythmia).

30. The proportion of patients with acute severe hyperkalaemia (serum K⁺ ≥ 6.5 mmol/l) treated with Sodium Zirconium Cyclosilicate [Audit Standard: 100%].

31. The frequency of bowel complications with the use of cation-exchange resins.

32. The proportion of patients in whom serum K⁺ was measured at least once within 2 hours of treatment for severe hyperkalaemia [Audit Standard: 100%].

33. The proportion of patients in whom a serum K⁺ was not performed within 6 hours of identification of hyperkalaemia [Audit Standard: 0%].

34. The proportion of patients who have at least one blood glucose test performed within 1 hour of completion of insulin-glucose infusion [Audit Standard: 100%].

35. The frequency of hypoglycaemia occurring in patients receiving treatment for hyperkalaemia.

36. The incidence of patients requiring emergency dialysis for severe hyperkalaemia.

37. The frequency of hospital transfer to facilitate emergency dialysis for treatment of severe hyperkalaemia.

38. The frequency of hyperkalaemia developing beyond 24 hours of hospital admission.

39. The frequency of prescribed drugs potentially contributing to hyperkalaemia.

40. All cardiac arrests should be audited – hospital participation in the National Cardiac Arrest Audit is encouraged as part of quality improvement and benchmarking.

41. The proportion of patients treated with intravenous calcium for hyperkalaemic cardiac arrest.

42. The proportion of patients treated with insulin-glucose for hyperkalaemic cardiac arrest.

43. The proportion of patients treated with sodium bicarbonate for hyperkalaemic cardiac arrest.

44. The proportion of patients with refractory hyperkalaemic cardiac arrest treated with dialysis initiation during CPR.

45. Number of patients with a serum K⁺ ≤ 6.0 mmol/l within 2 hours of treatment for severe hyperkalaemia.
Future Research

There are numerous unanswered questions about the treatment of patients with hyperkalaemia. Areas for future research include:

1. The optimal dose of insulin and glucose to treat acute hyperkalaemia required to minimise iatrogenic hypoglycaemia without compromising efficacy.
2. The efficacy of sodium zirconium cyclosilicate in combination with insulin-glucose infusion in the treatment of severe hyperkalaemia in hospitalised patients.
3. The efficacy of sodium zirconium cyclosilicate without insulin-glucose in the treatment of moderate hyperkalaemia in hospitalised patients.
4. The efficacy of sodium bicarbonate in the treatment of severe hyperkalaemia in patients with AKI.
5. The incidence and outcome of hyperkalaemic cardiac arrest.
6. The frequency of dialysis initiation for hyperkalaemic cardiac arrest.

Future Developments

The delivery of a specified dose of glucose is dependent on the available preparations. Hyperkalaemia is a medical emergency, therefore ease of administration is key. The only preparation available that provides the required amount of glucose (25g) is the 50% solution.

1. Preparations of 10% (250ml) and 20% (125ml) glucose solutions in volumes appropriate for the treatment of hyperkalaemia.
Section I

Management of Hyperkalaemia in the Community and Out-patient Clinic
Hyperkalaemia in the Community

Introduction

Hyperkalaemia is commonly detected in the community and the patient groups most at risk are those with CKD, diabetes mellitus and heart failure. Hyperkalaemia may also occur in the context of an AKI triggered by acute illness, initiation or titration of RAASi medications, or worsening of heart failure. Hyperkalaemia develops in approximately 10% of out-patients within one year after initiation of RAASi drugs, thereby limiting treatment in the patients who receive the greatest benefit from this therapy.

The management of patients with heart failure is challenging given the high prevalence of renal impairment and increased risk of hyperkalaemia. The reported incidence of hyperkalaemia in patients with heart failure differs depending on the study design, definition of hyperkalaemia, the presentation of heart failure (acute vs chronic) and therapy used (monotherapy vs combined). In clinical trials of RAASi monotherapy, the incidence of hyperkalaemia ranges from 3 – 7%. The overall incidence of hyperkalaemia was generally higher in clinical trials involving aldosterone antagonists. Combination therapy of RAASi and aldosterone antagonist increases the risk of hyperkalaemia and hospitalisation.

Mortality in patients with heart failure is significantly increased with worsening severity of hyperkalaemia: serum K+ levels between 4.8 – 5.0 mmol/l (HR 1.34), 5.1 – 5.5 mmol/l (HR 1.60) and 5.6 – 7.4 mmol/l (HR 3.31).

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Renal Failure</td>
<td>5.55</td>
<td>2.06</td>
<td>1.25 (eGFR &lt; 15)</td>
<td>1.04</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td>1.53</td>
<td>0.95</td>
</tr>
<tr>
<td>Heart Failure</td>
<td></td>
<td></td>
<td>0.95</td>
<td></td>
</tr>
<tr>
<td>≥2 Co-morbidities</td>
<td>2.22</td>
<td>1.30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum bicarbonate &lt; 25</td>
<td></td>
<td>1.30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARB</td>
<td>2.68</td>
<td>1.85</td>
<td>1.4</td>
<td>15.89</td>
</tr>
<tr>
<td>ACE-I</td>
<td>2.24</td>
<td>1.85</td>
<td>1.4</td>
<td>13.63</td>
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<tr>
<td>Spironolactone</td>
<td>2.53</td>
<td>2.10</td>
<td></td>
<td>7.77</td>
</tr>
<tr>
<td>NSAIDS</td>
<td>2.68</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta blocker</td>
<td>2.14</td>
<td>1.06</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Risk factors with odds ratio of developing hyperkalaemia in community studies.

Several risk factors have been identified that contribute to community-acquired hyperkalaemia as above shown in Table 1. The presence of renal failure is a common factor and the risk increases with the presence of other co-morbidities (e.g. diabetes mellitus, heart failure, hypertension and liver disease) and drugs known to exacerbate hyperkalaemia.

RAASi drugs are frequently implicated in AKI and hyperkalaemia, but there are conflicting reports in the literature. A meta-analysis reported by Whiting et al found an increased risk of AKI in the order of 15% in...
patients who continued RAASi drugs compared with those who temporarily discontinued medication.\textsuperscript{10} However, a large community based study found that treatment with RAASi drugs was associated with only a small rise in AKI risk and patient factors were more strongly correlated with AKI risk.\textsuperscript{11} Given the potential risk of AKI, guidance has been developed recommending the cessation of RAASi drugs during acute illness. Although the ‘sick day rules’ has received support from NICE, it remains controversial.\textsuperscript{1,10,12,13,14}

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Setting</th>
<th>N=</th>
<th>eGFR ml/min</th>
<th>Definition of HyperK mmol/l</th>
<th>Prevalence HyperK %</th>
<th>Mortality risk with HK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liamis 2013\textsuperscript{15}</td>
<td>Netherlands</td>
<td>General population (age &gt; 55)</td>
<td>5179</td>
<td>&gt;60</td>
<td>≥6.0</td>
<td>0.3</td>
<td># OR 2.08</td>
</tr>
<tr>
<td>Chang 2016\textsuperscript{16}</td>
<td>USA</td>
<td>Health care system – HBP (age ≥ 18)</td>
<td>155,695</td>
<td>&gt;60</td>
<td>&gt;5.5</td>
<td>10.8</td>
<td>NA</td>
</tr>
<tr>
<td>Hughes-Austin 2017\textsuperscript{17}</td>
<td>USA</td>
<td>Multi-ethnic general population (age ≥65)</td>
<td>9651</td>
<td>&gt;60</td>
<td>≥5.0</td>
<td>2.8</td>
<td>°HR 1.41</td>
</tr>
<tr>
<td>Horne 2019\textsuperscript{9}</td>
<td>UK</td>
<td>General population (age ≥ 18)</td>
<td>195,178</td>
<td>&gt;60</td>
<td>5.0 – 5.4; 5.5 – 6.0; &gt;6</td>
<td>91.2 7.2 1.6</td>
<td>°°2.51 °°3.83 °°12.57</td>
</tr>
</tbody>
</table>

Table 2: Prevalence and outcome of Hyperkalaemia in patients with eGFR> 60 ml/min in community studies.

\textsuperscript{9} OR- Odds Ratio; ° HR- Hazard Ratio; °° All-cause mortality; HBP – hypertensive; NA – not available

The reported incidence of hyperkalaemia in the general population is variable depending on the specific patient group, study design, level of renal function and definition of hyperkalaemia.\textsuperscript{6,9,15-19} The prevalence of hyperkalaemia in patients with an eGFR > 60 ml/min is shown in Table 2. In a large outpatient/primary care electronic database including over 700 primary care practices in the UK (n=195,178), the overall incidence rate of a hyperkalaemic event was 2.9 per 100 person years.\textsuperscript{9} In this study, the use of RAASi was strongly associated with hyperkalaemia with an odds ratio of 13.6 - 15.9, however most events occurred in patients with a serum K+ < 5.5 mmol/l. Hyperkalaemia is more common in patients with CKD and the incidence increases with declining renal function. Sarafadis et al undertook a study in the pre-dialysis setting (eGFR < 15 ml/min) and demonstrated that over 30% of patients experienced hyperkalaemia (K+ > 5.5 mmol/l).\textsuperscript{7} A summary of the prevalence of hyperkalaemia in patients with CKD is shown below in Table 3.
## Table 3: Prevalence of hyperkalaemia and mortality rate in patients with CKD.

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Setting</th>
<th>N=</th>
<th>eGFR ml/min</th>
<th>Definition of HyperK mmol/l</th>
<th>Prevalence HyperK %</th>
<th>Mortality by K⁺ level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Korgaonkar 2010</td>
<td>USA</td>
<td>Renal Clinic</td>
<td>820</td>
<td>25.4</td>
<td>≥5.5</td>
<td>7.9</td>
<td>¹HR 1.57</td>
</tr>
<tr>
<td>Sarafidis 2012</td>
<td>UK</td>
<td>Low Clearance clinic</td>
<td>238</td>
<td>14.5</td>
<td>5.0 – 5.4</td>
<td>22.7</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5.5 – 5.9</td>
<td>23.1</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥6.0</td>
<td>8.4</td>
<td>NA</td>
</tr>
<tr>
<td>Nakhoul 2015</td>
<td>USA</td>
<td>CKD Registry (USA)</td>
<td>36,359</td>
<td>47</td>
<td>5.0 – 5.4</td>
<td>11</td>
<td>²OR 1.12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;5.5</td>
<td>3.3</td>
<td>²OR 1.65</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥5.5</td>
<td>2.9</td>
<td>AUC values by age</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p&lt; 0.001</td>
</tr>
<tr>
<td>Turgutalp 2016</td>
<td>Turkey</td>
<td>Elderly population (age &gt; 65)</td>
<td>40,092</td>
<td>23-35</td>
<td>5.0 – 5.4</td>
<td>14.9</td>
<td>³IRR 1.01</td>
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<td>5.5 – 5.9</td>
<td>3.9</td>
<td>³IRR 1.11</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥6.0</td>
<td>1.1</td>
<td>³IRR 3.08</td>
</tr>
<tr>
<td>Luo 2016</td>
<td>USA</td>
<td>Health care system (age ≥ 18)</td>
<td>55,266</td>
<td>&lt; 60</td>
<td>5.0 – 5.4</td>
<td>45.1</td>
<td>³IRR 1.1</td>
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<td>5.5 – 5.9</td>
<td>15.9</td>
<td>³IRR 1.60</td>
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<td></td>
<td></td>
<td></td>
<td>≥6.0</td>
<td>4.9</td>
<td>³IRR 2.88</td>
</tr>
<tr>
<td>Furuland 2018</td>
<td>UK</td>
<td>Health care database</td>
<td>191,964</td>
<td>50.9</td>
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</tr>
</tbody>
</table>

Hyperkalaemia is associated with increased hospitalisation, prolongation of hospital stay and increased mortality. Horne et al showed the incidence rates for all-cause hospitalisation in adults was 14.1 per 100 person years.² Turgutalp et al demonstrated a higher incidence of hospitalisation for hyperkalaemia in the elderly population: age 65-74 years (46%), age 75-84 years (44%) and ≥ 85 years (74%).[6] Mortality increases with worsening severity of hyperkalaemia in the general population and in patients with CKD.⁸,⁹,¹⁸,¹⁹

This chapter focuses on the detection, treatment and prevention of hyperkalaemia in the community. It will address the management of patients receiving RAASi drugs, indications for hospital admission and the use of novel oral potassium lowering drugs.

### References:


Hyperkalaemia in the Community (Guidelines Hyperkalaemia 1.1 – 1.2) Patient monitoring

(Guidelines 1.1 – 1.2)

Guideline 1.1 – Monitoring of patients at risk of Hyperkalaemia in the community.
We recommend that patients known to have CKD, heart failure and/or diabetes, who are at risk of hyperkalaemia, undergo regular blood monitoring at a frequency (2-4 times per year) dependent on level of renal function and degree of proteinuria. (1B)

Guideline 1.2.1 – Monitoring of patients after an episode of mild hyperkalaemia detected in the community.
We recommend that the serum K⁺ is repeated within 3 days of an episode of mild hyperkalaemia (K⁺ 5.5 – 5.9 mmol/l) if detected unexpectedly in the community. (1C)

Guideline 1.2.2 – Monitoring of patients after an episode of moderate hyperkalaemia detected in the community.
We recommend that the serum K⁺ is repeated within 1 day of an episode of moderate hyperkalaemia (K⁺ 6.0 – 6.4 mmol/l) when detected in the community. (1C)

Guideline 1.2.3 – Monitoring of patients after an episode of severe hyperkalaemia detected in the community.
We recommend that patients with severe hyperkalaemia (K⁺ ≥ 6.5 mmol/l) detected in the community are admitted for immediate assessment and treatment. (1B)

Audit measure:
1. Incidence of hyperkalaemia detected on routine bloods tests in the community
2. Frequency of hospital admission for severe hyperkalaemia (serum K⁺ > 6.5 mmol/l) detected on routine blood test in the community.

Rationale (Guideline 1.1 – 1.2)
Patients with CKD are at risk of hyperkalaemia and progression of their underlying kidney disease, therefore require regular blood monitoring in the community. The NICE CKD Guideline suggests that the frequency of monitoring should be tailored to the level of renal function, rate of decline in renal function and degree of proteinuria.¹ Patients with CKD 1-3 require monitoring at least 1-2 times per year and patients with CKD 4-5 require monitoring at least 2-4 times per year. More frequent monitoring is indicated during acute illness and following an episode of AKI or hyperkalaemia.

Several observational studies have reported the frequency of blood monitoring in patients with CKD in relation to detection of hyperkalaemic events. Chang et al (n=194,456) investigated the prevalence of hyperkalaemia in patients taking anti-hypertensive medications that affect K⁺ level.² This study showed that the proportion of patients who had a serum K⁺ level performed over a 3 year period was 0 tests/ year (20%), <2 tests/ year (58%), 2-3 tests/ year (16%) and ≥4 tests/ year (6%). The 3-year risk of hyperkalaemia (K⁺ > 5.5 mmol/l) increased with frequency of monitoring: < 2 tests/year (0.6%), 2-3 tests/year (3.6%), ≥4 tests/ year (14.6%). In patients with an eGFR < 30ml/min who had ≥4 tests per year, hyperkalaemia was found in 30%.
Luo et al (n=55,266) reported the frequency of blood monitoring stratified by level of renal function and level of serum K⁺. In patients with an eGFR < 30 ml/min, the mean frequency of tests per year was 1.69 ± 1.35 (serum K⁺ 5.5 – 5.9 mmol/l) and 1.37 ± 0.98 (serum K⁺ ≥ 6 mmol/l) respectively. In patients with an eGFR 50-59 ml/min, the mean frequency of tests per year was 1.34 ± 0.92 (serum K⁺ 5.5 – 5.9 mmol/l) and 1.21 ± 0.73 (serum K⁺ ≥ 6 mmol/l) respectively. Similar to Chang et al, detection of hyperkalaemia increases with frequency of testing. Overall, the frequency of monitoring in these studies was generally 1-2 times per year, with more frequent testing in patients with an eGFR < 30 ml/min.

The interval between hyperkalaemic episodes was reported in a large retrospective cohort study of adults with CKD. This study utilised data from the Clinical Practice Research Datalink comprising of primary care records for approximately 7% of the UK population (n= 191,964) over a mean follow-up of 4.96 years. Patients experiencing at least one episode of hyperkalaemia was stratified in three groups: serum K⁺ 5.0 – 5.4 mmol/l (45.2%), 5.5 – 5.9 mmol/l (15.9%) and ≥ 6.0 mmol/l (4.9%). The time interval to a recurrent episode of hyperkalaemia progressively shortened in each severity group. The interval between the first to second episode in patients with serum K⁺ 5.5 – 5.9 mmol/l was 0.84 years and reduced to 0.59 years between the second and third episode and 0.48 years between the third and fourth episode. The interval between recurrent episodes was shorter in patients with serum K⁺ ≥ 6 mmol/l (0.65, 0.41 and 0.30 years respectively).

This collective data would suggest that monitoring serum K⁺ at least twice per year in patients at risk of hyperkalaemia is a reasonable approach. The frequency of monitoring should be increased to at least four times per year in patients with an eGFR < 30 ml/min and in patients with a serum K⁺ ≥ 6 mmol/l given the high risk of recurrence.

The interval for blood monitoring after a hyperkalaemic event is less well documented. Horne et al conducted a large population study including 700 Primary Care practices in the UK to investigate the epidemiology and impact of hyperkalaemia. This study demonstrated an overall incidence of hyperkalaemia (K⁺ ≥ 5.0 mmol/l) of 2.9 per 100 person-years. Only 5.8% of patients had a repeat serum K⁺ performed within 14 days of the hyperkalaemic event, but this likely reflects the large number of patients with a serum K⁺ < 5.5 mmol/l which may have been perceived to be non-urgent. A repeat level occurred more commonly in patients with K⁺ > 6.0 mmol/l (55.3%) compared with those with a serum K⁺ 5.6 – 6.0 mmol/l (23.4%) or serum K⁺ 5.0 – 5.5 mmol/l (3.9%). In patients with a serum K⁺ > 6.0 mmol/l at the index event, 36.8% had an elevated K⁺ level on re-testing. In this study, the recurrence of hyperkalaemia was higher than the index event at 8.1 per 100 person years.

‘Think Kidneys’ have provided practical guidance on repeat testing after a hyperkalaemic episode. The timing is guided by the level of hyperkalaemia and clinical context. In patients with mild hyperkalaemia (K⁺
5.5 – 5.9 mmol/l), a repeat test is recommended within 3 days if the result was unexpected or as soon as feasible if the patient is clinically stable. In patients with moderate hyperkalaemia (K⁺ 6.0 – 6.4 mmol/l), a repeat test is recommended within 1 working day if detected on a routine check in a stable patient, but referral to hospital should be considered if clinically unwell or if an AKI is present. Patients with severe hyperkalaemia (K⁺ ≥ 6.5 mmol/l) warrant urgent referral to hospital for immediate assessment and treatment. The recommended interval for repeat testing after a hyperkalaemic episode is summarised in Table 4.

<table>
<thead>
<tr>
<th>Severity of Hyperkalaemia</th>
<th>Clinically well (no AKI)</th>
<th>Unexpected result</th>
<th>Clinically unwell or AKI</th>
</tr>
</thead>
<tbody>
<tr>
<td>MILD</td>
<td>Repeat within 14 days</td>
<td>Repeat within 3 days</td>
<td>Consider if hospital referral is indicated</td>
</tr>
<tr>
<td>K⁺ 5.5 – 5.9 mmol/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MODERATE</td>
<td>Repeat within 1 working day*</td>
<td>Repeat within 24 hours</td>
<td>Refer to hospital</td>
</tr>
<tr>
<td>K⁺ 6.0 – 6.4 mmol/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEVERE</td>
<td>Refer to hospital for immediate assessment and treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K⁺ ≥ 6.5 mmol/l</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Need for hospital referral will be guided by clinical circumstance and risk of further deterioration.

*Routine bloods tests unavailable at weekends and out of hours from community.

(Modified from Think Kidneys Guideline)

There is increasing use of point of care testing (POCT) in the hospital setting for rapid potassium measurement, but achieving rapid blood analysis in the community can be challenging. POCT has been validated in several studies in the hospital setting within the Emergency Department and Critical Care. POCT has also been shown to improve early recognition of hyperkalaemia in patients with CKD presenting to the Emergency Department. Use of POCT in the pre-hospital setting is less well reported. A study of the utilisation and validation of POCT devices by community paramedics demonstrated good correlation with laboratory measurement. Technology is rapidly developing with the use of medical biosensors and Smart phone technology potentially making POCT easily accessible for patients.

References


Hyperkalaemia in the Community (Guidelines Hyperkalaemia 2.1 – 2.7) Management of patients receiving RAASi drugs (Guidelines 2.1 – 2.7)

Guideline 2.1 – Assessment of patients prior to initiation of ACE-I or ARB.
We recommend that renal function should be assessed prior to initiation of ACE-I or ARB and these drugs should be used with caution if the serum K+ is > 5.0 mmol. (1A)

Guideline 2.2 – Assessment of patients prior to initiation of Mineralocorticoid Receptor Antagonists (MRA).
We suggest that initiation of MRAs should be avoided in patients with a baseline serum K+ > 5.0mmol/l, serum creatinine > 221 μmol/l or eGFR < 30 ml/min. (1B)

Guideline 2.3 – Monitoring of patients after initiation of ACE-I and ARB.
We recommend that renal function should be assessed at 1 – 2 weeks after initiation of ACE-I or ARB and after every dose titration. (1A)

Guideline 2.4 – Monitoring of patients after initiation of MRAs.
We recommend that renal function should be assessed at 1 week after initiation of MRA or after dose up-titration, then monthly for the first 3 months, 3-monthly for the first year and 4-monthly thereafter. (1A)

Guideline 2.5 – Management of hyperkalaemia in patients treated with RAASi drugs.
We suggest increased frequency of monitoring in patients with a serum K+ between 5.5-5.9 mmol/l and consideration of dose reduction of RAASi drugs (ACE-I, ARB, MRA). (1B)

Guideline 2.6 – Management of hyperkalaemia in patients treated with RAASi drugs during acute illness.
We recommend that RAASi drugs be withheld during acute intercurrent illness (e.g. sepsis, hypovolaemia and/or AKI) at all severities of hyperkalaemia. (1D)

Guideline 2.7 – Cessation of RAASi drugs in patients with moderate or severe hyperkalaemia.
We recommend cessation of RAASi drugs in patients with serum K ≥ 6 mmol/l who do not meet the criteria for treatment with sodium zirconium cyclosilicate. (1B)

Audit measure
1. Frequency of blood monitoring of patients receiving RAASi drugs in the community.
2. Proportion of patients achieving optimal dosing of RAASi drugs with and without use of SZC.
3. Frequency of severe hyperkalaemia in patients receiving combination of RAASi drugs.

Rationale (Guidelines Hyperkalaemia 2.1 – 2.7)
Patients with CKD, heart failure and diabetes are particularly at risk of hyperkalaemia and these conditions often co-exist. RAASi drugs have become the standard of care to slow progression of CKD and in the management of patients with diabetes and heart failure. However, hyperkalaemia frequently limits use or
titration of RAASi drugs. Epstein et al conducted a large study (> 7 million of electronic patient records) to
determine the impact of hyperkalaemia on the optimal versus real-world treatment with RAASi.\(^1\) In patients
for whom RAASi was recommended by treatment guidelines for cardiorenal disease, \(>50\%\) were prescribed
lower than recommended dose and \(14-16\%\) discontinued RAASi therapy.\(^1\)

Sub-optimal treatment for patients with heart failure and renal disease also affects patient outcome.
Mortality rates has been shown to be higher in patients who receive sub-maximal dosing (8%) and in those
who have discontinued RAASi (11%) compared to those who received maximal dosing (4%).\(^2\) Similarly,
Ouwerkerk et al demonstrated increased hospitalisation and increased mortality in patients with heart
failure with reduced ejection fraction (HFrEF) who receive less than half of the recommended doses of ACE-I
or ARB (HR 1.72) and beta blockers (HR 1.70) compared to patients who reached optimal doses.\(^3\) The balance
between optimising treatment and compromising renal function poses a significant clinical dilemma.

Monitoring of serum K\(^+\) in patients receiving RAASi drugs reduces the risk of adverse events. Raebel et al
demonstrated that patients with diabetes who underwent potassium monitoring during the first year of
treatment with RAASi drugs were less likely to experience hyperkalaemia-associated adverse events
(hospitalisation, Emergency Department attendance or death) with an adjusted relative risk of 0.50 (0.37,
0.66) compared to those who were not monitored.\(^4\) The sub-set of patients with CKD had an adjusted
relative risk of 0.29 (0.18, 0.46). Park et al conducted an observational study of hospitalised patients newly
started on an ARB and demonstrated that the highest incidence of hyperkalaemia occurred on the first day
and 52.4% of hyperkalaemic events occurred within the first week of initiation.\(^5\) In this study, hyperkalaemia
also occurred earlier in patients with reduced GFR, higher baseline K\(^+\) level (patients with K\(^+\) >5.5 mmol/l
were excluded) and in patients with diabetes.

The KDIGO Guideline (2012) recommends measuring serum K\(^+\) level within 1 week of starting RAASi drugs
and after every dose increment in patients with reduced renal function.\(^6\) The NICE Guideline for CKD (2014)
recommends measuring serum K\(^+\) level before starting, within 1 to 2 weeks of initiation of RAASi therapy and
after every dose increment.

The NICE CKD Guideline (2014) recommends that RAASi drugs should be withdrawn if the serum K\(^+\) is \(\geq 6\)
mmol/l.\(^7\) However, NICE (2019) has recently approved the use of sodium zirconium cyclosilicate (SZC) in
selected patients with CKD 3b-5 (not on dialysis) or heart failure who have confirmed persistent
hyperkalaemia with a serum K\(^+\) \(\geq 6\) mmol/l and are not receiving an optimal dose of RAASi.\(^8\) The use of SZC
will be discussed in Guideline 10. RAASi should be withdrawn in all patients with serum K\(^+\) is \(\geq 6\) mmol/l who
do not meet the criteria for SZC.

The Renal Association and the British Society for Heart Failure (2019) have recently collaborated to provide
consensus recommendation for the use of RAASi in patients with heart failure with reduced left ventricular
ejection fraction (HFrEF).\(^9\) RAASi therapy has no known prognostic benefit in heart failure with preserved
ejection fraction. Monitoring of renal function is mandatory during initiation and titration of RAASi
treatment. Cessation of RAASi during intercurrent illness was advised in the context of acute illness (sepsis,
hypovolaemia and/or AKI) at all severities of hyperkalaemia (Table 5). RAASi re-introduction was
recommended after recovery and when K\(^+\) was < 5.5 mmol/l. Patients receiving multiple RAASi drugs and/or
MRA should re-start one drug at a time.
Table 5:  Guidance for RAASi therapy based on the severity of hyperkalaemia in patients with heart failure with reduced ejection fraction (HFrEF).

Adapted from Renal Association/ British Society for Heart Failure guideline (2019) and NICE Guideline for SZC in treating hyperkalaemia (2019).

*Mild hyperkalaemia (K⁺ 5.5-5.9 mmol/l):*
Clinically well (no AKI): Increase frequency of monitoring (no AKI) and consider dose reduction of RAASi.

*Acute illness:  Withhold RAASi and re-start when serum K⁺ < 5.5 mmol/l.

Decompensated heart failure:  Continue RAASi (with/ without AKI), but consider dose reduction.

*Moderate hyperkalaemia (K⁺ 6.0-6.4 mmol/l):*
Clinically well (no AKI): If moderate hyperkalaemia is confirmed, start SZC (see note below) and continue RAASi only if SZC initiated. Monitor serum K⁺.

*Acute illness: Withhold RAASi and monitor. Re-start at lower dose when serum K⁺ < 5.5 mmol/l.

Decompensated heart failure:  Start SZC (see note below), continue RAASi if SZC initiated and monitor renal function closely.

*Severe hyperkalaemia (K⁺ ≥6.5 mmol/l):*
All patients:  Admit to hospital for emergency treatment. Withhold RAASi. Restart RAASi when K⁺ < 5.5 mmol/l.

Decompensated heart failure:  Re-start when K⁺ < 6.0 mmol/l.

**Note:** NICE have approved SZC for restricted patient groups: CKD 3b-5 (not on dialysis) or heart failure who have confirmed persistent hyperkalaemia with a serum K⁺ ≥ 6 mmol/l and are not receiving an optimal dose of RAASi.

1 2 3 4 5 6 7 8 9 10 11 12 13

Mineralocorticoid receptor antagonists (MRAs) have significantly improved heart failure management, but their use alone or in combination with RAASi, may exacerbate hyperkalaemia. The current European Society of Cardiology and American Heart Association (AHA)/ American College of Cardiology (ACC) guidelines provide guidance on initiation, monitoring and response to treating hyperkalaemia in patients receiving MRAs (Table 6).
Table 6: Guidance for initiation and monitoring of patients receiving MRAs and strategies for managing hyperkalaemia.

Adapted from ESC\textsuperscript{10}, AHA/ACC\textsuperscript{11} and NICE\textsuperscript{8} Guidelines.

MRA - Mineralocorticoid receptor antagonists; HF – Heart failure
SZC – Sodium zirconium cyclosilicate

Adherence to guideline recommendations appears to be poor. In a large population-based study of new users of RAASi drugs, < 33% of patients had a K\textsuperscript+ measurement within 30 days of drug initiation and only 76% had at least one measurement within the first year of treatment.\textsuperscript{12} Chang et al reported that 20% of patients had no serum K\textsuperscript+ monitoring within 3 years of initiation of antihypertensive medication that affect potassium levels.\textsuperscript{13} Combined treatment of RAASi and an aldosterone antagonist increase the risk of hyperkalaemia, but Sinnott et al reported <33% of patients taking an RAASI had biochemical monitoring within two weeks of initiation of an aldosterone antagonist.\textsuperscript{14} This highlights the gap in knowledge and clinical practice.

References


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**Hyperkalaemia in the Community (Guidelines Hyperkalaemia 3.1)**

**Threshold for treatment of hyperkalaemia (Guideline 3.1)**

**Guideline 3.1 – Threshold for treating Hyperkalaemia in the community.**

We recommend that interventions to lower serum potassium be instituted in patients with a serum K⁺ ≥ 5.5 mmol/l. (1B)

**Audit Measures**

1. Proportion of patients with a serum K⁺ ≥ 5.5 mmol/l in whom an intervention for lowering serum potassium was instituted.

**Rationale (Guideline 3.1)**

The detection of hyperkalaemia in the community is frequently the result of blood monitoring in relation to the prescription of RAASi medication. Outwith this context, most observational studies have based diagnosis of hyperkalaemia on a single blood test. Pseudo-hyperkalaemia may occur in the community after long transit time to the laboratory, therefore unexpected results should be repeated.
Existing National guidelines recommend initiation of strategies to manage hyperkalaemia when the serum K⁺ rises to ≥ 5.5 mmol/l.\(^1,2\) Data from several studies performed in the general population and in patients with CKD show an increased mortality risk in patients with a serum K⁺ ≥ 5.5 mmol/l.\(^3\)\(^-\)\(^9\) Mortality risk increases further when the serum K⁺ exceeds 6 mmol/l, therefore measures should be taken to avoid a further rise in serum K⁺ level.

Drugs are frequently implicated in the development of hyperkalaemia in the community. Serum K⁺ levels increase by 0.4 – 0.6 mmol/l during RAASi treatment in patients with diabetic and non-diabetic kidney disease (serum creatinine level 133-265 μmol/l) and approximately 1 – 1.7% of patients develop hyperkalaemia.\(^1\) Although RAASi and non-selective beta-blockers can increase K⁺ levels, consider the degree of hyperkalaemia and the indication for use before reducing or withholding the drug.

Stop other medications known to exacerbate hyperkalaemia (e.g. oral potassium supplements, NSAIDs, trimethoprim). Other strategies for lowering serum K⁺ in the community include dietary interventions [Guideline 6], treating metabolic acidosis [Guideline 7] and controlling hyperglycaemia. Re-introduction of medications that influence K⁺ levels requires slow titration and close monitoring.

References
Hyperkalaemia in the Community (Guidelines Hyperkalaemia 4.1 – 4.2) **Indications for hospital admission (Guidelines 4.1 – 4.2)**

**Guideline 4.1 – Indication for hospital admission for patients with severe hyperkalaemia detected in the community.**

We recommend admission to hospital for urgent assessment and treatment for all patients with severe hyperkalaemia (serum $K^+$ ≥ 6.5 mmol/l) detected in the community. (1A)

**Guideline 4.2 – Indication for hospital admission for patients with mild-moderate hyperkalaemia detected in the community.**

We suggest hospital admission for assessment and treatment for acutely unwell patients with mild (serum $K^+$ 5.5 – 5.9 mmol/l) or moderate hyperkalaemia (serum $K^+$ 6.0 - 6.4 mmol/l), particularly in the presence of an acute kidney injury. (1B)

**Audit Measures**

1. Number of patients admitted from Primary Care with severe hyperkalaemia (serum $K^+$ ≥ 6.5 mmol/l) annually.

2. Proportion of patients admitted from Primary Care with severe hyperkalaemia who subsequently did not warrant emergency treatment on repeat testing.

**Rationale** (Guidelines Hyperkalaemia 4.1 – 4.2)

There is substantial variability in clinical practice relating to hospital admission for management of hyperkalaemia, which may be partly explained by incidental findings in clinically well patients. The detection of hyperkalaemia in the community is rising with the increasing use of RAASi drugs for multiple clinical indications and the necessity for regular biochemical surveillance. Drug up-titration or co-administration of another drug that affects $K^+$ level, as shown in Table 7, can precipitate severe hyperkalaemia. Acute illness is another common antecedent to acute kidney injury and hyperkalaemia.

### Table 7: Drugs that pose an additive effect on risk of hyperkalaemia in patients receiving RAASi and MRAs.

- Trimethoprim/co-trimoxazole
- Potassium supplements
- Potassium sparing diuretics
- Salt substitutes (lo-salt)
- NSAID
- Non-selective beta-blockers
- Digoxin toxicity
The risk of adverse events increases with worsening hyperkalaemia. Severe hyperkalaemia is an independent predictor of all-cause and in-hospital mortality as well as hospitalisation. Therefore, defined thresholds for triggering intervention in the community and for prompting referral to hospital could improve patient outcome.

There is little evidence for a specific threshold for hospital admission for management of hyperkalaemia. Charytan et al undertook a small study (n=23) to assess the practice relating to hospitalisation of patients for hyperkalaemia. In this study, 11 patients with hyperkalaemia at hospital admission were compared with 12 hyperkalaemic patients managed as an outpatient. The study lacked power to determine the relative safety of location of treatment. Horne et al demonstrated the impact of hyperkalaemia on mortality and healthcare utilisation, including hospital admission, in the UK general population, but did not provide a distinct threshold warranting hospital admission. However, this study noted a significantly higher incidence rate of all-cause hospitalisation for patients with a serum $K^+$ $> 6.0$ mmol/l of 28.93/ 100 person-years compared with patients with a serum $K^+$ 5.0-5.5 mmol/l of 13.86/ 100 person-years.

The position statement for 'Think Kidneys', a collaboration of The Renal Association and British Society for Heart Failure, recommend hospital admission in all patients with severe hyperkalaemia ($K^+ \geq 6.5$ mmol/l) and in patients with moderate hyperkalaemia ($K^+ 6.0-6.4$ mmol/l) who are acutely unwell or have an AKI. Hospital admission should be considered in patients with mild hyperkalaemia ($K^+ 5.5-5.9$ mmol/l) if acutely unwell or have an AKI.

An important consideration in the management of an episode of hyperkalaemia is the balance between the immediate risk versus the impact of cessation of RAASi drugs in patients for whom these drugs are crucial in controlling symptoms and improving survival. Minimising the duration of cessation of treatment and clear communication after hospital discharge is essential. Involvement of specialist services, renal and heart failure teams, may facilitate safer re-introduction of treatment.

References

**Hyperkalaemia in the Community (Guidelines Hyperkalaemia 5.1)**

**Treatment: Dietary interventions (Guideline 5.1)**

**Guideline 5.1 – Dietary Intervention for managing Hyperkalaemia in the community.**

We recommend that a low potassium diet is instituted for patients with a serum K⁺ > 5.5 mmol/l. (1B)

**Audit measures**

1. Proportion of patients with mild hyperkalaemia who have received dietary potassium advice.
2. Proportion of patients with moderate hyperkalaemia who have received dietary potassium advice.

**Rationale (Guideline 5.1)**

Many potassium-rich foods, including fruit and vegetables, are considered part of a normal healthy diet. In adults without kidney disease, the WHO recommends an average dietary K⁺ intake of approximately 3.9g/day (100mmol).[1] In the USA, the Institute of Medicine, Food and Nutrition Board recommend a higher daily K⁺ intake of 4.7g/day (120mmol/l).[2] In patients with kidney disease, the National Kidney Foundation (NKF) suggests an unrestricted potassium intake in patients with CKD 1-5 (non-dialysis) unless the serum K⁺ is elevated.[3] In advanced CKD and in ESRD, hyperkalaemia may result if the dietary input of potassium exceeds the output, therefore prevention of hyperkalaemia requires management of dietary K⁺ load.[4]

A low K⁺ diet is defined as a dietary intake of 2-3g/day (51-77 mmol/day).[4] In patients with CKD with a tendency to hyperkalaemia (serum K⁺ ≥ 5.5mmol/l), a dietary K⁺ restriction of < 3g/day (< 77 mmol/l) is recommended.[5] Excessive dietary restrictions can expose patients to a poorer diet that promotes cardiovascular disease. The development of constipation is also counterproductive as this will reduce K⁺ excretion by the gut. Therefore, a balanced intake of fresh fruit, vegetables and fibre is the goal.

Although dietary intervention has become standard practice, this has not been demonstrated in a randomised controlled trial. Three studies reported on dietary intervention for managing hyperkalaemia.[6,7,8] Ahuja et al reported a retrospective analysis of patients attending a renal clinic (n=119) to determine the predictors for development of hyperkalaemia in patients on ACE-I.[6] Overall, 46/119 patients (38.6%) of patients developed hyperkalaemia (mean serum K⁺ 5.68 mmol/l) and of these patients, 84% had diabetes mellitus and 30% had heart failure. Hyperkalaemia resolved in 20/46 patients (43%) with a low K⁺ diet alone (<2g/day; 51 mmol/l) and in 11/46 patients (24%) with dietary advice and dose reduction of ACE-I.

Hyperkalaemia persisted in the remaining 15/46 patients (33%) despite dietary advice and reduction of ACE-I necessitating discontinuation of ACE-I.

Bushinsky et al studied the difference in serum K⁺ in hyperkalaemic patients (K⁺ 5.5-6.2 mmol/l) with CKD 2-4 on a random diet versus controlled K⁺ diet during the 72-hour run-in phase of a treatment trial (n=25).[7] Patients were receiving a stable doses of RAASI medication. The study demonstrated a wide inter-individual variation in serum K⁺ on a random diet. Variation decreased significantly after 24 hours on a low K⁺ diet (2.4g or 60 mmol/day). The study concluded that this observation may have implications for the interpretation of clinical trials assessing directional change of serum K⁺ with a pharmaceutical intervention.

Maclaughlin et al prospectively investigated the prevalence of hyperkalaemia in a population of CKD patients (n=356) attending low clearance clinics who underwent regular nutritional assessment and dietary
education. All patients were pre-dialysis with an eGFR ranging from 8 – 20 ml/min. The prevalence of hyperkalaemia (serum K+ > 5.5 mmol/l) was 26.5% before the dietetic program in 2011 and 10.5% after it was instituted in 2014. The prevalence of hyperkalaemia also reduced in patients with K+ > 6.0 mmol/l from 8.4% to 2.5% during the same intervals. A dietary education program delivered by specialist renal dieticians can be very effective in reducing the prevalence of hyperkalaemia.

In patients receiving renal replacement therapy, the KDOQI guidelines suggest a potassium intake of approximately 2.7-3.1 g/day (69-79 mmol/day) in haemodialysis patients and 3-4g/day (77-102 mmol/day) in peritoneal dialysis patients. Adjustments are guided by the serum K+ level.

References

Renal Association Clinical Practice Guidelines – Treatment of Acute Hyperkalaemia in Adults – December 2019

Hyperkalaemia in the Community (Guidelines Hyperkalaemia 6.1) Treatment: Sodium bicarbonate (Guideline 6.1)

Guideline 6.1 – Sodium bicarbonate for management of Hyperkalaemia in the community

We recommend that sodium bicarbonate is used in CKD patients with a serum bicarbonate level < 22 mmol/l with or without hyperkalaemia. (1B)

Audit Measures

1. The proportion of patients attending renal clinics with serum bicarbonate < 22 mmol/l.
2. The frequency of hyperkalaemia in CKD patients with a serum bicarbonate < 22 mmol/l.
3. The frequency of persistent hyperkalaemia (serum K⁺ ≥ 5.5 mmol/l) despite correction of metabolic acidosis with sodium bicarbonate.

Rationale (Guideline 6.1)

Epidemiological studies show a prevalence of metabolic acidosis of 15-19% in patients with CKD stages 3-5.1 The prevalence increases with severity of kidney disease with metabolic acidosis found in 30-50% of patients with eGFR < 30 ml/min.2,3 Furthermore, serum bicarbonate levels steadily decrease with age > 60 years.4 Despite its prevalence, there is variability in clinical practice for treatment of mild acidosis in patients with CKD attending renal services and it is not routinely assessed or treated in primary care.

The benefit of treating chronic acidosis goes beyond the management of hyperkalaemia. Metabolic acidosis is also associated with muscle wasting, bone disease and increased mortality in patients with CKD.5 Additionally, there is growing evidence that metabolic acidosis contributes to the progression of CKD.1,6,7 Goraya et al demonstrated that an increase in serum bicarbonate by 4 - 6.8 mmol/l was associated with a reduction in decline in eGFR by 4 ml/min over 6 to 24 months compared with control patients.1

The mechanism for potassium lowering is the transcellular shift of K⁺ into cells following alkalinisation of the serum. Despite this theoretical benefit, few studies have shown any benefit of sodium bicarbonate in the treatment of acute or chronic hyperkalaemia. In two long-term studies (i.e. > 2 months), alkali therapy has been shown to be associated with a significant net decrease in the serum K⁺ by approximately 0.7 mmol/l, but no significant change was shown in short term studies (≤ 7 days).6,8

In the pre-dialysis setting, Sarafidis et al performed a prospective study to examine the factors influencing K⁺ metabolism in patients attending a low clearance clinic (mean eGFR 14.5 ± 4.8 mmol/l).9 This study demonstrated that patients with K⁺ ≥ 5.5 mmol/l had significantly higher urea, lower eGFR and lower serum bicarbonate levels. This sub-group also had a higher usage of sodium bicarbonate than in patients without hyperkalaemia (65.3% versus 45.4%, p=0.008).9

The potential detrimental effect of sodium load with sodium bicarbonate replacement is an important consideration, particularly in patients at risk of fluid overload. Dubey et al showed that patients with CKD 3 and 4 with co-existing diabetes, hypertension and coronary artery disease had a trend towards worsening hypertension and oedema necessitating a greater use of diuretics.7 Similar findings have been reported in other studies with alkali replacement in CKD patients necessitating discontinuation of sodium bicarbonate due to hypertension and oedema although these studies did not focus on management of hyperkalaemia.8,10,11
There remains a paucity of evidence from clinical trials on the efficacy and safety of bicarbonate therapy, therefore many existing guidelines are based on the sparse evidence and expert consensus opinion. KDOQI guidelines recommend the maintenance of serum bicarbonate level ≥ 22 mmol/l to reduce metabolic complications.12 The 2007 Cochrane Review of alkali therapy in CKD found insufficient evidence of benefit.13 The NICE CKD Guideline 2014 suggests that oral sodium bicarbonate should be considered in patients with CKD 4 or 5 with a serum bicarbonate < 20 mmol/l.14 The National Kidney Foundation ‘Best Practices In Managing Hyperkalaemia in CKD’ suggests the use of oral sodium bicarbonate for chronic hyperkalaemia.15

Further research is underway to evaluate the benefits and adverse effects of sodium bicarbonate in patients with CKD. The BiCARB Trial is a double-blind placebo-controlled RCT which includes 380 community-based patients in the UK aged ≥ 60 years with an eGFR < 30 ml/min and serum bicarbonate < 22 mmol/l.16 Patients have been recruited from primary care and out-patient clinics. The primary outcome is functional performance at 12 months, but this study will also provide serial measurements of K⁺ level up to 24 months.

References
Hyperkalaemia in the Community (Guidelines Hyperkalaemia 7.1) Treatment: Diuretics (Guideline 7.1)

Guideline 7.1 – Use of diuretics for managing Hyperkalaemia in the community

We suggest that loop diuretics may be a useful adjunct for the treatment of chronic hyperkalaemia in patients who are non-oliguric and volume replete. (2C)

Audit measures
1. The proportion of patients with persistent hyperkalaemia (K+ > 5.5 mmol/l) treated with RAASi and loop diuretic.

Rationale (Guideline 7.1)

In patients with preserved renal function, the kidneys are the primary route of potassium elimination. Loop and thiazide diuretics enhance K+ excretion by increasing flow and delivery of sodium to the collecting ducts and may be useful in treating mild to moderate hyperkalaemia in patients with adequate renal function.1,2 Loop diuretics (e.g. furosemide, bumetanide) are the most effective class that promote urinary K+ excretion and remain effective in patients with moderate renal impairment.1,3 On the other hand, thiazide diuretics are effective in patients with an eGFR > 30ml/min.3 Diuretics should be avoided in patients who are hypovolaemic or oliguric.

Patients with heart failure are susceptible to both hyperkalaemia and volume overload. RAASi therapy is frequently used in this setting and loop diuretics are a useful adjunct in controlling chronic hyperkalaemia whilst treating congestion.4,5 Patients admitted to hospital with decompensated heart failure pose a challenge in the presence of mild-moderate hyperkalaemia as reduction or cessation of cardioprotective medication may worsen heart failure. The joint guideline from the Renal Association and British Society of Heart Failure (2019) recommends consideration of combination therapy with a loop and thiazide diuretic in patients with decompensated heart failure (HFrEF) and mild-moderate hyperkalaemia.4 This combination potentiates diuresis and should theoretically enhance K+ excretion.

Diuretic therapy has a place in the management of chronic hyperkalaemia in patients who are normovolaemic or hypervolaemic. There is little evidence to support its use in acute hyperkalaemia.6 A multi-modal approach including diuretics, treatment of metabolic acidosis and dietary potassium restriction may allow the continuation of cardioprotective medications in patients with mild hyperkalaemia.

**Hyperkalaemia in the Community (Guideline 8.1)**

**Treatment: Calcium resonium (Guideline 8.1)**

**Guideline 8.1 – Calcium resonium for the management of Hyperkalaemia in the community.**

We suggest that calcium resonium may be used as a short-term measure to lower serum potassium to a level of ≤ 5 mmol/l in patients with mild to moderate hyperkalaemia. (2C)

**Audit measures**

1. Duration of treatment with calcium resonium required to lower serum K⁺ to a level of ≤ 5 mmol/l.

**Rationale (Guideline 8.1)**

Calcium polystyrene sulphonate (CPS, Calcium resonium) and sodium polystyrene sulphonate (SPS, Kayexalate) are cation exchange resins that work in the lower GI tract to enhance the elimination of K⁺ in the faeces. Each gram of resin has a theoretical in vitro exchange capacity of approximately 1.3 – 2 mmol of K⁺, but in vivo, it will be less.¹ Resins cause constipation, therefore laxatives are given to accelerate resin transit and to increase K⁺ excretion in stools.² Lactulose is an osmotic laxative and is commonly used in the UK. Macrogol 3350 (Laxido®, Movicol®) should be avoided as it contains potassium (46.6mg or 5.4mmol/l per sachet).

CPS is approved for use in Europe and SPS approved for use in the USA. SPS was approved by the Food and Drug Administration (FDA) in 1958 on the basis of two small uncontrolled case series undertaken in the 1950’s.³ This approval preceded the Kefauver-Harris Drug Amendment (1962) and the European Union EC/65/65 directive (1965) requiring drug manufacturers to prove the effectiveness and safety of their drug.⁴ Following multiple reports of colonic necrosis and other serious gastrointestinal adverse events (perforation, bleeding), the FDA applied safety recommendations in 2009. The FDA also advised against the concomitant administration of sorbitol, but serious complications have also been reported without the use of sorbitol.⁵ There are 3 RCTs including SPS as an intervention. Gruy-Kapral (1998) reported a placebo-controlled randomised study of SPS in normokalaemic patients with ESRD on haemodialysis (n=6) and failed to show any significant reduction in serum K⁺.⁶ The size, design and insufficient baseline data renders this study
weak. Nasir et al (2014) performed a RCT to compare the efficacy and safety of CPS and SPS in CKD patients (n=97) with hyperkalaemia. Although both drugs lowered serum K⁺, the study lacked adequate statistical analysis to substantiate the claim of equal efficacy and there was no control arm (i.e. placebo group). Of note, fewer side effects were reported with CPS than SPS. Lepage et al (2015) conducted a single centre double-blind RCT (n=33) in outpatients with CKD and mild hyperkalaemia (K⁺ 5.0-5.9 mmol/l) comparing efficacy of SPS 30g daily to placebo for 7 days. This study reported an absolute reduction of serum K⁺ level of 1.25 mmol/l (p<0.001), but the proportion of patients who achieved normokalaemia did not reach statistical significance (p=0.07). This trial lacked intermediate efficacy time points. None of these studies met the inclusion criteria for the Cochrane Review (2015).

The evidence for use of SPS is otherwise sparse. Chernin et al (2012) conducted a retrospective study (n=14) to assess the efficacy of SPS in CKD patients receiving RAASI medication, and observed a reduction in serum K⁺ from 6.4 ± 0.3 mmol/l to 4.6 ± 0.6 mmol/l (p<0.01) over a median follow up of 14.5 months. The size, lack of a control group and other confounding factors rendered this study difficult to interpret. Fordjour et al (2014) conducted a prospective chart review of treatment of hyperkalaemia in hospitalised patients and found that SPS was included in 95% of treatment regimens with potassium reduction ranging from 0.7 – 1.1 mmol/l. Effectiveness was deemed to be similar among patients with CKD and those receiving dialysis. Combination regimens yielded the greatest K⁺ reduction. Batterink et al (2015) conducted a retrospective study (n=138) and reported that SPS reduces serum K⁺ by 0.14 mmol/l more than control, but concluded that this level of treatment effect may not be clinically important.

The evidence for use of CPS is equally sparse. Chaaban et al (2013) conducted a retrospective study (n=70) to assess the effectiveness of calcium resinium in controlling hyperkalaemia in haemodialysis patients. This study showed poor efficacy attributed to lack of adherence to the drug and dietary restrictions as well as poor tolerability. Yu et al (2017) reported a retrospective analysis of 247 CKD patients in an out-patient setting treated with low dose CPS (8.0 ± 3.6 g/day) over a variable duration from > 3 months to beyond 1 year. Baseline eGFR was 30 ± 15 ml/min and serum K⁺ was ≥ 5.0 mmol/l. Serum K⁺ decreased significantly from 5.8 ± 0.3 mmol/l to 4.9 ± 0.7 mmol/l (p<0.001) with CPS treatment without any serious adverse effects over a long period.

CPS and SPS have been used widely for decades for the non-emergency treatment of hyperkalaemia despite the lack of robust randomised clinical trials to document efficacy or safety. Tolerability and the risk of severe gastrointestinal adverse effects limit their longterm use.

References


### Hyperkalaemia in the Community (Guideline 9.1)

#### Treatment: Patiromer (Guideline 9.1)

- **Guideline 9.1 – Patiromer for the management of Hyperkalaemia in the community**

We recommend that Patiromer is not used routinely for the management of hyperkalaemia. (1B)

#### Rationale (Guideline 9.1)

Patiromer is a non-absorbed, sodium free, K⁺-binding polymer. Calcium is used, rather than sodium, as the counterion for K⁺ exchange. This avoids the potential for excessive sodium absorption and volume overload. The drug is active throughout the gastrointestinal tract but mostly in the colon. The onset of action is slow at 4-7 hours. Patiromer has the potential to bind to some co-administered oral medication (e.g. metformin, levothyroxine and ciprofloxacin), therefore administration needs to be separated from other oral medications by ≥3 hours. Clinical trials have focused on the use of Patiromer to facilitate initiation and titration of RAASI drugs by controlling K⁺ level.

The definition of hyperkalaemia used in the Patiromer trials differs from the Renal Association (2014) and European Resuscitation Council (2015) guidelines. In the Patiromer trials, mild hyperkalaemia was defined as serum K⁺ 5.1 - 5.4 mmol/l and moderate to severe hyperkalaemia as serum K⁺ 5.5 - 6.4 mmol/l. Importantly, the treatment threshold in these studies was lower than in routine medical practice and maintenance therapy was a key focus. Early studies included 3 Phase I clinical pharmacology studies and 12 single dose drug-drug interaction studies. A summary of the 6 key Patiromer clinical trials is shown overleaf and in Table 8.
PEARL-HF Trial (Pitt, Eur Heart J 2011)

This was the first prospective, placebo-controlled, double blind trial of Patiromer in patients with chronic heart failure receiving standard therapy.

Eligibility was determined by the presence of either:
1) CKD and receiving RAASi or B-blocker for HF or
2) History of HK leading to discontinuation of RAASi or B-blocker within the previous 6 months.

Patients:
104 patients with a baseline serum $K^+$ ranging from 4.3 to 5.1 mmol/l followed for 4 weeks.

Intervention:
Patients were randomised to receive either Patiromer (n=55) or placebo (n=49).
Patiromer dose: 15g twice daily. (phosphate binders were not allowed)
Spironolactone 25mg/ day was started on Day 1.
On Day 15, the dose of spironolactone was unchanged if serum $K^+$ was 5.2-5.5 mmol/l, increased to 50mg / day if serum $K^+$ was 3.5 – 5.1 mmol/l, or stopped if serum $K^+$ was > 5.5 mmol/l.

Results:
Primary efficacy end-point: There was a mean reduction in serum $K^+$ of 0.22 mmol/l in the Patiromer group and a mean increment of 0.23 mmol/l in Placebo group at Day 28.

Secondary end-points: 1) the proportion of patients with $K^+$ > 5.5 mmol/l at any time during the study was 7% in the Patiromer group vs 25% in the Placebo group (p=0.015). 2) the proportion of patients whose spironolactone dose could be increased to 50mg/ day was 91% in the Patiromer Group vs 74% in the Placebo group (p =0.019).

Limitation: The dose of Patiromer was fixed, but dose adjustment of spironolactone was allowed to maintain the serum $K^+$ within the target range, therefore this confounder may have influenced the outcome of the study. The significant difference in serum $K^+$ reported between the groups of 0.45 mmol/l, reflects the divergence in serum $K^+$ after titrating spironolactone with a predictable rise in serum $K^+$ in the Placebo group (0.23 mmol/l) and a modest fall in serum $K^+$ in the Patiromer group (0.22 mmol/l).

HK - hyperkalaemia
OPAL-HK (Weir, NEJM 2015)

Multi-centre prospective trial examining efficacy of Patiromer in CKD patients receiving RAASi drugs.

Eligibility:
Patients with a serum K⁺ level of 5.1 – 6.4 mmol/l (62% had a baseline K⁺ ≥ 5.5 mmol/l).

The study was conducted in two phases:

**Phase 1 (n=243)** was the initial single-blind treatment phase over 4 weeks. Patients were assigned to receive Patiromer 4.2g twice daily (serum K⁺ 5.1 – 5.4 mmol/l) or Patiromer 8.4g twice daily (serum K⁺ level 5.5 – 6.4 mmol/l). Mean daily dose was 12.8g in patients with mild HK and 21.4g in moderate-severe HK. RAASi could not be adjusted during initial phase and were stopped if K⁺ ≥ 6.5 mmol/l.

Primary efficacy end point: mean change in serum K⁺ level from baseline to week 4 was −1.01 ± 0.03 mmol/l (P<0.001). The target serum K⁺ (3.8 – 5.0 mmol/l) was achieved in 76% of patients at week 4.

Although 219 patient completed Phase 1, 109 were not eligible to enter Phase 2 largely because the baseline serum K⁺ level was < 5.5 mmol/l.

**Phase 2 (n=107)** was the randomised, placebo-controlled, single-blind withdrawal period over 8 weeks. There was no wash-out period. Patients were eligible if they had a serum K⁺ ≥ 5.5 mmol/l at baseline of Phase 1 and if their serum K⁺ at the end of Phase 1 was within the target range.

Patients were randomly assigned to continue Patiromer (n=55) or switch to placebo (n=52).

Recurrence of HK was managed by either increasing dose of Patiromer (Patiromer group) or reducing RAASI (Placebo group) for the first event. Subsequent events required cessation of RAASI.

Primary efficacy end point: the between-group difference in the median change in serum K⁺ level at week 4 which was 0.72 mmol/l (0 mmol/l in the Patiromer group vs 0.72 mmol/l in the Placebo group).

Recurrence of hyperkalaemia (K⁺ ≥5.5 mmol/l) occurred in 15% in the Patiromer group compared with 60% of the patients in the placebo group by week 8. At the end of the randomized withdrawal phase, 94% of the Patiromer group and 44% in the placebo group were still receiving RAASI.

Limitations: the study was short and neither Phase of the trial was double-blind. No alternative drug was used as a comparator.
AMETHYST-DN (Bakris, JAMA 2015)

This was a Phase 2 multi-centre, open-label randomised study to determine the starting doses for a Phase 3 study and to evaluate the safety and efficacy of Patiromer.

Patients:
306 patients with Type 2 diabetes and CKD (eGFR 15-59 ml/min) on RAASi prior to and during study. Patients with a baseline serum K⁺ of 4.3-5.0 mmol/l and uncontrolled hypertension (systolic BP of 131-180 mmHg and diastolic BP of 81-110) were enrolled.

The study was designed in 3 Phases and the aim was to achieve and maintain serum K⁺ ≤ 5.0 mmol/l.
Phase 1: Run-in period of 4 weeks
Phase 2: 8 week treatment phase
Phase 3: Maintenance phase for up to 44 weeks

Intervention:
Patients were then randomly assigned in a 3:1 ratio into Cohort 1 or 2.
Cohort 1: RAASi was discontinued and replaced with Losartan 100mg. Spironolactone 25mg daily was added in Week 2 if BP did not meet target of 130/80.
Cohort 2: Maintained on previous RAASi therapy and started Spironolactone 25mg daily.
Spironolactone could be increased to 50mg if required in both cohorts if required for BP control.
Patients who developed HK during the run-in period (77%), were eligible for Phase 2 (median time was 15 days).
Cohort 3: Patients who were excluded from initial study due to HK (serum K⁺ 5.1-5.9 mmol/l) were continued on their previous RAASi therapy and entered directly into the Treatment phase without a run-in period.

Patients from all 3 Cohorts were stratified by baseline serum K⁺ level into:
Stratum 1 (n=222): ‘Mild’ hyperkalaemia (K⁺ 5.1 – 5.5 mmol/l).
Patients were randomised to receive Patiromer 4.2g, 8.4g or 12.6g twice daily.
OR
Stratum 2 (n=84): ‘Moderate’ hyperkalaemia (K⁺ 5.6 – 5.9 mmol/l).
Patients were randomised to receive Patiromer 8.4g, 12.6g or 16.8g twice daily (bd).

Results
Lowest starting dose was selected to be 8.4g/ day for mild HK and 16.8 g/day for moderate HK.
Mean reduction in serum K⁺:
Mild HK: 0.35 mmol/l (4.2g bd), 0.51 mmol/l (8.4g bd) and 0.55 mmol/l (12.6g bd)
Moderate HK: 0.87 mmol/l (8.4g bd), 0.97 mmol/l (12.6g bd) and 0.92 (16.8g bd)

Maintenance phase: majority of patients had a serum K⁺ level within the target range of 3.8 – 5.0 mmol/l.
Rebound in serum K⁺ occurred after discontinuation of Patiromer at the end of 52 weeks:
At 3 days: serum K⁺ rose in patients with mild (0.25 mmol/l) and moderate (0.33 mmol/l) HK.
At 28 days: serum K⁺ level rose in patients with mild (0.39 mmol/l) and moderate (0.48 mmol/l) HK.

Limitations: Serum K⁺ level was normal at enrolment. Lack of blinding and lack of a comparator (i.e. placebo or another drug). Study recruited patients with sub-optimal BP control, but the proportion of patients who actually achieved the target (130/80) is unclear. Despite the study duration, there was no clinically significant change in albuminuria.
Bushinsky (KI 2015)

This small prospective study was designed to evaluate the onset of action of Patiromer within the first 48 hours of treatment. *(data was not available in the AMETHYST-DN or OPAL-HK trials)*

Patients:
25 patients taking at least one RAASi, with a mean baseline K⁺ of 5.93 mmol/l, were admitted to an in-patient clinical research unit.

Intervention:
Study protocol included a 3-day dietary potassium restricted (2.4g; 60mmol/ day) run-in period. Patiromer 8.4g twice daily was given to all patients for two days with serial monitoring of the serum K⁺. Serum K⁺ was assessed at baseline, 4hrs post-dose, then every 2-4 hours up to 48 hrs, 58 hours and during out-patient follow-up.

Results:
There was a significant reduction of 0.21 mmol/l at 7 hours after the first dose. Significant reductions were also demonstrated from 7 – 48 hours.
A mean serum K⁺ < 5.5 mmol/l was achieved within 20 hours of the first dose of Patiromer.
At 48 hours, there was a significant reduction in serum K⁺ of 0.75 mmol/l.

Limitations: Patients received a low K⁺ diet and were closely monitored in an in-patient facility, which does not reflect real-world setting. The degree of adherence in the out-patient follow-up period is unknown.

TOURMALINE (Pergola, Am J Nephrol 2017)

This study was an open-label, randomised parallel group study to determine the efficacy of once daily dosing of Patiromer taken with or without food over a 4-week duration.

Patients:
112 patients with a serum K⁺ level > 5.0 mmol/l were included. Approximately 59% were on RAASi drugs. Mean baseline serum K⁺ level was similar in both groups – 5.34 mmol/l (with food) and 5.44 mmol/l (without food).

Intervention:
Patients were randomly assigned to receive Patiromer with food (n=55) or without food (n=57). Maximum dose of Patiromer was 25.2g/ day.

Results:
Primary efficacy end-point was the proportion of patients with serum K⁺ within target (3.8 – 5.0 mmol/l) at Week 4 and was achieved in 87.3% (with food) and 82.5% (without food).
The mean daily dose of Patiromer was similar in both groups - 8.4g.
The mean reduction in serum K⁺ from baseline to Week 4 was 0.65 mmol/l (with food) and 0.62 mmol/l (without food). Patiromer appears to be equally effective with or without food.
The PEARL-HF extension study is the only Patiromer trial with all participants having a diagnosis of chronic heart failure. Fewer patients in OPAL-HK (42%) and AMETHYST-DN (35%) had heart failure (Appendix 3). In the PEARL-HF study, almost half of the patients treated with Patiromer developed hypokalaemia (K⁺ < 4 mmol/l) which also infers a higher risk of mortality in heart failure. However, in the PEARL-HF extension study, spironolactone could be optimised with a lower starting dose of Patiromer whilst reducing the incidence of hypokalaemia.

In the OPAL-HK trial, 76% of patients with HF (NYHA Class I–III) achieved serum K⁺ levels within the target range with Patiromer treatment. Hypokalaemia (K⁺ < 3.5 mmol/l) occurred in 3% of patients. During the withdrawal phase, hyperkalaemia (|K⁺| ≥ 5.5 mmol/l) recurred in 52% of patients compared with 8% in patients who remained on Patiromer. By the end of the 8-week period, 100% in the Patiromer group remained on RAASi compared with only 55% in the placebo group.

PEARL-HF Extension Study (Pitt, ESC Heart Failure 2018)

This was an 8-week open-label follow-up study to the PEARL-HF trial to determine the effectiveness of a lower starting dose of Patiromer in preventing HK when initiating spironolactone.

Patients:
63 patients with chronic heart failure (NYHA Class II and III) and CKD (mean eGFR 46.2 ml/min). At baseline, 98% were receiving RAASi and 76% were receiving beta blockers, but many were not receiving an optimal dose.
The mean serum K⁺ at baseline was 4.78 mmol/l (4.3 – 5.1 mmol/l).

Intervention:
Patients received Spironolactone 25mg/ day and Patiromer 8.4g twice daily.
Spironolactone was increased to 50mg in all patients.
Patiromer was titrated to maintain serum K⁺ between 4.0 – 5.1 mmol/l.

Results:
Primary endpoint - a serum K⁺ between 3.5 – 5.5 mmol/l and was reached in 90.5% of patients.
The mean reduction in serum K⁺ from baseline to the end of the study was 0.13 mmol/l.
The incidence of hyperkalaemia (K⁺ > 5.5 mmol/l) was 24%.
Dose titration was required in 68% of patients and the mean dose at the end of study was 19.6g/ day. One week following dose titration, the serum K⁺ decreased by 0.34 mmol/l after an up-titrated dose of spironolactone and increased by 0.46 mmol/l after a down-titrated dose of 8.4g/ day on average.
The dose of spironolactone was successfully up-titrated in 98% of patients by Day 14.

Limitations: Patients did not have HK at baseline. There was no control group, however the PEARL-HF study showed a significant reduction in incidence of HK with placebo as a control.
<table>
<thead>
<tr>
<th>STUDY</th>
<th>N=</th>
<th>Study Duration</th>
<th>Mean Baseline K⁺ (mmol/l)</th>
<th>Study Groups</th>
<th>CHANGE IN SERUM K⁺ by PATIROMER DOSE (dose in g twice daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEARL – HF Pitt 2011¹² Phase II trial</td>
<td>104</td>
<td>4 weeks</td>
<td>4.69</td>
<td>Patiromer N= 55</td>
<td>4.2g  8.4g  12.6g  15g  16.8g -0.22</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4.65</td>
<td>Placebo N= 49</td>
<td>+0.2  3</td>
</tr>
<tr>
<td>OPAL-HK Weir 2015⁶ Phase III trial</td>
<td>243</td>
<td>Phase 1 Treatment 4 weeks</td>
<td>5.3</td>
<td>Mild HK 5.0-5.4 N= 92</td>
<td>-0.65</td>
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<td></td>
<td></td>
<td></td>
<td>5.7</td>
<td>Mod-Sev HK 5.5-6.4 N= 151</td>
<td>-1.23</td>
</tr>
<tr>
<td></td>
<td>107</td>
<td>Phase 2 Withdrawal 8 weeks</td>
<td>4.49</td>
<td>Patiromer N=55</td>
<td>0 Daily dose on entry: 12.8g (mild) and 21.4g (mod) After first 4 weeks, dose increase was allowed only for the first occurrence of K ≥ 5.1 mmol/l</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4.45</td>
<td>Placebo N=52</td>
<td>+0.72</td>
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<tr>
<td>AMETHYST-DN Bakris 2015⁷ Phase II trial</td>
<td>306</td>
<td>52 weeks</td>
<td>5.3</td>
<td>Mild HK 5.0-5.5 N=222</td>
<td>-0.35  -0.51  -0.55</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mod HK 5.6-5.9 N=84</td>
<td>-0.87  -0.97  -0.92</td>
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<tr>
<td>Bushinsky 2015⁸ Prospective</td>
<td>25</td>
<td>48 hours</td>
<td>5.93</td>
<td>All</td>
<td>7hrs: -0.21 20hrs: -0.52 48hrs: -0.75</td>
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<tr>
<td>TOURMALINE Pergola 2017⁹ Randomised Open label</td>
<td>112</td>
<td>4 weeks</td>
<td>5.34</td>
<td>With Food N=55</td>
<td>-0.65 median daily dose was 8.4g (8.4, 12.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5.44</td>
<td>Without Food N=57</td>
<td>-0.62 median daily dose was 8.4g (8.4, 14.1)</td>
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<tr>
<td>PEARL-HF extension study Pitt 2018¹⁰ Open-label</td>
<td>63</td>
<td>8 weeks</td>
<td>4.78</td>
<td>All</td>
<td>-0.13</td>
</tr>
</tbody>
</table>

Table 8: Studies of efficacy of Patiromer in the treatment of hyperkalaemia.
Patients with CKD were well represented in the clinical trials – Bushinsky (100%), OPAL-HK (100%), PEARL-HF extension study (100%), AMETHYST-DN (87%) and Tourmaline (76%). Notably, the original PEARL-HF involving MRA titration, included few patients with CKD (27%) and the study duration may have been too short (4 weeks) to detect a worsening of renal function. In contrast, worsening of renal function was found in 9.2% of participants of the AMETHYST-DN trial (52 weeks) and 13% of participants in the PEARL-HF extension study (8 weeks).[10]. In both of these studies, spironolactone was implicated in some cases. In AMETHYST-DN, this was the most frequently reported adverse event and was the most common cause for discontinuation. Despite its duration, this study also failed to show any clinically significant reduction in albuminuria.

Without K+-lowering drugs, the standard approach to treating chronic hyperkalaemia is a dose reduction or cessation of cardioprotective medication along with the institution of a low K+ diet. Dietary K+ restriction has been the mainstay of treatment for patients with mild to moderate hyperkalaemia. During the AMETHYST-DN and OPAL-HK trials, patients were counselled at each visit to restrict their intake of high- K+ foods and to maintain a low-K+ diet (≤3 g/day). The short in-patient trial designed to determine the rate of onset of Patiromer also instituted dietary K+ restriction in the run-in period.[8] Potassium-lowering drugs are unlikely to replace a low K+ diet, but conceivably may allow a less restrictive intake.

There are several limitations to the available studies on Patiromer. Most study participants did not have hyperkalaemia at recruitment and the threshold for initiating treatment was lower than standard clinical practice. This increases the risk of hypokalaemia (K+ < 3.5 mmol/l) which was reported in 6% of patients in PEARL-HF, 3% of patients in OPAL-HK, 5.6% of patients in AMETHYST-DN and 2% of patients in the PEARL-HF extension study. Some studies lacked a control group (see Table 8) and no studies compared Patiromer with another active drug. All studies were performed in stable out-patients, therefore a role for Patiromer in the acute setting has not been investigated. Given that the onset of action is slow (4-7 hours), its role in the acute hyperkalaemia is limited. Patients with CKD Stage 5, who are most at risk of hyperkalaemia, were not included in the studies. Rebound in K+ level occurs on cessation of Patiromer. Although the rebound levels shown in the reports may not have been clinically relevant, this could be problematic if patients had significant hyperkalaemia.

The main rationale for using Patiromer is controlling hyperkalaemia to allow initiation and optimisation of RAASI therapy. Theoretically, this might control heart failure, slow decline in renal function and improve survival. However, there were non-significant improvements in serious cardiovascular (CV) events in the PEARL-HF, OPAL-HK and AMETHYST-DN trials. There was a non-significant improvement in all-cause mortality during the treatment period of the PEARL-HF, OPAL-HK (Phase 1) and AMETHYST-DN trials.[13] There was no evidence that Patiromer reduces hospitalisation in the clinical trials currently available.

Following these clinical trials, Patiromer was approved for the treatment of chronic hyperkalaemia in the USA in 2015 and in the EU in 2017. The major caveat is that twice daily Patiromer dosing was utilized in most trials, whereas the FDA-approved dose is once daily. This modification stems from concern over the potential for drug interaction between Patiromer and other co-administered medications as discussed above.

The appraisal of Patiromer by NICE is underway and the pharmaceutical company submission has focussed on patients with Stage 3 and 4 CKD receiving RAASI with a serum K+ > 5.5 mmol/l.[14] Notably, many patients with Stage 3 CKD are managed in the community, whereas the initiation of Patiromer was intended for secondary care.
The key evidence for clinical effectiveness was derived from the OPAL-HK study which demonstrated a reduction in serum K+ by a mean of 1.01 mmol/l after 4 weeks (Phase 1). The mean serum K+ was 0.72 mmol/l higher in patients who were withdrawn compared with those who remained on Patiromer (Phase 2). The sub-group of patients with serum K+ ≥ 5.5 mmol/l who responded to Patiromer maintained the reduction in serum K+ with ongoing treatment and fewer patients (15%) developed rebound compared with the placebo group (60%).

However, several shortfalls have been identified in the OPAL-HK study failing to demonstrate clinical effectiveness:

- The treatment threshold (K+ > 5.1 mmol/l) was lower than standard NHS practice.
- At recruitment, only 44% of patients were considered to be on ‘maximal dose’ RAASi and the study did not permit dose optimisation.
- The study was not designed to demonstrate any important health outcomes from continuing RAASi (mortality, CV events or CKD progression).
- There was no control group in Phase 1, therefore effectiveness compared with standard care is unknown.
- The NICE CKD Guideline recommends cessation of RAASi drugs in patients with a serum K+ ≥ 6.0 mmol/l making this the clinically relevant objective, but this was not an outcome in the trial.
- The serum K+ levels in both arms of the Phase 2 study were within a range that would not warrant treatment in standard practice.
- Phase 2 also focussed on cessation of Patiromer, rather than assessing patients who would benefit from treatment.
- Phase 2 was short (8 weeks) and by the end of the study, patients receiving placebo had K+ level which would not warrant treatment (5.2 mmol/l). Although AMETHYST-DN provided supporting data over 52 weeks, the data were non-comparable.

The Scottish Medicines Consortium (SMC) did not approve Patiromer for the treatment of hyperkalaemia in NHS Scotland. The preliminary statement released by NICE also does not recommend Patiromer as there is no evidence that Patiromer reduces hospitalisation, improves quality of life or improves survival compared with standard treatment. The SMC undertook cost-effective analysis and concluded that there were several weaknesses and uncertainties with the economic analysis of the OPAL-HK study given its short duration and endpoints that do not readily correlate with long-term CKD or cardiovascular outcomes. NICE did not assess the cost-effectiveness of Patiromer given the lack of evidence to support relevant clinical-effectiveness. The final NICE publication is due to be released in February 2020.

Bounthavong et al reported a cost-effectiveness analysis of Patiromer and spironolactone in patients with NHYA Class III and IV heart failure unable to tolerate spironolactone due to hyperkalaemia. The findings suggested that combining Patiromer and spironolactone may provide clinical benefit and may be cost-effective when compared to ACE-I therapy alone. A multi-national Phase II trial (AMBER) is currently underway to determine if Patiromer will enable the use of spironolactone in approximately 290 patients with CKD and resistant hypertension (NCT03071263).
Patiromer studies in longterm haemodialysis (HD) patients

Bushinsky (Am J Nephrol, 2016)

Prospective inpatient metabolic study.
Patients: 6 chronic HD patients with moderate-to-severe HK (serum K⁺ ≥5.5 mmol/l) after one week on a low K⁺ diet.
Intervention:
Patiromer 12.6 g/day for 1 week (phosphate binders were stopped at the time of admission)
Results:
The mean (SE) serum K⁺ decreased from baseline was 0.6 (0.2) mmol/l (p = 0.009) and faecal K⁺ excretion increased.

Chatoth (NDT, 2017)

Retrospective study of Patiromer in patients undergoing long-term HD over 6 months.
Patients: 27, 155 patients with a baseline serum K⁺ > 5.5 mmol/l.
Intervention:
Patiromer group: 106 patients (any baseline serum K⁺ with Patiromer initiated at 8.4g/day in most patients)
SPS Group: 649 patients
Control group: 26, 400 patients with (baseline serum K⁺ ≥ 5.1 mmol/l without K⁺ binder)
Results:
Patiromer group had lowest number of hyperkalaemic events and hospitalisation.
All-cause mortality in patients with serum K⁺ > 6.0 was 0% (Patiromer), 1.8% (SPS) and 2.5% (control).

Kovesky (KI Reports, 2019)

Retrospective study of Patiromer in patients receiving chronic HD with a median follow-up of 141 days.
Patients: 10,126 chronic HD patients included. The mean dialysis vintage was 4 years. Given the retrospective design, all patients were already established on K⁺-lowering treatment at study initiation.
Intervention:
Patiromer group: 527 patients (8.4g once daily in 61% of patients and 89% of these patients had no dose alteration; approx 20% of patients received 8.4g less frequently than once daily and 4% received 16.8 g daily).
SPS Group: 852 patients
Control group: 8747 patients received neither drug.
Results:
The mean reduction in serum K⁺ observed was 0.5 mmol/l.
The largest K⁺ reduction (< 1mmol/l) was observed in patients with a baseline K⁺ ≥ 6.5 mmol/l. The proportion of patients with a serum K⁺ > 6.0 mmol/l was reduced from approx 50% to 22% after Patiromer initiation.
Patiromer group had a higher incidence of recurrent hyperkalaemia, previous use of SPS which failed to control hyperkalaemia and hyperkalaemia-related hospital admissions compared with the other groups. Patiromer group were also more likely to have more severe hyperkalaemia, received longer dialysis sessions (> 4hrs) and lower potassium dialysate (< 2mmol/l) than the other groups. 60% of patients were still receiving Patiromer at 6 months.
Treatment options for patients on haemodialysis who develop hyperkalaemia have been limited to dietary K+ restriction and low K+ dialysates. There is limited evidence for the use of Patiromer in dialysis patients as shown above.\(^{18-20}\) Given that Patiromer uses Ca\(^{2+}\) as the counter exchange cation for K\(^+\), there is a potential risk of increased vascular calcification. Phosphate binders were generally withheld during Patiromer trials, therefore these factors may have implications for longterm management in dialysis patients. Compliance with medication and diet can be challenging in dialysis patients and the consequence of poor adherence to Patiromer in patients with a liberal diet could be potentially serious.

References


Hyperkalaemia in the Community (Guidelines 10.1 – 10.3) Treatment: Sodium zirconium cyclosilicate (Guidelines 10.1 – 10.3)

**Guideline 10.1 – Sodium Zirconium Cyclosilicate for the management of Hyperkalaemia**

We recommend that Sodium Zirconium Cyclosilicate (SZC) is used in out-patients for the management of persistent hyperkalaemia with a confirmed serum K$^+$ ≥ 6.0 mmol/l in patients with CKD Stage 3b-5 (not on dialysis) or heart failure receiving a sub-optimal dose of RAASi therapy. (1A)

**Guideline 10.2 – Sodium Zirconium Cyclosilicate for the management of Hyperkalaemia**

We recommend that treatment with Sodium Zirconium Cyclosilicate (SZC) in out-patients is discontinued if RAASi therapy is stopped. (1A)

**Guideline 10.3 – Sodium Zirconium Cyclosilicate for the management of Hyperkalaemia**

We recommend that Sodium Zirconium Cyclosilicate (SZC) is initiated in secondary care only. (1A)

Audit measures:

1. The proportion of out-patients with moderate hyperkalaemia (serum K$^+$ 6.0 - 6.4 mmol/l) treated with SZC who achieved a serum K$^+$ ≤ 5.0 mmol/l within 48 hours.

2. The proportion of out-patients who achieve maximal dose RAASi therapy whilst taking SZC.

**Rationale (Guideline 10.1 – 10.3)**

Sodium Zirconium Cyclosilicate (SZC) is a non-absorbed potassium binder that preferentially exchanges H$^+$ and Na$^+$ for K$^+$ and ammonium ions throughout the entire gastrointestinal tract.$^1$ SZC selectively entraps monovalent cations (i.e. K$^+$ and ammonium) compared with divalent cations (Ca$^{2+}$ and Mg$^{2+}$). Therefore, unlike Patiromer, SZC does not affect Mg$^{2+}$ levels. SZC binding of ammonium ions increases serum bicarbonate levels, which is favourable in the context of hyperkalaemia. In-vitro studies have shown that the K$^+$-binding capacity of SZC is up to 9 times greater than that of sodium polystyrene sulphonate (SPS).$^2$ The K$^+$-
exchange capacity of SZC is also > 25 times more selective for K⁺ over Ca²⁺ or Mg²⁺ compared with SPS.³ A comparison of the mechanism of action of all of the oral potassium binders is shown in Appendix 2.

The onset of action of SZC is within 1 hour after ingestion and there is a close correlation between the initial serum K⁺ level and the size of the treatment effect, therefore the higher the serum K⁺ reduction,³ SZC is generally well tolerated. The most common adverse effects are oedema (5.7%) and hypokalaemia (4.1%). SZC exchanges Na⁺ for K⁺, accounting for the potential risk of worsening oedema, hypertension and heart failure. Product information and administration is described in Appendix 4E.

Three randomised controlled trials and one open label clinical trial have been reported. The first was double-blind RCT to investigate the safety and efficacy of SZC across a range of doses over a 2-day period.⁴ A dose-dependent reduction in serum K⁺ was demonstrated. The primary endpoint of rate of decline of serum K⁺ was achieved at the approved dose of 10g three times daily. This was followed by two multi-national Phase III RCT trials (ZS-003, ZS-004) to evaluate the efficacy and safety of SZC over a longer duration.⁵,⁶ The most recent study, ZS-005, is an open-label study to assess the efficacy of SZC with longer-term use (52 weeks).⁷ Patients with CKD, heart failure, diabetes mellitus and receiving RAASI medication were included in these studies. The studies were conducted in stable out-patients and excluded patients on dialysis, with life-threatening hyperkalaemia or diabetic ketoacidosis. There was also no restriction on dietary K⁺ intake in all of SZC trials.

The key clinical trials for SZC in the treatment of hyperkalaemia are summarised below.

**ZS-002 (Ash, 2015)⁴**

Phase II multi-centre randomised, double-blind, placebo-controlled trial to investigate the safety and efficacy of SZC in the treatment of hyperkalaemia.

**Patients:**
90 patients with stable Stage 3 CKD and a serum K⁺ 5.0 – 6.0 mmol/l (mean K⁺ 5.1 mmol/l).

**Intervention:**
Dose-escalation protocol over 2 days in 4 arms to determine safety, efficacy and optimal dosing of SZC:
- 0.3g (n=12), 3g (n=24), 10g (n=24) or placebo (n=30); each taken three times daily with meals.

All participants completed the study.

Only 24 patients received the licensed dose of SZC of 10g.

**Results:**
Primary efficacy end-point: rate of serum K⁺ decline in the first 48 hours. This was achieved in patients receiving 3g and 10g dosing regimen compared with placebo (Table 1).

The sub-group of patients receiving RAASI only achieved the primary end-point at a dose of 10g.

In the group receiving ZSC 10g regimen:
- the mean reduction in serum K⁺ from baseline was 0.11 mmol/l at 1 hour after the first dose.
- the mean reduction in serum K⁺ from baseline was 0.92 mmol/l after 38 hours.
- approximately 42% of patients achieved a reduction in serum K⁺ of ≥ 1mmol/l at 48 hours.
- K⁺ level remained significantly lower than placebo for up to 3.5 days after last dose.

**Limitation:** Small sub-group sizes. Few patients were receiving spironolactone alone (5.6%) or combined RAAS blockade (11%). The additive effect of a low K⁺ diet was not assessed.
Phase III multi-centre, double blind, placebo-controlled trial conducted in two stages.

Patients:
753 patients of whom 70% were receiving RAASi medication. Patients with a serum K⁺ level between 5.0 and 6.5 mmol/l were included, but approximately 77% of participants (n=579) had a baseline serum K⁺ ≤ 5.5 mmol/l.
Mean baseline serum K⁺ was 5.3 mmol/l.

Intervention:
Stage 1: Patients were randomised to SZC dose of 1.25g (n=154), 2.5g (n=141), 5g (n=157), 10g (n=143) or placebo (n=158) three times daily for 48 hours in the initial phase.
Stage 2: Patients who achieved a normal serum K⁺ (3.5-4.9 mmol/l) at 48 hours were randomly assigned to receive SZC or placebo once daily from Days 3 to 14 in the maintenance phase.

Results:
The primary efficacy end-point was the exponential rate of change in mean serum K⁺ level.
Stage 1
Mean serum K⁺ decreased from a baseline of 5.3 mmol/l to: 5.1 mmol/l (1.25g group), 4.9 mmol/l (2.5g group), 4.8 mmol/l (5g group), and 4.6 mmol/l (10g group) at 48 hours.
In patients with a baseline K⁺ > 5.5 mmol/l treated with 10g three times daily, the mean reduction of serum K⁺ at 48 hours in the group was 1.1 mmol/l, demonstrating the effect of dose and severity of HK on efficacy.
Stage 2
The efficacy end point for the maintenance phase was the between-group difference in the mean serum K⁺ level during the 12-day treatment period.
Serum K⁺ level was maintained within the normal range with SZC 5g (4.7 mmol/l) and 10g (4.5 mmol/l) daily.
HK (K⁺ > 5.0 mmol/l) recurred in patients treated with placebo who had received SZC 5g or 10g during the initial phase.
The mean exponential rate of change from baseline in serum K⁺ for patients treated with:
- SZC 5g was an increase of 0.09% per hour vs 0.47% per hour with placebo.
- SZC 10g was an increase of 0.14% per hour vs 1.04% per hour with placebo.

Limitations: Most of the study population had a level of serum K⁺ below the conventional threshold for treatment of hyperkalaemia.

HK - hyperkalaemia
The HARMONIZE study was a Phase III multi-centre, double-blind placebo controlled trial conducted to determine the efficacy of treating hyperkalaemia defined as a serum $K^+ \geq 5.1$ mmol/l.

Patients:
258 patients of whom 70% were receiving RAASi medication.
Approximately 46% of patients had a baseline serum $K^+$ level < 5.5 mmol/l.

Intervention:
The study was designed in two phases:
Phase 1: an open-label phase over the first 2 days; all patients received SZC 10g three times daily.
Phase 2: randomised phase extending to 28 days

Results:
The primary end-point was the absolute and percentage change in serum $K^+$ from baseline at 24 and 48 hrs.
Normokalaemia (serum $K^+$ 3.5 – 5.0 mmol/l) was achieved in 84% of patients by 24 hrs and 98% by 48 hrs.
The mean reduction in serum $K^+$ from baseline was 1.1 mmol/l at 48 hrs.
In patients with a baseline $K^+$ > 6.0 mmol/l, the mean reduction of serum $K^+$ was 1.5 mmol/l at 48 hrs.
Patients achieving normokalaemia were entered into the randomised phase of the study to receive SZC 5g (n=45), 10g (n=51), 15g (n=56) and placebo (n=85). There was a dose-dependent reduction in serum $K^+$ (Table 9).

Limitations: The definition of hyperkalaemia ($K^+ > 5.1$ mmol/l) was below the conventional treatment threshold.

<table>
<thead>
<tr>
<th>ZS-004 (Kosiborod, 2014)$^6$</th>
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<tbody>
<tr>
<td>The HARMONIZE study was a Phase III multi-centre, double-blind placebo controlled trial conducted to determine the efficacy of treating hyperkalaemia defined as a serum $K^+ \geq 5.1$ mmol/l.</td>
</tr>
<tr>
<td>Patients: 258 patients of whom 70% were receiving RAASi medication. Approximately 46% of patients had a baseline serum $K^+$ level &lt; 5.5 mmol/l.</td>
</tr>
<tr>
<td>Intervention: The study was designed in two phases: Phase 1: an open-label phase over the first 2 days; all patients received SZC 10g three times daily. Phase 2: randomised phase extending to 28 days</td>
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<tr>
<td>Results: The primary end-point was the absolute and percentage change in serum $K^+$ from baseline at 24 and 48 hrs. Normokalaemia (serum $K^+$ 3.5 – 5.0 mmol/l) was achieved in 84% of patients by 24 hrs and 98% by 48 hrs. The mean reduction in serum $K^+$ from baseline was 1.1 mmol/l at 48 hrs. In patients with a baseline $K^+$ &gt; 6.0 mmol/l, the mean reduction of serum $K^+$ was 1.5 mmol/l at 48 hrs. Patients achieving normokalaemia were entered into the randomised phase of the study to receive SZC 5g (n=45), 10g (n=51), 15g (n=56) and placebo (n=85). There was a dose-dependent reduction in serum $K^+$ (Table 9).</td>
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<td>Limitations: The definition of hyperkalaemia ($K^+ &gt; 5.1$ mmol/l) was below the conventional treatment threshold.</td>
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</tbody>
</table>
ZS-004E (Product Information sheet)

This was an 11-month extension study of HARMONIZE and included patients who had completed the maintenance period with a serum K⁺ between 3.5-6.2 mmol/l or who had discontinued treatment prematurely due to hypokalaemia or persistent hyperkalaemia.

Patients:
123 patients included with no changes to RAASi therapy required.
Mean serum K⁺ was 4.66 mmol/l (range 3.5 – 6.2 mmol/l).

Intervention:
Patients with a serum K⁺ of 3.5-5.5 mmol/l at the end of HARMONIZE directly entered the maintenance phase of ZS-004E and received SZC 10g once daily.
Patients with a serum K⁺ > 5.5 mmol/l received 10g three times daily for 24-48 hours before entering the maintenance phase. The dose of SZC was adjusted up or down guided by the serum K⁺ level.

Results:
At the end of 11 months, the mean serum K⁺ was 4.7 mmol/l.
93% of patients had a mean serum K⁺ between 3.5 - 5.5 mmol/l.
77% of patients had a mean serum K⁺ between 3.5 - 5.1 mmol/l.
ZS-005 (Spinowitz, 2019)²
This was a Phase III open-label single-arm trial to determine the longterm efficacy of SZC in treating patients with hyperkalaemia for up to 12 months.

Patients:
751 patients with a serum K⁺ ≥ 5.1 mmol/l with no changes in RAASi therapy required.

Intervention:
There were two phases of the study:
Acute Phase: patients received SZC 10g three times daily for 24-72 hours depending on serum K⁺ levels. Baseline serum K⁺ levels were < 5.5 mmol/l in 38% of patients, 5.5-5.9 mmol/l in 45% of patients and ≥ 6.0 mmol/l in 17% of patients. Five patients (1%) did not complete the acute phase.

Maintenance Phase: patients who achieved a serum K⁺ level between 3.5 – 5.0 mmol/l at the end of the acute phase (n=746) were included and treated with SZC 5mg daily for 12 months. The dose was titrated up to 10g or 15g once daily or titrated down to 5g alternate days guided by the serum K⁺ level. Patients with diabetes more frequently required 10g daily. Approximately 10% of patients required 15g daily.

Results:
Acute Phase: The primary end-point was the restoration of normal serum K⁺ level (3.5 – 5.0 mmol/l). Normokalaemia was achieved in:
- 66% of patients within 24 hrs
- 75% of patients within 48 hrs
- 78% of patients within 72 hrs
Approximately 92% of patients achieved a serum K⁺ level between 3.5-5.5 mmol/l at 24 hrs and 99% by 72 hrs.

Maintenance Phase: The primary end-point was sustaining normokalaemia (K⁺ 3.5 - 5.0 mmol/l) from 3 to 12 months which was achieved in 88% of patients irrespective of diabetes status (diabetic - 88.3%, non-diabetic 88.5%).
A secondary end-point was the mean serum K⁺ level in months 3-12 (4.7mmol/l), 6-9 (4.7 mmol/l) and 9-12 (4.6 mmol/l).
Approximately 64% of patients were taking RAASI at baseline and the majority continued on the same dose.
In the patients already established on RAASi therapy, 13% increased their dose, 14% decreased their dose and 11% discontinued RAASi use.
Of the patients not receiving RAASi at baseline, 14% were initiated on RAASi therapy.
Limitation: Approximately 38% of patients did not complete the maintenance phase of the study. The most common reasons for termination were withdrawal of consent (11%), adverse event (7%), and need for RRT or other treatment (5%).
<table>
<thead>
<tr>
<th>STUDY</th>
<th>Study Design</th>
<th>N =</th>
<th>Study duration</th>
<th>Dose of SZC (x3/day)</th>
<th>Renal function eGFR (ml/min)</th>
<th>Mean Baseline K⁺ (mmol/l)</th>
<th>K⁺ Change (mmol/l)</th>
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<tbody>
<tr>
<td>ZS-002[^4] Ash 2015</td>
<td>Phase II RCT</td>
<td>90</td>
<td>48 hrs</td>
<td>Placebo 0.3g 3g 10g</td>
<td>58.1 ± 26.5 56.5 ± 24.0 57.1 ±22.1</td>
<td>5.1 ± 0.4 5.2 ± 0.3 5.0 ± 0.3 5.1 ± 0.4</td>
<td>- 0.26 ± 0.4 - 0.39 ± 0.4 - 0.42 ± 0.4 - 0.92 ± 0.5</td>
</tr>
<tr>
<td>ZS-003[^5] Packman 2015</td>
<td>Phase III RCT</td>
<td>753</td>
<td>Stage 1 48 hrs</td>
<td>Induction (randomised) Placebo 1.25g 2.5g 5g 10g</td>
<td>5.3 5.4 5.3 5.3</td>
<td>- 0.25 (0.19-0.32) 0.30 - 0.46 (0.39-0.53) - 0.54 (0.47-0.62) - 0.73 (0.65-0.82)</td>
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<td>Stage 2 Days 3-14</td>
<td>Maintenance (randomised) Placebo SZC 5g Placebo SZC 10g</td>
<td>3.5 – 4.9</td>
<td>+ 0.47%/ hr + 0.09%/ hr + 1.04%/ hr + 0.14%/ hr</td>
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<tr>
<td>ZS-004[^6] HARMONIZE Kosiborod 2014</td>
<td>Phase III RCT</td>
<td>258</td>
<td>Stage 1 48 hrs</td>
<td>Induction (open label) 10g</td>
<td>46.3 ± 30.5 5.6 ± 0.4</td>
<td>- 1.1 (1.0-1.1)</td>
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<td>Stage 2 28 days</td>
<td>Maintenance (randomised) Placebo 5g 10g 15g</td>
<td>48.0 ± 28.8 48.0 ± 30.7 44.7 ± 30.7 44.9 ± 29.5</td>
<td>4.6 ± 0.4 4.5 ± 0.4 4.4 ± 0.4 4.5 ± 0.4</td>
<td>- 0.4 (0.3-0.6) - 0.8 (0.6-0.9) - 1.1 (0.9-1.3) - 1.2 (1.0-1.4)</td>
</tr>
<tr>
<td>ZS-004E[^1]</td>
<td>Extension of ZS-004</td>
<td>123</td>
<td>11 mths</td>
<td>Maintenance (open label) 10g once daily</td>
<td>46.3 ± 30.5 4.6</td>
<td>88% of patients achieved K &lt; 5.1 mmol/l</td>
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<tr>
<td>STUDY</td>
<td>Study Design</td>
<td>N =</td>
<td>Study duration</td>
<td>Dose of SZC (x3/day)</td>
<td>Renal function eGFR (ml/min)</td>
<td>Mean Baseline K⁺ (mmol/l)</td>
<td>K⁺ Change (mmol/l)</td>
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<tr>
<td>ZS-005 Spinowitz 2019</td>
<td>Phase III Open-label Prospective (single arm)</td>
<td>751</td>
<td>24-72 hrs</td>
<td>Acute Phase 10g</td>
<td>&lt; 60: 73.5% ≥ 60: 25.3%</td>
<td>5.6</td>
<td>- 0.8</td>
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<td>Extended Phase 5g once daily titrated to 10 or 15g/day OR 5g alt days</td>
<td></td>
<td>5.6</td>
<td>- 1.0</td>
</tr>
</tbody>
</table>

Table 9: Studies of the efficacy of SZC in treatment of Hyperkalaemia

SZC – Sodium zirconium cyclosilicate; hrs – hours; mths - months

The studies summarised above in Table 9 were designed to determine the efficacy of SZC in controlling hyperkalaemia over a 48-hr induction phase, followed by sustained control during a maintenance phase of variable duration – 14 days (ZS-003), 28 days (ZS-004) and 52 weeks (ZS-005). The proportion of patients with CKD, diabetes, heart failure and taking RAASi drugs were similar in these studies (see Appendix 3).

A comprehensive meta-analysis of the key studies, ZS-004 and ZS-005, was not feasible due to the heterogeneity of the studies – different duration of acute phase (48hrs vs 72hrs) and maintenance phase (28 days vs 52 weeks). Dose titration was permitted in ZS-005, but a fixed regimen was used in ZS-004. ZS-005 also lacked a control arm. Both studies achieved normalisation of serum K⁺ within 24 hours in 66% of patients.

Approval for SZC was delayed given concerns about the manufacturing processes, but was granted in the EU in March 2018, followed by the FDA in May 2018. Although the marketing authorisation states SZC may be used for the ‘treatment of hyperkalaemia in adults’, the submission to NICE was limited to patients with CKD and/ or heart failure. NICE has assessed the clinical and cost effectiveness of SZC based on the ZS-004 and ZS-005 clinical trials.

A few short-falls have been identified in the SZC trials:

- The definition of hyperkalaemia used (K⁺ ≥ 5.1 mmol/l) was lower than Renal Association and European Resuscitation Council guidelines (K⁺ ≥ 5.5 mmol/l).
- Most clinicians would not institute drug treatment for hyperkalaemia in patients with a serum K⁺ < 6.0 mmol/l.
- The clinical trials did not impose dietary K⁺ restriction and did not compare the efficacy of SZC versus dietary restriction.
- There was no comparison with any other active K⁺-lowering drug.
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1. ZS-005 measured changes to RAASi use, but the single-arm study design provided no comparison with standard care to determine if SZC allowed more patients to be treated with RAASi.

2. The evidence for reduced hospitalisation and mortality in relation to serum K⁺ levels was based on observational data and surrogate markers.

3. There is no evidence that SZC improves quality of life or extends life.

4. SZC provides a potential option for treating persistent hyperkalaemia in the community. It has a rapid rate of onset of action within 1 hour and the median time to normalisation of serum K⁺ was 2.2 hours. SZC lowers serum K⁺ by 1.1 mmol/l within 48 hours. The ZS-003 and ZS-004 clinical trials also demonstrated a greater K⁺-lowering effect with increasing severity of hyperkalaemia. In patients with a serum K⁺ > 6.0 mmol/l, SZC lowers serum K⁺ by 1.5 mmol/l within 48 hours.

5. NIC has approved SZC in the treatment of persistent hyperkalaemia in the out-patient setting under these circumstances:
   - Patients with CKD Stage 3b-5 OR Heart Failure
   - Serum K⁺ confirmed to be ≥ 6.0 mmol/l
   - Patient is receiving a sub-optimal dose of RAASi due to hyperkalaemia
   - Not on dialysis

Stop SZC if RAASi therapy is discontinued.

6. NICE has approved SZC in the treatment of persistent hyperkalaemia in out-patients with CKD Stage 3b-5 or heart failure, if serum K⁺ is confirmed to be ≥ 6.0 mmol/l in patients receiving a sub-optimal dose of RAASi who are not on dialysis. Stop SZC if RAASi therapy is discontinued. Given the strong evidence for use of RAASi drugs in patients with CKD and heart failure, the cost-effectiveness analysis suggests that the use of SZC in facilitating patients staying on RAASi drugs is a good use of NHS resources.

7. Safety and efficacy has been shown up to 52 weeks of therapy, but the duration of treatment in clinical practice will likely be lifelong unless RAASi is discontinued. SZC will complement, rather than replace, a low-K⁺ diet. SZC may allow less strict dietary restrictions, thereby improving quality of life for patients.

8. Prescription of SZC has been restricted to initiation in secondary care. The aim is to achieve the minimum effective dose of SZC to prevent recurrence of hyperkalaemia. The recommended starting dose is 5g once daily, with up-titration to a maximum dose of 10g once daily or down-titration to 5g alternate days if required (Appendix 4E). Dose titration or cessation will be led by secondary care. In real-world practice, blood monitoring will shared with primary care, therefore clear guidance or protocols will be necessary. Based on the ZS-005 trial conducted over 12 months, blood monitoring should be performed weekly for the first month, then monthly thereafter. Serum K⁺ should also be assessed one week after drug cessation.
Dialysis patients were excluded from the original studies, but evidence has been recently reported. DIALIZE 1 is a Phase 3b RCT (NCT03303521) designed to evaluate SZC in controlling hyperkalaemia in haemodialysis (HD) patients. This is the first randomised, double-blind, placebo controlled trial to assess a potassium binder in HD patients. The study included 196 patients with a serum K⁺ > 5.4 mmol/l after the long interdialytic period (i.e. weekend break). SZC was titrated from a starting dose of 5g to a maximum dose of 15g on non-dialysis days over the first 4 weeks until a stable dose was reached. The primary end-point was the proportion of patients who maintained pre-dialysis serum K⁺ of 4.0 – 5.0 mmol/l during at least 3 long interdialytic periods over the 4-week evaluation period that followed dose titration. The investigators reported a significantly greater proportion of patients treated with SZC (n=97) versus placebo (n=99) met the primary end-point (41.2% vs 1.0%). Rescue therapy for hyperkalaemia was required for 2.1% of patients taking SZC vs 5.1% taking placebo during the treatment period. The safety profile observed was similar in both arms and comparable to previous clinical trials.

The role for SZC in the treatment of hyperkalaemia is likely to evolve as clinical experience is gained and as further evidence becomes available.

References

Hyperkalaemia in the Community (Guidelines 11.1 – 11.3) Prevention (Guidelines 11.1 – 11.3)

Guideline 11.1 – Prevention of Hyperkalaemia in the community: monitoring

We recommend monitoring of renal function in patients at risk of hyperkalaemia with known CKD, heart failure, diabetes and in any patient taking RAASi medication. (1A)

Guideline 11.2 – Prevention of Hyperkalaemia in the community: prescribing

We recommend caution in prescribing trimethoprim to patients with renal impairment or those taking RAASi drugs. (1A)

Guideline 11.3 – Prevention of Hyperkalaemia in the community: sick day rules

We recommend that healthcare professionals provide advice to patients regarding the risks of AKI and hyperkalaemia during acute illness and measures to avoid these complications. (1B)

Audit measures

1. The number of patients treated with trimethoprim who develop moderate-severe hyperkalaemia (serum K+ ≥ 6.0 mmol/l) in hospital or community setting.
2. Proportion of patients with severe hyperkalaemia (Serum K+ ≥ 6.5 mmol/l) on admission to hospital who had been provided with ‘Sick Day Rules’ advice compared with those who had not received this advice.

Rationale (Guideline 11.1 - 11.3)

Hyperkalaemia is an anticipated complication in patients with a history of CKD, heart failure or diabetes mellitus. Patients requiring RAASi drugs for other indications, e.g. spironolactone for decompensated liver disease, also require surveillance for hyperkalaemia. Blood monitoring is discussed in Guidelines 1.1-1.2. Good communication between primary and secondary care regarding monitoring and drug titration is essential.

Drug prescribing in the community and out-patient setting is a major factor for the development of hyperkalaemia. The elderly are very susceptible to hyperkalaemia and polypharmacy is a common problem. Increased awareness of drugs that can cause hyperkalaemia and monitoring patients at risk may reduce morbidity, hospital admissions and mortality.

Drugs commonly implicated in hyperkalaemia are shown below in Table 10.
Table 10: Drugs implicated in development of hyperkalaemia and exacerbating factors.

<table>
<thead>
<tr>
<th>RAASi (ACE Inhibitors, Angiotensin II receptor blockers, Mineralocorticoid receptor antagonists)</th>
<th>RISK OF HYPERKALMAEMIA INCREASED IN:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium supplements</td>
<td>Renal Impairment</td>
</tr>
<tr>
<td>Potassium-sparing diuretics</td>
<td>Diabetes Mellitus</td>
</tr>
<tr>
<td>Trimethoprim/ Cotrimoxazole</td>
<td>Elderly</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Use of &gt; 1 RAASi drug</td>
</tr>
<tr>
<td>Non-selective beta-blockers</td>
<td>Combining any of these groups of drugs</td>
</tr>
</tbody>
</table>

NICE Clinical Guideline on ‘CKD in adults: assessment and management’ states that RAASi should not be routinely started in patients with a serum K⁺ level ≥ 5.0 mmol/l and should be discontinued if serum K⁺ is ≥ 6.0 mmol/l.¹ The NICE Clinical Guideline on ‘Chronic Heart Failure in adults: assessment and management’ states that serum K⁺ should be monitored before and after starting a RAASi or changing the dose, but does not specify the K⁺ level at which RAASi should be avoided or discontinued.² Given the potential benefits to RAASi therapy in patients with CKD and heart failure, NICE has recently approved the use of SZC to facilitate continuing RAASi therapy in selected patients.³

The Medicines and Healthcare products Regulatory Agency (MHRA) issued a safety alert, initially in June 2014, regarding the concomitant use of ACEi or ARB with MRAs (i.e. spironolactone or eplerenone) given the increased risk of severe hyperkalaemia particularly in patients with advanced renal impairment.⁴ The MHRA recommend caution in co-prescription of these drugs with regular monitoring of serum biochemistry and discontinuation if hyperkalaemia develops.

Trimethoprim is a first-line antibiotic, most commonly prescribed for simple urinary tract infections. It can be prescribed alone or in combination with sulfamethoxazole (co-trimoxazole). The mechanism by which trimethoprim causes hyperkalaemia is by reducing renal K⁺ excretion through competitive inhibition of epithelial sodium channels in the distal nephron.⁵ An increase in serum K⁺ level of 0.36 – 1.21 mmol/l or higher can occur within 3-10 days of treatment.⁶ Treatment with RAASi or NSAIDs exacerbates hyperkalaemia.⁵

There have been multiple reports confirming the risk of hyperkalaemia and AKI in patients treated with trimethoprim.⁷⁹ Antoniou et al reported a 7-fold increased risk of hospital admission for hyperkalaemia in elderly patients (age ≥ 66 years) taking trimethoprim- sulfamethoxazole compared with other antibiotics for urinary tract infection.⁷ In a large UK cohort study (n=1,191, 905) of older adults (age ≥ 65 years), Crellin et al demonstrated an increased risk of developing hyperkalaemia (OR 2.27) and AKI (OR 1.72) within 14 days of trimethoprim prescription compared with amoxicillin.⁸ The risk of hyperkalaemia has been shown in patients receiving high-dose¹⁰,¹¹ and low-dose⁹ trimethoprim.
Nutritional intake is another important factor in preventing hyperkalaemia, particularly in patients with CKD. In patients with advanced CKD, the ability to adapt to an increased potassium intake diminishes and becomes almost negligible in ESRD, making these patients very susceptible to hyperkalaemia. A low-K⁺ diet is usually instituted when the serum K⁺ is consistently ≥ 5.5 mmol/l. Dietary modification in CKD has been discussed in Guideline 5.1.

The bowel compensates for the reduction in renal K⁺ loss as renal function declines. The capacity for the bowel to secrete K⁺ is inversely related to residual renal function and becomes the main route of K⁺ excretion in patients with ESRD. Therefore, constipation can cause hyperkalaemia and conversely, diarrhoea can cause hypokalaemia in patients with renal impairment.

The ‘Sick day rules’ provides information to patients taking drugs known to cause AKI and hyperkalaemia (e.g. RAASI, NSAIDs) advising temporary discontinuation of these medications during acute illness, particularly in the context of volume depletion (e.g. diarrhoea and/or vomiting, fevers/ rigors). The use of this strategy is controversial. The NICE ‘Clinical Guideline on AKI’ advocates use of sick day guidance. On the other hand, ‘Think Kidneys’ urges caution as the evidence-base for this guidance is weak, discontinuation of cardio-protective medication could exacerbate underlying condition and patients may not restart medication on recovery or achieve previous dosage. The ‘Think Kidneys’ Programme Board recommends that it is reasonable to provide sick day guidance to patients at high risk of AKI based on an individual risk assessment, but a more systematic roll-out of the ‘Sick day rules’ should be undertaken in the context of a formal evaluation.

In clinical practice, many patients admitted to hospital with an AKI at initial presentation are receiving one or more drugs that can exacerbate hyperkalaemia. It is standard practice to withhold these until renal recovery. The Sick Day rules moves the timeline to discontinuation earlier in patients at risk of AKI and if applied appropriately, may reduce the risk of severe hyperkalaemia during acute illness.

References


Hyperkalaemia in the Community (Guideline 12.1) **Treatment algorithm: Community (Guideline 12.1)**

**Guideline 12.1 – Treatment Algorithm for Hyperkalaemia in the community**

We recommend that the treatment of hyperkalaemia in patients in the community and out-patient setting is guided by its severity and clinical condition of the patient as summarised in the treatment algorithm. (1A)

**Rationale (Guideline 12.1)**

Hyperkalaemia is commonly detected in the community and the approach to monitoring and treatment is variable. An algorithm has been designed to assist clinicians in the out-patient and primary care settings as shown in Appendix 6.

Patients with a serum K⁺ < 5.5 mmol/l do not require any specific treatment. Patients with mild hyperkalaemia (K⁺ 5.5 – 5.9 mmol/l) warrant a review of medication (RAASi, potassium supplements, trimethoprim, NSAIDs, non-selective beta-blockers) and dietary intake. Treatment of metabolic acidosis (serum bicarbonate < 22 mmol/l) and initiation of diuretics may be helpful in chronic hyperkalaemia.

Patients with moderate hyperkalaemia (K⁺ 6.0 – 6.4 mmol/l) who are not acutely unwell require similar considerations – medication review, treatment of metabolic acidosis and a low K⁺ diet. However, some patients may be candidates for SZC if they meet the NICE criteria as discussed in Guideline 10.1-10.3 and illustrated in the treatment algorithm.

Patients with moderate hyperkalaemia who are acutely unwell and those with severe hyperkalaemia (K⁺ ≥ 6.5 mmol/l) warrant hospital admission for emergency treatment. RAASi drugs should be withheld until recovery.

Blood monitoring is essential after a hyperkalaemic event and the urgency is guided by the severity. Recommended intervals for blood monitoring are discussed in Guideline 1.1-1.2. Recurrence of hyperkalaemia is common, particularly in patients with CKD, therefore it is important to consider preventative measures.
Section 2

Management of Hyperkalaemia in Hospital
Hyperkalaemia in Hospital

Introduction

Hyperkalaemia is a potentially life-threatening medical emergency. The incidence in hospitalised patients ranges from 1 – 10%. It has relevance to all clinicians and is encountered in a variety of clinical settings. Despite this, there is limited evidence to guide treatment. This may account for the observed variability in the treatment of patients with hyperkalaemia, even within the same hospital. Therefore, guidance on the treatment of hyperkalaemia based on the current evidence is needed.

The most serious consequences of hyperkalaemia are arrhythmias and cardiac arrest. The risk of these events increases with K⁺ level ≥ 6.5 mmol/L and even small elevations in K⁺ above this concentration can lead to rapid progression from peaked T waves to ventricular fibrillation or asystole. The longer a patient has a high K⁺ level, the greater the risk of sudden deterioration. Urgent treatment can avoid life-threatening complications.

The threshold for emergency treatment varies, but most guidelines recommend that emergency treatment should be given if the serum K⁺ is ≥ 6.5 mmol/L with or without ECG changes. It is also accepted that emergency treatment should be initiated before serum biochemistry is known if hyperkalaemia is suspected on clinical grounds or in the presence of ECG changes.

The evidence base for drug treatment in hospitalised patients is limited. Indeed, the Cochrane review for treatment of acute hyperkalaemia in adults included only 7 studies. Intravenous calcium salts (gluconate and chloride) are life-saving, but there are no clinical trials to prove efficacy. Insulin-glucose infusion is the most effective treatment to lower serum K⁺, but the conventional treatment regimen is based on small historical studies mostly in dialysis patients. Beta-agonists appear to be effective in lowering serum K⁺, but some patients are unresponsive. Sodium bicarbonate was frequently used in clinical practice, but there is little favourable evidence of its efficacy in treating acute hyperkalaemia.

Over the past 5 years, there has been some progress in the treatment of hyperkalaemia relating to management in hospitalised patients. Several retrospective studies have been conducted to investigate the incidence and causes of iatrogenic hypoglycaemia following insulin-glucose administration. Other studies have compared conventional versus low dose insulin regimens. The use of variable dosing regimens of insulin and glucose in these reports is a confounding factor. Ultimately, iatrogenic hypoglycaemia appears to be multifactorial with a low pre-treatment blood glucose being a consistent risk factor. Another important development is a novel potassium binder, sodium zirconium cyclosilicate (SZC), which has was recently approved by NICE for the treatment of life-threatening hyperkalaemia although its efficacy in the acute setting has not yet been reported.

The management of acute hyperkalaemia in hospital requires a systematic and consistent approach. This section of the guideline reviews clinical assessment, ECG and laboratory tests, the 5-step approach to treatment, timely specialist referral, escalation of care and prevention in hospitalised patients. This is applicable to patients in the Emergency Department and all ward areas.
References

Guideline 13.1 – Hyperkalaemia: Clinical Assessment; ABCDE and Early Warning Scoring (EWS) Systems.
We recommend that all patients with known or suspected hyperkalaemia undergo urgent clinical assessment using an early warning scoring system. (1C)

Audit measures
1. Length of hospital stay of patients admitted with hyperkalaemia.
2. In-hospital mortality of patients admitted with hyperkalaemia.

Rationale (Guideline 13.1)
The most significant consequences of hyperkalaemia are arrhythmias and cardiac arrest, therefore early recognition, cardiac monitoring and prompt treatment are essential. Early identification of hyperkalaemia, with or without adverse clinical signs, enables specific interventions, specialist referral (if required) and appropriate escalation of care.

The ABCDE approach, shown in Table 12, is an established method for rapid systematic assessment of the acutely ill patient and allows problems, including hyperkalaemia, to be identified and treated promptly.¹

<table>
<thead>
<tr>
<th>ABCDE APPROACH</th>
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<tbody>
<tr>
<td><strong>A – Airway</strong></td>
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<tr>
<td><strong>B – Breathing</strong></td>
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<tr>
<td><strong>C – Circulation</strong></td>
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<tr>
<td><strong>D – Disability</strong></td>
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<tr>
<td><strong>E – Exposure</strong></td>
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Figure 1. National Early Warning score.

The National Early Warning Score (NEWS), as shown in Figure 1, was developed by the Royal College of Physicians. NEWS uses several vital signs to detect abnormalities and identify acute ill patients. Baseline assessment and serial monitoring is essential in identifying patients who are deteriorating and the NEWS can facilitate timely decisions for escalation of care.

These standardised methods of patient assessment and monitoring improve patient safety and facilitates clear communication about acutely unwell patients.

References


**Guideline 13.2 – Hyperkalaemia: Clinical Assessment; History and examination**

We recommend that all patients presenting with hyperkalaemia undergo a comprehensive medical and drug history and clinical examination to determine the cause of hyperkalaemia. (1B)

**Rationale (Guideline 13.2)**

A careful medical history may identify risk factors for hyperkalaemia as shown in Table 12. It is important to elicit any history of pre-existing kidney disease and any factors which may contribute to an acute kidney injury (e.g. diarrhoea & vomiting, infection, medications). Access to electronic patient records and historical biochemical results can help establish baseline renal function. Symptoms are often non-specific and may be overshadowed by the acute illness whilst other patients are asymptomatic. Muscle weakness and/or paraesthesiae may occur in severe cases.

The medication history is an important part of determining the aetiology of hyperkalaemia. Ask about current medication, recent changes and use of over the counter medications.

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**Risk factors for Hyperkalaemia:**

- Acute Kidney Injury
- Dialysis dependency (haemodialysis or peritoneal dialysis)
- Chronic Kidney Disease Stages 4 & 5 (CKD, eGFR < 30 ml/min/1.73m²)
- Nephrotoxic medications (e.g. renin-angiotensin drugs, NSAIDs)
- Cardiac failure (e.g. renin-angiotensin drugs)
- Diabetes mellitus (e.g. renin-angiotensin drugs, diabetic keto-acidosis)
- Liver disease (e.g. spironolactone, hepato-renal failure)
- Adrenal insufficiency

**Table 12: Factors associated with an increased risk of hyperkalaemia.**

Haemodialysis patients have a high risk of hyperkalaemia and the aetiology is complex and multifactorial. Emergency teams may be less familiar with assessment of patients with ESRD. Useful information to obtain in HD patients is summarised in Table 13. Observational studies have shown an increased mortality in dialysis patients due to hyperkalaemia. The most common time for hyperkalaemic events in HD patients is immediately after the 3-day weekend break (i.e. Mondays for patients dialysed on Mon/Wed/Fri or Tuesdays for patients dialysed on Tue/Thu/Sat).
Important Information in Haemodialysis (HD) patients:

- Duration since last dialysis session
- Type of dialysis access - central venous catheter or AV fistula
- Problems with dialysis access - poor blood flow via dialysis access, recent access interventions, recirculation
- Medication
- Dietary intake
- Diabetic status – glycaemic control
- Compliance – poor attendance, shorten treatment time

Table 13: Factors associated with an increased risk of hyperkalaemia in HD patients.

Inform the Renal Team immediately if a dialysis patient presents with hyperkalaemia to the Emergency Department, Admissions Unit or a non-renal ward, as medical interventions will only temporarily control hyperkalaemia.

References

Hyperkalaemia in Hospitalised Patient (Guidelines 14.1 – 14.2) ECG and cardiac monitoring

(Guidelines 14.1 – 14.2)

Guideline 14.1 – Hyperkalaemia: ECG
We recommend that all patients with a serum K⁺ level ≥ 6.0 mmol/L have an urgent 12-lead ECG (electrocardiogram) performed and assessed for changes of hyperkalaemia. (1B)

Audit measures
1. Proportion of patients with a serum K⁺ level ≥ 6.0 mmol/L who had a 12-lead ECG recorded before treatment [Audit Standard 100%].
2. Proportion of patients with a serum K⁺ level ≥ 6.0 mmol/L and an ECG showing features of hyperkalaemia who had their 12-lead ECG repeated following treatment [Audit Standard 100%].

Rationale (Guideline 14.1)
The ECG is used to assess cardiac toxicity and risk of arrhythmias in patients with known or suspected hyperkalaemia and may be the most readily available diagnostic tool. In terms of clinical significance, the type of ECG changes is a more important predictor of outcome than the actual serum K⁺ level.¹ The most commonly recognised ECG sign is peaked T waves, but on its own is rarely a sign of life-threatening hyperkalaemia.² Freeman et al reported peaked T waves at presentation in only 35% of patients with a serum K⁺ > 6.0 mmol/L.³ ECG abnormalities may reflect the rate of rise of serum K⁺.² The typical ECG features of hyperkalaemia are shown in Figure 2.

Figure 2: ECG in a patient with severe hyperkalaemia (serum K⁺ 9.1 mmol/l) illustrating peaked T waves (a), diminished P waves (b) and wide QRS complexes (c).

When the diagnosis of hyperkalaemia can be established based on the ECG, treatment can be initiated even before serum biochemistry is available. However, the reported utility of the ECG is variable. Some reports suggest that 50-64% of patients with a serum K⁺ ≥ 6.5 mmol/L show no ECG changes consistent with hyperkalaemia.⁴⁻⁵ In contrast, Durfee et al analysed the incidence of hyperkalaemic ECG changes by severity: K⁺ 6.5 – 6.9 mmol/l (66%), K⁺ 7.0 – 7.4 mmol/l (70%), K⁺ 7.5 – 7.9 mmol/l (74%), K⁺ 8.0 – 8.4 mmol/l (100%) and K⁺ 8.5 mmol/l (100%).¹ This would suggest that the ECG become more reliable with increasing severity, although there are reports of a normal ECG in extreme hyperkalaemia.⁶
The ECG changes associated with hyperkalaemia are attributable to the physiological effect of a raised serum K⁺ on myocardial cells. The atrial myocardium is more sensitive than the ventricular myocardium to the effects of hyperkalaemia and the specialised tissue (sinoatrial node and bundle of His) is the least sensitive. Hyperkalaemia is associated with depression of conduction between adjacent cardiac myocytes, manifesting in prolongation of the PR interval and QRS duration. The P wave amplitude is diminished in the early stages as T wave amplitude increases. Suppression of sinoatrial function results in bradycardia or standstill. Suppression of atrioventricular (AV) conduction will give rise to varying degrees of AV block.

Traditional teaching suggests that the ECG changes are progressive with worsening severity – peaked T waves, PR interval prolongation, QRS prolongation, loss of P waves, sine wave, VF, PEA or asystole as shown in Figure 3. However, these changes do not always occur sequentially and multiple changes may occur concurrently.

**Figure 3: Progressive changes in ECG with increasing severity of hyperkalaemia.**

The ECG can be used to risk stratify in patients with severe hyperkalaemia. Durfey et al conducted a study of patients (n=188) with severe hyperkalaemia (serum K⁺ ≥ 6.5 mmol/l), examining the ECG performed within 1 hour of K⁺ measurement. Adverse events occurred in 15% of patients within the first 6 hours including symptomatic bradycardia (11.7%), ventricular tachycardia (1.1%), cardiac arrest (1.1%), and death (2.1%). All occurred before IV calcium was administered and all but one occurred before any K⁺-lowering treatment was initiated. All patients with an adverse event had a preceding ECG demonstrating at least one hyperkalaemic abnormality. An et al demonstrated a higher in-hospital mortality in patients with serum K⁺ ≥ 6.5 mmol/l with typical ECG findings of hyperkalaemia compared with those with no ECG changes.

Although the ECG is useful in assessing patients with hyperkalaemia, there are some shortfalls. Firstly, the value of the ECG is dependent on the skill of the interpreter. Physician interpretation of the ECG in hyperkalaemia is variable. Rafique et al reported a mean sensitivity of 0.19 (± 0.16) and specificity 0.97 (± 0.04). This suggests that the ECG can be used to rule in a diagnosis of hyperkalaemia, but not to rule it out. Secondly, the ECG may be normal even in the presence of severe hyperkalaemia. Thirdly, the ECG...
appearance may be atypical with a pseudo-STEMI pattern or Brugada phenocopy. Finally, the first presentation with severe hyperkalaemia may be ventricular fibrillation or asystole. Patients with pacemaker devices are not protected from the cardiac effects of hyperkalaemia. It can affect the function of both temporary and permanent pacemakers, particularly when the serum K⁺ exceeds 7.0 mmol/l. Hyperkalaemia causes three important clinical abnormalities in patients with pacemakers: 

1. widening of the paced QRS complex 
2. increased atrial and ventricular pacing thresholds that may cause failure to capture 
3. increased latency manifested by a greater delay from pacemaker stimulus to onset of depolarization.

References


**Guideline 14.2 – Hyperkalaemia: Cardiac monitoring**

We recommend a minimum of continuous 3-lead ECG monitoring for all patients with a serum $K^+ ≥ 6.5$ mmol/L, patients with features of hyperkalaemia on 12-lead ECG, and in patients with a serum $K^+ 6.0-6.4$ mmol/L who are clinically unwell or in whom a rapid rise in serum $K^+$ is anticipated, ideally in a higher-dependency setting. (1C)

**Audit measure**

1. Proportion of patients with a serum $K^+$ value ≥ 6.5 mmol/L who have documented evidence of continuous ECG monitoring [Audit standard: 100%].

**Rationale (Guideline 14.2)**

Continuous ECG monitoring will enable early recognition and prompt treatment of life-threatening arrhythmias in patients with hyperkalaemia. Hyperkalaemia causes arrhythmias by causing hyperpolarisation of cells, making them less able to depolarise when necessary. Arrhythmias can occur at any time in the patient’s presentation without prior toxic ECG changes. All arrhythmias have been reported in patients with hyperkalaemia, including atrial fibrillation, bradycardia, and ventricular tachycardia. Some typical arrhythmias are shown in Figure 4.

Patients with a presenting ECG suggestive of hyperkalaemia are at a high risk for adverse events, highlighting the need for cardiac monitoring. Durfey et al demonstrated that arrhythmias occurred in 15% of patients within 6 hours of detection of hyperkalaemia before treatment could be initiated. ECG signs most closely correlating with adverse events were QRS prolongation, bradycardia (HR < 50), and/or junctional rhythms. In this study, there was also no statistically significant difference between the frequency of hyperkalaemic ECG changes and adverse events in haemodialysis versus non-dialysis patients.
Bradycardia and/or complete heart block associated with severe hyperkalaemia may be resistant to conventional treatment with atropine and even temporary pacing may be ineffective and induce arrhythmias.\textsuperscript{2,7} Negatively chronotropic drugs (e.g. beta blockers) exacerbate bradycardia in hyperkalaemic patients.\textsuperscript{11} External pacing may be useful whilst treatment for hyperkalaemia is initiated. Although bradycardia is documented to be a potential adverse effect of IV calcium salts, IV calcium can increase the heart rate in patients with hyperkalaemia-induced bradycardia.\textsuperscript{6,12,13}

References


### Hyperkalaemia in Hospitalised Patient (Guidelines Hyperkalaemia 15.1 – 15.3)

#### Laboratory analysis (Guidelines 15.1 – 15.3)

**Guideline 15.1 – Hyperkalaemia: Laboratory tests**

We recommend that a lithium heparin anti-coagulated specimen is the sample type of choice when rapid turnaround of urea and electrolytes results is required. (1B)

**Audit Measure**

1. The average laboratory analysis time for K+ concentration using clotted (serum) and lithium heparin (plasma) samples [Audit standard: within 60 minutes].

**Rationale (Guideline 15.1)**

The treatment of hyperkalaemia requires timely access to accurate serum K+ measurements. Potassium measurement can be undertaken in the laboratory or at the point of care using a variety of techniques. Laboratory measurements of K+ focus on those in blood plasma or serum. This provides an advantage over whole blood measurements from blood gas analysers because haemolysis can be identified by visual inspection after centrifugation or by spectrophotometric analysis of the specimen for the presence of haemoglobin.

The impact of in-vitro haemolysis of blood samples is a variable increase in K+ concentrations leading to misclassification of normokalaemic patients as hyperkalaemic, and hypokalaemic patients as normokalaemic.¹ The use of hospital pneumatic tube systems for delivering samples to the central laboratory reduces result turnaround time, but may contribute to a degree of haemolysis due to the impact of speed, air pressure and vibration in transit.² Automated assessment of haemolysis using the haemolysis index has standardised the process for identification of haemolysed samples.³

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**Send Lithium Heparin tube for urgent analysis of K+ level.**
The choice of specimen sent to the laboratory will depend on the tests requested and the urgency. Routine samples for measurement of urea and electrolytes are usually requested in a clotted serum sample. In emergencies where hyperkalaemia is suspected, specimens collected in a lithium heparin tube can be analysed more rapidly as there is no requirement to wait for the sample to clot before centrifugation. Laboratories may differ in their requirements for other tests and different reference intervals may also apply.

References


Guideline 15.2 – Hyperkalaemia: Blood gas analysis

We recommend that in emergencies, K⁺ level is measured from an arterial or venous blood sample using a point-of-care blood gas analyser whilst awaiting the results from a formal laboratory measurement. (1B)

Rationale (Guideline 15.2)

Blood gas analysers (BGA) are increasingly available at the point-of-care with analytical repertoires that include electrolyte measurements. This method provides rapid results, can shorten time to clinical intervention and reduce cost.¹ Despite these advantages, there is frequently doubt about the validity of point-of-care methods compared with central laboratory tests. Haemolysis is an important confounding factor in the measurement of K⁺, especially when using whole blood specimens via BGA. A greater concordance has been reported between BGA and the laboratory results when the K⁺ concentration is greater than 3 mmol/L.² A larger blood sample (i.e. more than 1mL) can reduce the extent of haemolysis and improve accuracy.³

BGA potassium measurement has been compared with central laboratory venous analysis in many clinical settings with variable recommendations.

1. During cardiac arrest, blood analysis is time-sensitive and rapid correction of an electrolyte disorder could help achieve return of spontaneous circulation. One study in cardiac arrest reported that the limits of agreement between ABG analysis and the central laboratory was wide and recommended caution.⁴ However, other studies have demonstrated that ABG analysis enhances resuscitation.⁵-⁷ Ahn et al reported that all cases of life-threatening hyperkalaemia was detected using ABG analysis with a sensitivity of 85% and specificity of 97%.⁵
2. In the ICU, several studies have demonstrated good agreement between $K^+$ values measured using BGA analyser and the central laboratory allowing timely clinical decisions in critically ill patients.\(^1\)\(^8\)\(^\text{10}\)

3. In the emergency department (ED), early identification of electrolyte disturbances has the potential benefits of ensuring prompt treatment, appropriate triage, safe patient transfer and appropriate ward placement. Several studies have validated the use of BGA analyser in measuring serum $K^+$ in the ED.\(^1\)\(^1\)\(^-\)\(^1\)\(^5\) Point of care testing in the ED can also reduce length of stay and improve patient flow.\(^1\)\(^5\)

**Use a point of care blood gas analyser to provide rapid and reliable $K^+$ level when an urgent result is required.**

**Send a formal laboratory sample, but initiate treatment if indicated based on BGA result.**

Local laboratory medicine specialists should ensure that all methods used for measurement of potassium are fit for purpose and that the methods are appropriately quality controlled and quality assessed. Point of care testing systems and processes, used for the measurement of potassium, should follow best practice as identified by the MHRA (Medicines and Healthcare Regulatory Agency, 2010).\(^1\)\(^6\) Local risk assessments of the relative value and safety of point of care versus laboratory delivery of potassium measurements should form part of the development process.

**References**


Guideline 15.3 – Hyperkalaemia: Pseudo-hyperkalaemia

We recommend that urea and electrolytes are measured using paired lithium heparin and clotted serum samples from a large vein using gentle traction with prompt laboratory analysis if pseudo-hyperkalaemia is suspected. (1A)

Rationale (Guideline 15.3)

Ideally, the laboratory measurement will reflect the $K^+$ concentration in the extra-cellular fluid in vivo. Pseudo-hyperkalaemia, first reported in 1955, describes the finding of a raised serum (clotted blood) $K^+$ value concurrently with a normal plasma (non-clotted blood) $K^+$ value.\(^1\) The clotting process releases $K^+$ from cells and platelets increasing the serum $K^+$ concentration by an average of 0.4 mmol/L.

Pseudo-hyperkalaemia can be excluded by performing simultaneous measurements of plasma $K^+$ in a lithium heparin anti-coagulated specimen and in a clotted sampled.\(^2\) Pseudo-hyperkalaemia is detected when the serum $K^+$ level exceeds that of the plasma by more than 0.4 mmol/L. Consider pseudo-hyperkalaemia in the context of normal renal function, normal ECG and in patients with haematological disorders.\(^3\)

If pseudo-hyperkalaemia is suspected, send paired blood samples in a clotted tube (serum) and a lithium heparin tube (plasma).

Send FBC to exclude a haematological disorder.

Pseudo-hyperkalaemia is present if:

$$[\text{Serum } K^+] - [\text{Plasma } K^+] > 0.4 \text{ mmol/L}$$
The most common cause of pseudo-hyperkalaemia is a prolonged transit time to the laboratory or poor storage conditions. Other causes of pseudo-hyperkalaemia include difficult venepuncture, a high platelet count, haemolysis, erythrocytosis, prolonged storage time of clotted samples, or cold storage conditions. When using evacuated tubes for blood collection, if the order of draw is wrong, the sample can be contaminated with potassium EDTA (for full blood count). Another common cause of contamination is sampling from the arm into which potassium-containing fluids are being infused. An inverse relationship between ambient temperature and potassium concentration has been reported with higher K⁺ values in the winter months and has been termed ‘seasonal’ pseudo-hyperkalaemia.

Laboratories have developed standard protocols to reduce the risks of pseudo-hyperkalaemia and pseudo-normokalaemia. Labelling the time of collection on specimens, reducing transit times, and optimising storage conditions (i.e. avoiding wide fluctuations in temperature) for specimens from primary care are important strategies. These measures may in turn reduce out-of-hours calls to deputising services and admissions to acute medicine units for the investigation of hyperkalaemia.

The importance of recognition of pseudo-hyperkalaemia is the avoidance of unnecessary treatment which could cause harm.

References

Hyperkalaemia in Hospitalised Patient (Guidelines Hyperkalaemia 16.1 – 16.6) Treatment (Guidelines 16.1 – 16.6)

Guideline 16.1 – Hyperkalaemia: Summary of treatment strategy

We recommend that the treatment of hyperkalaemia in hospital follow a logical 5-step approach. (1B)

Rationale (Guideline 16.1)

The treatment of hyperkalaemia currently varies considerably. A systematic approach, as shown in Figure 5, takes into account clinical priorities, may reduce variability, enhance patient outcome and reduce adverse events related to hyperkalaemia and its treatment.¹

Figure 5: There are five key steps in the treatment of hyperkalaemia (never walk away without completing all of these steps).

This process begins with an assessment of the risk of arrhythmias, followed by action to reduce the serum K⁺ concentration by shifting K⁺ back into cells and removing it from the body. Treatment efficacy is assessed by monitoring the serum K⁺. Hypoglycaemia is a serious adverse effect of insulin-glucose, therefore frequent blood glucose monitoring is essential. Treatment is not complete until the cause is identified and steps taken to prevent recurrence. The hyperkalaemia treatment algorithm for hospitalised patients outlines this sequential approach [Guideline 21.1]. Drug therapies with mechanism of action and interventions for treating hyperkalaemia are shown in Table 14.
The use of drugs to shift $K^+$ from the extra- to intracellular space reduces serum $K^+$ without reducing the total body $K^+$. This transcellular shift is thought to reduce the amount of $K^+$ available in the serum to be removed during haemodialysis (HD). Driver et al conducted a retrospective study ($n=479$) in patients presenting to the Emergency Department with hyperkalaemia who subsequently underwent HD. Shifting medication was administered in 50% of patients. Recurrent hyperkalaemia within 24 hours occurred in 27% of patients who received shifting drugs versus 18% in those who did not. Repeat haemodialysis within 24 hours was required in 30% of patients who received shifting drugs and 25% in those who did not. The authors concluded that transcellular potassium shifting before emergent dialysis is not associated with recurrent hyperkalaemia or need for multiple haemodialysis sessions, however it is noteworthy that the median time from drug administration to start of HD was 4.2 hours (2.5-8.4 hours) and the effect of drugs may have worn off.

<table>
<thead>
<tr>
<th>Guideline 16.2 – Hyperkalaemia: STEP 1 - Protect the heart; intravenous calcium salts</th>
</tr>
</thead>
<tbody>
<tr>
<td>We recommend that intravenous calcium chloride or calcium gluconate, at an equivalent dose (6.8mmol), is given to patients with hyperkalaemia in the presence of ECG evidence of hyperkalaemia. (1A)</td>
</tr>
</tbody>
</table>

Audit Measures
1. The frequency of ECG changes in patients treated with intravenous calcium salts.
2. Adverse events as a result of treatment with intravenous calcium salts.

Rationale (Guideline 16.2)

The use of intravenous (IV) calcium in the treatment of hyperkalaemia is well established in clinical practice but is based on sparse evidence. The toxic effects of potassium on the heart and antagonism by calcium was first demonstrated in an animal model in 1883\textsuperscript{1} and later confirmed in 1939.\textsuperscript{2} Much of the evidence to support its use is based on case reports and anecdotal experience, but there is little doubt of the importance of IV calcium in the emergency treatment of hyperkalaemia.\textsuperscript{3,5}

The electrophysiological effect of K\textsuperscript{+} on the heart is dependent on its extracellular concentration, direction of change (hypokalaemia or hyperkalaemia) and rate of change. The effect of K\textsuperscript{+} on the resting membrane potential of cardiac myocytes is modulated by the simultaneous calcium concentration such that an elevated calcium concentration decreases the depolarisation effect of an elevated K\textsuperscript{+} level.\textsuperscript{6}

IV calcium antagonises the cardiac membrane excitability provoked by excess potassium, thereby protecting the heart against arrhythmias. It is effective within 3 minutes at improving adverse ECG appearances (e.g. narrowing of the QRS complex).\textsuperscript{4,7,9} The dose should be repeated if there is no effect within 5-10 minutes. The duration of action is only 30-60 minutes, so further doses may be necessary if hyperkalaemia remains uncontrolled. As IV calcium does not lower serum K\textsuperscript{+}, other interventions are urgently required.

<table>
<thead>
<tr>
<th>10 ml 10% Calcium Chloride</th>
<th>6.8 mmol Ca\textsuperscript{2+}</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 ml 10% Calcium Gluconate</td>
<td>2.26 mmol Ca\textsuperscript{2+}</td>
</tr>
</tbody>
</table>

Table 15: Calcium content of IV calcium salts used in treatment of hyperkalaemia.

The choice of calcium salt (chloride or gluconate) is guided by practicalities such as availability, local practice and the clinical condition of the patient. There are some important differences between the two available solutions. Both preparations, calcium chloride\textsuperscript{10} and calcium gluconate\textsuperscript{11}, are available in the form of 10ml of 10% solution but calcium chloride contains 3 times more calcium than calcium gluconate as shown in Table 15. The bioavailability of both preparations appear to be similar with a study in patients with poor liver function (pre-transplant) demonstrating that calcium gluconate does not require hepatic activation to become effective.\textsuperscript{12} Calcium gluconate is less irritant to the skin than calcium chloride, but both salts can cause tissue necrosis. Calcium chloride has been recommended in the setting of haemodynamic instability, including cardiac arrest.\textsuperscript{13}

Adverse effects reported from the use of IV calcium salts include:\textsuperscript{8,9}

- tissue necrosis if extravasation occurs
- hypotension, peripheral vasodilation, hot flushes and/or chalky taste (mainly after too rapid infusion)
- bradycardia, arrhythmias (frequency unknown)
Report all adverse events via the Yellow Card system.

Historical evidence suggests that the administration of intravenous calcium may potentiate digoxin toxicity, but this is limited to case reports.\textsuperscript{14-16} In contrast, no dysrhythmias or increased mortality was demonstrated in a retrospective study over a 17-year period in which 23/161 patients identified with digoxin toxicity received IV calcium,\textsuperscript{17} but some methodological concerns in this paper has been highlighted.\textsuperscript{18} In instances where digoxin toxicity was unrecognised at presentation, no adverse event after IV calcium administration was reported.\textsuperscript{19,20}

In clinical practice, there have been several pitfalls in the administration of IV calcium:

1. A single dose of 10ml 10% calcium gluconate is often administered irrespective of the response which may have been inadequate.

2. The 12-lead ECG is frequently not repeated after administration to assess response. Look for a narrowing of the QRS complex (Figure 5), reduction in T wave amplitude (Figure 5), increase in heart rate if bradycardic or reversal of arrhythmia.

3. IV calcium can cause bradycardia, therefore there may be reluctance to administer if the patient’s heart rate is already slow. IV Calcium remains indicated and may be live-saving in hyperkalaemia-induced bradycardia.\textsuperscript{21}

4. The relatively short duration of action of IV calcium (30-60 minutes) may not be considered in patients with prolonged hyperkalaemia. Repeat ECG and consider a further dose if patient remains hyperkalaemic.

5. IV calcium may not be deemed necessary when emergency dialysis is planned or being initiated for severe hyperkalaemia, but this remains essential.

There is general agreement that IV calcium salts should be used in the presence of:

- life-threatening ECG changes (absent P waves, wide QRS, sine-wave pattern)\textsuperscript{3,13}
- cardiac arrhythmias\textsuperscript{13}
- cardiac arrest\textsuperscript{13,22}

There is no consensus about using IV calcium in the following circumstances:

- isolated peaked T waves
- normal ECG
Figure 6: ECG on admission (a) and following 20ml 10% calcium gluconate IV (b) in a patient with serum $K^+ 9.3\text{ mmol/L}$ who presented with generalised weakness.

In summary, IV calcium has been widely recommended for the treatment and prophylaxis of arrhythmias in patients with hyperkalaemia. The use of IV calcium buys time for other interventions to take effect. Given that 1) the ECG is the best tool for assessing cardiac toxicity, 2) the effect of IV calcium is assessed by an improvement in ECG appearance, and 3) IV calcium is not without risk, it seems reasonable to reserve IV calcium for patients with ECG changes of hyperkalaemia. When 10% calcium gluconate is used, sequential doses of 10ml solution are often required whereas a single dose of calcium chloride is more likely to be effective. Therefore, we recommend an equivalent dosage of calcium chloride or gluconate (6.8 mmol) for initial therapy.

References


10. Calcium Chloride Intravenous Infusion, 10% w/v: Summary of Product Information. www.medicines.org.uk/emc/product/4126/smpc


Guideline 16.3.1 – Hyperkalaemia: STEP 2 - Shift K⁺ into cells; insulin-glucose infusion

We recommend that insulin-glucose (10 units soluble insulin in 25g glucose) by intravenous infusion is used to treat severe hyperkalaemia (K⁺ ≥ 6.5 mmol/l). (1B)

Guideline 16.3.2 – Hyperkalaemia: STEP 2 - Shift K⁺ into cells; insulin-glucose infusion

We suggest that insulin-glucose (10 units soluble insulin in 25g glucose) by intravenous infusion is used to treat moderate hyperkalaemia (K⁺ 6.0 – 6.4 mmol/l). (2C)

Guideline 16.3.3 – Hyperkalaemia: STEP 2 - Shift K⁺ into cells; avoiding hypoglycaemia

We suggest pre-emptive initiation of an infusion of 10% glucose at 50ml/hour for 5 hours (25g) following insulin-glucose treatment in patients with a pre-treatment blood glucose < 7.0 mmol/l to avoid hypoglycaemia (target blood glucose 4-7 mmol/l). (2D)

Audit measure

1. The proportion of patients with severe hyperkalaemia (K⁺ ≥ 6.5 mmol/L) treated with insulin-glucose infusion [Audit Standard: 100%].

Rationale (Guidelines 16.3.1 – 16.3.4)

Insulin is the most reliable drug for shifting K⁺ into cells in patients with hyperkalaemia. Insulin shifts K⁺ into cells by activating Na⁺-K⁺ ATPase and recruiting intracellular pump components into the plasma membrane. Insulin binding to specific membrane receptors results in extrusion of Na⁺ and cellular uptake of K⁺. This effect is independent of its hypoglycaemic action.

Following insulin-glucose infusion, serum K⁺ level starts to fall within 15 minutes, with the peak reduction (ranging from 0.65-1.0 mmol/l) occurring between 30-60 minutes. The reduction in serum K⁺ may be sustained for up to 2 hours after administration following which there is usually a gradual rebound. The main risk of insulin-glucose therapy is hypoglycaemia. Insulin sensitivity varies from patient to patient and is affected by diabetic status and level of renal function.

The efficacy of insulin-glucose is increased if given in combination with salbutamol. The peak K⁺ lowering effect with combination therapy at 60 minutes is 1.5 mmol/L with intravenous beta-agonist therapy and 1.2 mmol/L with nebulised beta-agonist therapy. Co-administration of salbutamol also appears to reduce the risk of insulin-induced hypoglycaemia.

Hyperkalaemia may occur in the context of diabetic emergencies, in particular, diabetic ketoacidosis (DKA). In this setting, the primary problem is the redistribution of K⁺ out of cells although the total body K⁺ may be reduced. The K⁺ level falls as hyperglycaemia is controlled with fluids and insulin administration. Follow the DKA treatment protocol and monitor the serum K⁺ and blood glucose level closely.

The evidence guiding treatment recommendations for the insulin-glucose regimen has been analysed by assessing the:

- Incidence of iatrogenic hypoglycaemia
- Dose of insulin for optimal efficacy
- Dose of insulin to reduce the risk of hypoglycaemia
- Dose of glucose to reduce the risk of hypoglycaemia
- Patient-related factors increasing the risk of hypoglycaemia

Iatrogenic Hypoglycaemia after Insulin-glucose therapy

Hypoglycaemia is the most serious complication of treatment with insulin-glucose for acute hyperkalaemia. Over the last decade, several observational studies, using variable treatment regimens, have highlighted this risk as shown in Table 16.10-15 In clinical practice, monitoring for hypoglycaemia following treatment with insulin-glucose has been inconsistent and undoubtedly resulted in patient harm. This highlights the need for education and more robust measures to prevent hypoglycaemia.
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>N=</th>
<th>Baseline Blood glucose (BG)</th>
<th>Time Interval to Hypo (hrs)</th>
<th>Hypo (%)</th>
<th>*Severe Hypo (%)</th>
<th>Risk factors for Hypo</th>
</tr>
</thead>
<tbody>
<tr>
<td>#Schafers 2012</td>
<td>US</td>
<td>219</td>
<td>8.6 (No hypo group) 6.7 (Hypo group)</td>
<td>3.0</td>
<td>8.7</td>
<td>2.3</td>
<td>Low pre-treatment blood glucose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Renal impairment</td>
</tr>
<tr>
<td>#Apel 2014</td>
<td>US (ESRD)</td>
<td>221</td>
<td>9.0 (no hypo group) 5.8 (hypo group)</td>
<td>2.0</td>
<td>13</td>
<td>5.9</td>
<td>Low pre-treatment blood glucose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No history of diabetes</td>
</tr>
<tr>
<td>#Estep 2015</td>
<td>US</td>
<td>86</td>
<td>8.3 (No hypo group had BG 2.4 mmol/l higher than hypo group)</td>
<td>1.45</td>
<td>17.4</td>
<td>3.5</td>
<td>Low pre-treatment blood glucose</td>
</tr>
<tr>
<td>Coca 2017</td>
<td>Spain</td>
<td>164</td>
<td>8.5 (No hypo group) 6.2 (Hypo group)</td>
<td>3.5</td>
<td>6.1</td>
<td>1.2</td>
<td>Low pre-treatment blood glucose</td>
</tr>
<tr>
<td>#Scott 2019</td>
<td>US (ED)</td>
<td>409</td>
<td>7.3 (Hypo occurred in 34% of patients with baseline BG &lt; 5.6)</td>
<td>NA</td>
<td>17</td>
<td>8</td>
<td>Low pre-treatment blood glucose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower glucose dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Higher insulin dose</td>
</tr>
<tr>
<td>Boughton 2019</td>
<td>UK</td>
<td>662</td>
<td>8.7 (No hypo group) 5.8 (Hypo group)</td>
<td>NA</td>
<td>17.5</td>
<td>7.1</td>
<td>Low pre-treatment blood glucose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Older age</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low body weight</td>
</tr>
</tbody>
</table>

Table 16: Incidence and risk factors associated with iatrogenic hypoglycaemia after insulin-glucose infusion for treatment of hyperkalaemia.

*Definition of Severe hypoglycaemia: glucose < 3.0 mmol/l [Boughton]; glucose < 2.8 mmol/l [Apel, Scott]; glucose < 2.2 mmol/l [Schafers, Coca, Estep]

*Studies without a standardised Insulin-glucose protocol

ESRD – end-stage renal disease; ED – Emergency Department

Schafers et al used 5 different treatment regimens and reported an overall hypoglycaemic rate of 8.7%: 5% in patients receiving the conventional regimen (insulin 10 units and 25g glucose), <1% occurred in patients receiving insulin 10 units and 50g glucose and 1% in patients treated with insulin 5 units with 25g glucose.  

Scott et al reported an independent association between lower baseline blood glucose (5.4 vs 7.9 mmol/l), lower glucose dose (40 ± 25 vs 33 ± 28g) and higher insulin dose (10.3 ± 5.0 vs 9.6 ± 3.5 units) with the development of hypoglycaemia using multivariate analysis.
Boughton et al used the UK Renal Association Hyperkalaemia Guideline (2014) protocol, however 10 units 1 insulin was given in 100ml 20% glucose (~ 20g), slightly lower than the guideline recommendation of 125 ml 2 20% glucose (25g). This may have influenced hypoglycaemic events. Hospital mortality was higher for 3 patients treated for hyperkalaemia (13%) compared with the general inpatient population (3%).

In summary, the most consistent factor contributing to hypoglycaemia after insulin-glucose treatment 4 appears to be a low pre-treatment blood glucose level (< 7 mmol/l). This is an important consideration in 5 designing a safe and effective treatment protocol.

9 **Insulin and Glucose dose: Efficacy**

The evidence-base for efficacy of insulin-glucose in the treatment of acute hyperkalaemia is heterogenous 10 consisting of variable study designs, insulin doses, glucose doses, method of administration (bolus or 11 infusion), and study populations as shown in Table 17.

Early prospective studies 2, 3, 5, 6, 16, 17 and one more recent study, 18 were performed predominantly in stable 14 haemodialysis patients and included small patient cohorts. Few prospective studies included patients with 15 acute kidney injury. 4, 8, 19

Retrospective studies reported over the past decade have attempted to address the optimal regimen to 16 reduce the risk of hypoglycaemia without compromising efficacy. 22, 20, 25 Some studies have considered 18 reduced insulin dose (5 units), 20, 22, 23 higher glucose dose (50g), 10, 12, 21, 22, 24 body weight, 21, 25 glycaemic status 19 and level of renal function 20, 26 to tailor treatment regimens. Importantly, assessment of efficacy is 20 dependent on the timing of blood monitoring after treatment. Given the retrospective design of these 21 studies, the timing of blood monitoring was variable with K+ measurements ranging between 1 to 4 hours 22 after administration of insulin-glucose.
<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Insulin Dose</th>
<th>Glucose Dose (g)</th>
<th>Potassium Level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>10 Units</td>
<td>Other Units</td>
<td>Mean Baseline K⁺ (mmol/L)</td>
</tr>
<tr>
<td>Lens 1989⁴</td>
<td>10</td>
<td>10</td>
<td>25</td>
<td>6.7</td>
</tr>
<tr>
<td>Allon 1990²</td>
<td>12</td>
<td>10</td>
<td>25</td>
<td>5.48</td>
</tr>
<tr>
<td>Ljutic 1993⁵</td>
<td>9</td>
<td>10</td>
<td>25</td>
<td>6.33</td>
</tr>
<tr>
<td>Allon 1996³</td>
<td>8</td>
<td>0.5 U/kg/min</td>
<td>60</td>
<td>4.28</td>
</tr>
<tr>
<td>Duranay 1996¹⁶</td>
<td>20</td>
<td>10</td>
<td>30</td>
<td>6.71</td>
</tr>
<tr>
<td>Kim 1996⁶</td>
<td>8</td>
<td>0.5 U/kg/min</td>
<td>40</td>
<td>6.3</td>
</tr>
<tr>
<td>Ngugi 1997⁸</td>
<td>70</td>
<td>10</td>
<td>25</td>
<td>6.9</td>
</tr>
<tr>
<td>Mahajan 2001¹⁷</td>
<td>30</td>
<td>12</td>
<td>25</td>
<td>6.59</td>
</tr>
<tr>
<td>Mushtaq 2006²³</td>
<td>15</td>
<td>10</td>
<td>25</td>
<td>6.5</td>
</tr>
<tr>
<td>Chothia 2014¹⁸</td>
<td>10</td>
<td>10</td>
<td>0</td>
<td>6.01 [10 units]</td>
</tr>
<tr>
<td>Pierce 2015²⁰</td>
<td>149</td>
<td>10</td>
<td>5</td>
<td>6.3</td>
</tr>
<tr>
<td>Wheeler 2016²¹</td>
<td>132</td>
<td>10</td>
<td>0.1 U/kg</td>
<td>6.1</td>
</tr>
<tr>
<td>La Rue 2017²²</td>
<td>675</td>
<td>10</td>
<td>25 + 25 ± 25</td>
<td>6.4</td>
</tr>
<tr>
<td>Coca 2017¹²</td>
<td>164</td>
<td>10</td>
<td>50</td>
<td>6.85</td>
</tr>
<tr>
<td>Garcia 2018²³</td>
<td>401</td>
<td>10</td>
<td>5</td>
<td>6.15 [10 units]</td>
</tr>
<tr>
<td>Farina 2018²⁴</td>
<td>240</td>
<td>10</td>
<td>25</td>
<td>6.5 [25g]</td>
</tr>
</tbody>
</table>

Table 17: Prospective and Retrospective studies of Insulin-glucose therapy.
Insulin dose – Conventional Regimen: Insulin 10 units in 25g glucose

The majority of the prospective studies used a dose of 10 units of soluble insulin. The most commonly used dose of glucose was 25g. The mean baseline serum K⁺ ranged from 5.48 – 6.9 mmol/l in patients treated with this conventional regimen. The efficacy demonstrated in these studies showed a reduction in serum K⁺ ranging from 0.65 – 1.14 mmol/l as shown below in Table 18. This evidence formed the basis of the historical recommendation to treat acute hyperkalaemia with insulin 10 units and glucose 25g. Recent observational studies have shown similar efficacy (0.9-1.08 mmol/l) with this regimen.

<table>
<thead>
<tr>
<th>STUDY</th>
<th>Insulin dose (units)</th>
<th>Glucose Dose (g)</th>
<th>Baseline K⁺ (mmol/l)</th>
<th>K⁺ lowering (mmol/l)</th>
<th>DM (%)</th>
<th>Baseline blood glucose (mmol/l)</th>
<th>Hypo (BM ≤ 3.9) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allon 1990</td>
<td>10</td>
<td>25</td>
<td>5.48</td>
<td>0.65</td>
<td>0</td>
<td>4.8</td>
<td>*75</td>
</tr>
<tr>
<td>Ljutic 1993</td>
<td>10</td>
<td>25</td>
<td>6.33</td>
<td>0.77</td>
<td>NA</td>
<td>NA</td>
<td>11</td>
</tr>
<tr>
<td>Ngugi 1997</td>
<td>10</td>
<td>25</td>
<td>6.9</td>
<td>1.14</td>
<td>NA</td>
<td>NA</td>
<td>20</td>
</tr>
<tr>
<td>Mushtaq 2006</td>
<td>10</td>
<td>25</td>
<td>6.5</td>
<td>0.8</td>
<td>NA</td>
<td>7.5</td>
<td>0</td>
</tr>
<tr>
<td>Pierce 2015</td>
<td>10</td>
<td>25</td>
<td>6.3</td>
<td>1.08</td>
<td>55</td>
<td>NA</td>
<td>16.7</td>
</tr>
<tr>
<td>Garcia 2018</td>
<td>10</td>
<td>25</td>
<td>6.15</td>
<td>0.9</td>
<td>36.2</td>
<td>8.7</td>
<td>10.7</td>
</tr>
<tr>
<td>Farnia 2018</td>
<td>10</td>
<td>25</td>
<td>6.5</td>
<td>1.0</td>
<td>26.7</td>
<td>7.0</td>
<td>15.8</td>
</tr>
</tbody>
</table>

Table 18: Efficacy and risk of hypoglycaemia with conventional regimen - 10 units Insulin with 25g glucose (studies without efficacy data excluded)


Other studies have combined 10 units of insulin with a dose of glucose ranging from 30 – 50g with K⁺-lowering ranging from 0.83 – 1.18 mmol/l. This suggests that increasing the dose of glucose does not enhance efficacy.
**Insulin dose – 5 versus 10 units**

Three retrospective studies, consisting of large cohorts of up to 675 patients, have compared the efficacy and hypoglycaemic risk with regimens using 5 versus 10 units of insulin in patients with renal impairment as shown in Table 19.[20, 22, 23] The $K^+$-lowering achieved using 10 units insulin was 0.9 – 1.08 mmol/l compared with 0.81 – 1.1 mmol/l using 5 units insulin. No significant reduction in hypoglycaemia was reported in patients treated with low dose insulin with an incidence of up to 19.7% shown.

<table>
<thead>
<tr>
<th>STUDY</th>
<th>Insulin dose (units)</th>
<th>Albuterol Use (%)</th>
<th>Baseline $K^+$ (mmol/l)</th>
<th>$K^+$ lowering (mmol/l)</th>
<th>DM (%)</th>
<th>Baseline blood glucose (mmol/l)</th>
<th>Hypo (BM ≤ 3.9) (%)</th>
<th>*Severe Hypo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pierce 2015 [20] (n =149)</td>
<td>10</td>
<td>NA</td>
<td>6.3</td>
<td>1.08</td>
<td>55</td>
<td>NA</td>
<td>16.7</td>
<td>8.9</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>NA</td>
<td>6.3</td>
<td>1.1</td>
<td>46</td>
<td>NA</td>
<td>19.7</td>
<td>7.0</td>
</tr>
<tr>
<td>La Rue 2017 [22] (n=675)</td>
<td>10</td>
<td>30.3</td>
<td>6.4</td>
<td>1.0</td>
<td>49.1</td>
<td>7.6</td>
<td>28.6</td>
<td>6.8</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>36.8</td>
<td>6.4</td>
<td>1.0</td>
<td>42.9</td>
<td>6.9</td>
<td>19.5</td>
<td>3.0</td>
</tr>
<tr>
<td>Garcia 2018 [23] (n=401)</td>
<td>10</td>
<td>15.2</td>
<td>6.15</td>
<td>0.9</td>
<td>36.2</td>
<td>8.8</td>
<td>10.7</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>#25</td>
<td>6.24</td>
<td>0.81</td>
<td>29.4</td>
<td>7.6</td>
<td>8.7</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Table 19: Comparison of studies performed using 5 versus 10 units insulin (studies without efficacy data excluded).*

Proportion of patients treated with 5 units insulin: Pierce: 48% [20]; La Rue: 20% [22]; Garcia: 23% [23]

Dose of glucose: Pierce: 25g [20]; La Rue: 25g + 25g at 1hr ± 25g at 3hrs if blood glucose < 3.9 mmol/l (poor adherence to this protocol) [22]; Garcia: 0-50g (25g used in 68% of patients treated with 5 units insulin and 82% of patients treated with 10 units insulin; 50g used in 19.5% treated with 5units insulin and 11% treated with 10 units insulin) [23]

*Definition of Severe hypoglycaemia: Pierce: glucose < 2.8 mmol/l [20]; La Rue: glucose < 2.2 mmol/l [22]

# p = 0.03

NA – not available; DM- Diabetes mellitus; Hypo – hypoglycaemia; BM – blood glucose.

Interpretation of the data in these studies is confounded by the low proportion of patients receiving 5 units insulin in two of the studies,[22,23] the use of variable glucose regimens which may have influenced the incidence of hypoglycaemia, and the use of concomitant $K^+$-lowering drugs which may have influenced efficacy. Albuterol, a beta-agonist, was used in more patients treated with 5 units insulin in two of the reports[22,23] and was not stated in the other report.[20]
Impact of severity of hyperkalaemia

Although there is no definitive evidence of a dose-dependent effect of insulin on lowering K⁺ level, Garcia et al reported a post-hoc analysis of patients with a serum K⁺ ≥ 6.0 mmol/l and showed a trend towards higher K⁺-lowering in patients treated with 10 units insulin compared with those treated with 5 units insulin. (difference -0.238 mmol/l; p=0.018). 23

It is also unproven if the severity of hyperkalaemia affects the degree of K⁺-lowering with insulin. The efficacy reported in studies conducted using 10 units of insulin (Table 17) was compared between patients with a mean K⁺ ≥ 6.5 mmol/l (n=6) vs those with a mean K⁺ < 6.5 mmol/l (n=6). Interestingly, this showed a trend towards higher K⁺-lowering in studies with more severe hyperkalaemia (mean reduction 1.02 mmol/l vs 0.87 mmol/l; difference -0.15 mmol/l). The studies providing mean K⁺ levels and efficacy are plotted in Figure 6. The degree of correlation may be affected by the narrow range in K⁺ level with no studies exceeding a mean K⁺ level of > 7.0 mmol/l. This observation requires confirmation in a prospective study, but seem to suggests that the higher the serum K⁺, the greater the efficacy of insulin.

Figure 6: K⁺-lowering efficacy in studies using 10 units insulin over a range of baseline serum K⁺ levels (5.48 – 6.9 mmol/l) showing a trend towards greater efficacy with increasing severity of hyperkalaemia.

Studies without mean K⁺ levels or efficacy data are not included.

Data for studies using low dose insulin are not presented as most studies had a mean serum K⁺ < 6.5 mmol/l.

Insulin and Glucose dose: Strategies to Reduce the Risk of Hypoglycaemia

Factors influencing the risk of hypoglycaemia are the dose of insulin, dose of glucose, and patient-related factors.

Insulin dose – Conventional regimen

The studies conducted prior to 2010, using a regimen of 10 units of insulin with 25g glucose, showed a wide variation in incidence rate of hypoglycaemia ranging from 11 – 20% in two studies, 5,8 no episodes in one study 23 and as high as 75% in a study including only patients without diabetes. 2 Similarly, over the past decade, the incidence of hypoglycaemia reported using this regimen ranged from 5 - 28%. 10,11,14,20 23,24,26

Insulin dose – Low dose regimen

Studies assessing the hypoglycaemic risk using regimens of 5 vs 10 units of insulin were confounded by the proportion of patients who received 5 units insulin (range 20 – 48%) and the variable glucose dosing (Table 19). 20,22,23 This may have contributed to the inconsistent findings.
Pierce et al, the only study with almost equal study arms, showed no significant difference in incidence of hypoglycaemia between conventional vs low-dose insulin treatment groups (16.7% vs 19.7%, \( p=0.79 \)). However, the low-dose regimen was associated with a 31.5% lower incidence of hypoglycaemia in patients with ESRD. More than 28% of hypoglycaemic episodes in patients treated with 10 units insulin occurred after 4 hours (median = 2.5 hours) compared with 14.3% in patients treated with 5 units insulin (median = 2.38 hours).

La Rue et al reported a lower rate of hypoglycaemia in patients treated with 5 units insulin compared with 10 units insulin (19.5% vs 28.6%). However, despite the large study cohort, this outcome may have been confounded by 80% of the study population receiving 10 units insulin and the dose of glucose delivered was lower than intended (34-39g instead of 50g in two divided doses) due to nonadherence to the treatment protocol. The authors suggest that 5 units insulin may be sufficient when used in combination with other K\(^+\)-lowering therapies.

Garcia et al reported a similar incidence of hypoglycaemia in patients treated with 5 units or 10 units (8.7% vs 10.7%; \( p=0.581 \)). Disproportionally fewer patients received low dose vs conventional dose insulin (23% vs 79%) and multiple glucose dosing regimens were used in this study.

A further study by McNicholas et al conducted as a 2-part audit, compared hypoglycaemic incidence in patients treated with 5 vs 10 units insulin with 25g glucose. The treatment protocol recommended 10 units insulin for patients with eGFR >30 ml/min and 5 units for patients with eGFR <30 ml/min or ESRD. In Audit 1, 26% of patients received 10 units and 72% of patients received 5 units of insulin. Hypoglycaemia occurred in 28% of patients overall. The K\(^+\)-lowering rate was similar in both 5 and 10 units insulin groups. In Audit 2 after an education initiative, protocol use improved from 62% to 74%. The number of patients with CKD/ESRD treated with 5 units insulin (as per protocol) increased from 75% to 93%. The time to first blood glucose check improved from 2.37 to 1.33 hours. There was a reduction in hypoglycaemic events from 28% to 11% with no severe episodes.

**Insulin dose – Weight-based regimen**

Tailoring insulin dose to body weight is another potential strategy as shown in Table 20. Two small early studies in haemodialysis patients reported no hypoglycaemic events. More recently, Wheeler et al demonstrated a significant reduction in hypoglycaemic events with a weight based regimen. However this study only reported the lowest serum K\(^+\) level achieved in the 12 hours following treatment, making it difficult to assess efficacy.
<table>
<thead>
<tr>
<th>STUDY</th>
<th>Insulin dose (units)</th>
<th>Glucose Dose (g)</th>
<th>Baseline (K^+) (mmol/l)</th>
<th>(K^+) lowering (mmol/l)</th>
<th>DM (%)</th>
<th>Baseline blood glucose (mmol/l)</th>
<th>Hypo (BM ≤ 3.9) (%)</th>
<th>*Severe Hypo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allon</td>
<td>5 mU/kg/min</td>
<td>60</td>
<td>4.28</td>
<td>0.85</td>
<td>0</td>
<td>4.8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Kim</td>
<td>5 mU/kg/min</td>
<td>40</td>
<td>6.3</td>
<td>0.7</td>
<td>NA</td>
<td>NA</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Wheeler</td>
<td>0.1U/kg</td>
<td>50</td>
<td>6.1</td>
<td><strong>NI</strong></td>
<td>NA</td>
<td>8.2</td>
<td>12.1</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>6.1</td>
<td><strong>NI</strong></td>
<td>NA</td>
<td>9.2</td>
<td>27.3</td>
<td>NA</td>
</tr>
<tr>
<td>Brown</td>
<td>0.1U/kg (8.3)</td>
<td>24</td>
<td>6.1</td>
<td>0.6</td>
<td>52</td>
<td>9.0</td>
<td>6.7</td>
<td>2.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8.7</td>
<td>6.2</td>
<td>0.6</td>
<td>45</td>
<td>8.5</td>
<td><strong>5.8</strong></td>
<td>10.1</td>
</tr>
</tbody>
</table>

**Table 20: Comparison of studies performed using weight-base Insulin regimen.**

*Severe hypoglycaemia – glucose < 2.8 mmol/l.  **p=0.05  NA – not available.

*NI – not included as study reported the lowest serum \(K^+\) level achieved in the 12 hours following treatment.

Brown et al, compared a weight-based protocol (via an order panel) vs physician-led protocol and found a marginally significant difference in hypoglycaemic rates (6.67% vs 5.8%, p=0.05) in favour of the weight-based cohort. Efficacy was equivocal in the groups. Although these studies showed equal efficacy, a weight-based regimen is harder to safely and reliably implement in a medical emergency.

**Glucose dose**

Studies assessing the effect of glucose dose on hypoglycaemic risk are shown in Table 21.

Farnia et al compared the efficacy of 10 units insulin administered with 25g or 50g glucose in two equal cohorts. Efficacy was equivalent and there was a trend towards a lower incidence of hypoglycaemia at 60 minutes in patients treated with 50g glucose. Sub-group analysis of patients with a baseline blood glucose < 6.1 mmol/l and those without diabetes showed a significant reduction in hypoglycaemic events when treated with 50g glucose. The use of 50g glucose did not result in a greater risk of prolonged hyperglycaemia relative to patients treated with 25g glucose, including in patients with diabetes.

Coca et al treated patients with 10 units insulin with 50g glucose by infusion over 240 minutes. Efficacy was comparable with Farnia et al in patients treated with 50% glucose (1.18 vs 1.1 mmol/l). Similarly, the hypoglycaemic incident rate was also low at 6.1% and the incidence of severe hypoglycaemia was very low at 1.2%. This may be explained by the continuous infusion of glucose over 4 hours.

Schafer et al examined all hypoglycaemic events and noted that the highest rate (58%) occurred in patients receiving the conventional regimen (insulin 10 units and 25g glucose) and the lowest rate (5.5%) occurred in patients receiving insulin 10 units and 50g glucose.
Garcia et al included multiple glucose regimens, but the majority of patients received 25g (79%) and relatively few received 50g (13%). Outcome data was analysed by the dose of insulin administered, therefore the impact of glucose concentration is not interpretable in this study.

Wheeler et al appears to be the only study investigating different insulin regimens in patients treated with 50g glucose and showed a lower incidence of hypoglycaemia using a weight-based regimen, but efficacy could not be accurately assessed.

<table>
<thead>
<tr>
<th>STUDY</th>
<th>Glucose dose (units)</th>
<th>Insulin Dose (units)</th>
<th>Baseline K⁺ (mmol/l)</th>
<th>K⁺ lowering (mmol/l)</th>
<th>DM (%)</th>
<th>Baseline blood glucose (mmol/l)</th>
<th>Hypo (BM ≤ 3.9) (%)</th>
<th>*Severe Hypo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chothia 2014</td>
<td>50</td>
<td>0</td>
<td>6.23</td>
<td>0.50</td>
<td>NA</td>
<td>5.1</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>(n=10)</td>
<td>50</td>
<td>10</td>
<td>6.01</td>
<td>0.83</td>
<td>NA</td>
<td>5.6</td>
<td>20</td>
<td>NA</td>
</tr>
<tr>
<td>Wheeler 2016</td>
<td>50</td>
<td>0.1 U/kg</td>
<td>6.1</td>
<td>#NI</td>
<td>NA</td>
<td>8.2</td>
<td>12.1</td>
<td>NA</td>
</tr>
<tr>
<td>(n=132)</td>
<td>50</td>
<td>10</td>
<td>#NI</td>
<td>9.2</td>
<td>NA</td>
<td>*27.3</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Coca 2017</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(n=164)</td>
<td>50</td>
<td>10</td>
<td>6.85</td>
<td>1.18</td>
<td>-</td>
<td>8.3</td>
<td>6.1</td>
<td>1.2</td>
</tr>
<tr>
<td>Garcia 2018</td>
<td>0</td>
<td>5</td>
<td>(2%)</td>
<td>6.24</td>
<td>0.81</td>
<td>29</td>
<td>7.6</td>
<td>8.7</td>
</tr>
<tr>
<td>(n=401)</td>
<td>25</td>
<td>5</td>
<td>(16%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Garcia 2018</td>
<td>0</td>
<td>10</td>
<td>(4%)</td>
<td>6.15</td>
<td>0.9</td>
<td>36</td>
<td>8.8</td>
<td>10.7</td>
</tr>
<tr>
<td>(n=401)</td>
<td>25</td>
<td>10</td>
<td>(63%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Farnia 2018</td>
<td>25</td>
<td>10</td>
<td>(50%)</td>
<td>6.5</td>
<td>1.0</td>
<td>27</td>
<td>7.0</td>
<td>**15.8</td>
</tr>
<tr>
<td>(n=240)</td>
<td>50</td>
<td>10</td>
<td>(50%)</td>
<td>6.3</td>
<td>1.1</td>
<td>27</td>
<td>5.9</td>
<td>8.3</td>
</tr>
</tbody>
</table>

Table 21: Studies using 50% glucose in treatment of hyperkalaemia.

*p<0.5; **p=0.11
#NI – not included as study reported the lowest serum K⁺ level achieved in the 12 hours following treatment.

Glucose without Insulin

Theoretically, administering glucose alone should stimulate insulin release and reduce the risk of hypoglycaemia and some studies have shown K⁺-lowering of 0.2-0.6 mmol/l with this approach. Chothia et al showed a reduction in serum K⁺ was 0.83 mmol/l (insulin-glucose group) compared with 0.5 mmol/l (glucose-only group). However, endogenous insulin levels are unlikely to rise to the necessary therapeutic level to cause a rapid, reliable and clinically useful degree of K⁺ shift into cells. This approach also risks a paradoxical worsening of hyperkalaemia by causing a shift of K⁺ out of cells. This strategy is not recommended.
Other risk factors

Several risk factors have been identified that may contribute to hypoglycaemia after insulin-glucose treatment. Patient-related factors are listed below in Table 22. Insulin has a longer half-life in patients with renal failure making them more at risk of hypoglycaemia. The reported incidence of hypoglycaemia in patients with ESRD is up to 33%. Treatment-related factors include the dose of insulin and dose of glucose used.

<table>
<thead>
<tr>
<th>Potential risk Factors for iatrogenic Hypoglycaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient-related:</strong></td>
</tr>
<tr>
<td>Low pre-treatment blood glucose</td>
</tr>
<tr>
<td>Renal impairment (AKI, CKD 4-5, ESRD)</td>
</tr>
<tr>
<td>Low body weight</td>
</tr>
<tr>
<td>Older age</td>
</tr>
<tr>
<td>Non-diabetic status (no prior history and no diabetic medication)</td>
</tr>
<tr>
<td><strong>Treatment-related:</strong></td>
</tr>
<tr>
<td>High Insulin dose regimen (≥ 10 units soluble insulin)</td>
</tr>
<tr>
<td>Low Glucose dose regimen (≤ 25g glucose)</td>
</tr>
</tbody>
</table>

Table 22: Risk Factors for Hypoglycaemia following treatment with Insulin-Glucose

Most of the patient-related factors are not modifiable with the exception of the baseline blood glucose. Based on the available studies, a pre-treatment blood glucose < 7 mmol/l appears to be the threshold for identifying patients potentially at risk of hypoglycaemia. Both treatment-related factors are modifiable.

Tailoring the treatment protocol to address one or more of these risk factors will increase complexity and likely affect adherence as seen in two reports. However, a single protocol to fit all will continue to risk hypoglycaemia.

Summary

Historical evidence has guided the development of previous guidelines with the conventional regimen of 10 units soluble insulin with 25g glucose being standard practice for decades. The incidence of hypoglycaemia following this treatment regimen remains high, therefore recent studies have been comprehensively reviewed to determine if a change in practice is warranted. Unfortunately, the available evidence is limited by small cohort sizes in the early prospective studies, retrospective design in recent studies and use of multiple insulin-glucose treatment regimens.

The risk of hypoglycaemia is increased in patients without diabetes and in patients with a pre-treatment blood glucose < 7 mmol/l. In a sub-group of patients without diabetes, hypoglycaemia developed in 7.9% within 1 hour. Reducing the dose of insulin alone is insufficient to reduce hypoglycaemic events which
remains at 8.7-19.7% with low-dose insulin, although it does appear to reduce the incidence of severe hypoglycaemia in some studies.

There appears to be more evidence that increasing the dose of glucose more consistently reduces hypoglycaemic events with the larger studies (with efficacy data) reporting rates of 6.1-8.3%. Farnia et al found that the incidence of hypoglycaemia was significantly lower in the sub-group of patients without diabetes and those with a baseline glucose < 6.1 mmol/l when treated with 50g compared with 25g glucose.24

The method of administration of glucose may be important. LaRue et al attempted sequential doses of 25g glucose (i.e. second dose after 1 hour and third dose after 3 hours if the blood glucose < 3.9 mmol/l, but non-adherence to the protocol resulted in a lower dose of glucose administered (34 - 39g).22 Coca et al administered 50g glucose with insulin over a 4-hour infusion and reported a low rate of hypoglycaemia (6.1%) and the lowest rate of severe hypoglycaemia (1.2%), but this strategy delays assessment of efficacy.12 Another approach is the initiation of a continuous infusion of 10% glucose at 50ml/hr following initial treatment with 25g glucose.29,38 If the infusion is given over 5 hours (25g), this would deliver a total glucose dose of 50g. This method allows continuous delivery of glucose throughout the risk period for hyperglycaemia, titration of the infusion guided by blood glucose level and avoids the transient hyperglycaemia after a 50g glucose dosing.

Achieving a lower hypoglycaemic rate without compromising efficacy is the ultimate goal. Although most studies have shown that reducing the dose of insulin does not appear to compromise efficacy, one report has highlighted a dose-dependent trend with 10 units insulin showing greater efficacy than 5 units insulin in patients with a serum K⁺ ≥ 6.0 mmol/l.23 There also appears to be a trend for greater efficacy with increasing severity of hyperkalaemia in patients treated with 10 units insulin (Figure 6).

These observations raise potential concern for the treatment of patients with potentially life-threatening hyperkalaemia. The standard multi-modal approach to treating hyperkalaemia is hampered in critical illness and in cardiac arrest, leaving insulin-glucose as the main therapeutic option. Although SZC enhances K⁺-lowering, oral administration may not be feasible in a peri-arrest patient and both SZC and salbutamol cannot be given in cardiac arrest. On balance, the risk of sub-optimal K⁺-lowering treatment appears to outweigh the risk of hypoglycaemia in the setting of life-threatening hyperkalaemia. Further study is required before a reduction in insulin dosage to 5 units can be recommended.

The KDIGO guideline (2019) on the management of acute hyperkalaemia acknowledges that there is limited evidence, but has recommended the administration of 5 units in place of 10 units insulin.39 This guideline also advocates other treatment options without a clear evidence base including sodium bicarbonate (if acidosis present) and diuretics. The implications of this change in dose of insulin to patients in whom a multi-modal treatment approach may not be feasible (i.e. peri-arrest or cardiac arrest) was not considered.

The Renal Association guideline has comprehensively reviewed the literature to provide an evidence-based approach to treating hyperkalaemia whilst considering patient safety. There is currently insufficient evidence to support reducing the dose of insulin to 5 units. The efficacy of low-dose vs conventional dose insulin in patients with severe hyperkalaemia (K ≥ 6.5 mmol/l) requires clarification to ensure that patients with life-threatening hyperkalaemia do not receive sub-optimal treatment.

There is more evidence in support of increasing the glucose load. High risk groups have also been identified and allows a tailored approach. On this basis, we recommend the use of 10 units soluble insulin with 25g
Renal Association Clinical Practice Guidelines – Treatment of Acute Hyperkalaemia in Adults – December 2019

1. Check blood glucose prior to insulin administration.
2. Give 10 units soluble Insulin with 25 g glucose.
3. Give 10% glucose by infusion at 50ml/hr (25g) for 5 hours in patients with a pre-treatment blood glucose < 7.0 mmol/l.
   - target blood glucose: 4.0 – 7.0 mmol/l
   - titrate rate of infusion if required
4. Monitor serum K⁺ and blood glucose (see treatment algorithm).
5. Anticipate and treat hypoglycaemia promptly.

Table 23: Protocol for Insulin-Glucose in treatment of acute hyperkalaemia.

Further research is required with well-designed prospective randomised studies to confirm the optimal insulin and glucose dosing regimen to maintain efficacy whilst avoiding hypoglycaemia.

References


Guideline 16.4.1 – Hyperkalaemia: STEP 2 – Shift K⁺ into cells; Salbutamol
We recommend nebulised salbutamol 10-20 mg is used as adjuvant therapy for severe (K⁺ ≥ 6.5 mmol/L) hyperkalaemia. (1B)

Guideline 16.4.2 – Hyperkalaemia: STEP 2 – Shift K⁺ into cells; Salbutamol
We suggest that nebulised salbutamol 10-20 mg may be used as adjuvant therapy for moderate (K⁺ 6.0-6.4 mmol/L) hyperkalaemia. (2C)

Guideline 16.4.3 – Hyperkalaemia: STEP 2 – Shift K⁺ into cells; Salbutamol
We recommend that salbutamol is not used as monotherapy in the treatment of severe hyperkalaemia. (1A)

Audit Measure
1. The proportion of patients who develop adverse effects of salbutamol (e.g. tachycardia, arrhythmia).

Rationale (Guideline 16.4.1 – 16.4.3)
Salbutamol is a beta-2 adrenoceptor agonist and promotes the intracellular shift of K⁺ by activation of the Na-K⁺ ATPase pump.¹ Salbutamol and other beta-agonists are equally effective given intravenously or by nebuliser.²-⁴ The nebulised route is easier to administer and causes fewer side-effects, such as tremor, palpitations and headache.⁵ There are no studies to assess the safety of salbutamol in patients with cardiac disease, therefore a lower dose and cardiac monitoring is recommended.

<table>
<thead>
<tr>
<th>Dose</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>10mg</td>
<td>decreases serum K⁺ by 0.53 - 0.88 mmol/L</td>
</tr>
<tr>
<td>20mg</td>
<td>decreases serum K⁺ by 0.66 - 0.98 mmol/L</td>
</tr>
</tbody>
</table>

Table 24: Efficacy of Nebulised Salbutamol.
The effect of salbutamol is dose-dependent as shown above in Table 24. The onset of action is within 30 minutes and duration of action is for at least 2 hours as shown below in Table 25.²,³,⁶-¹¹ The peak effect of 10mg nebulised salbutamol is seen at 120 minutes and at 90 minutes for the 20mg nebulised dose.⁴ The degree of potassium lowering is variable and 20-40% of patients have a decline in serum K⁺ < 0.5 mmol/L.¹² The combination of salbutamol with insulin-glucose is more effective than either treatment alone.⁹,¹³ The peak K⁺ lowering effect with combination therapy at 60 minutes was 1.5 mmol/L with intravenous beta-agonist therapy¹³ and 1.2 mmol/L with nebulised beta-agonist therapy.⁹ Mild hyperglycaemia (2-3 mmol/L increase) has also been reported and this may partly protect against insulin-induced hypoglycaemia.
<table>
<thead>
<tr>
<th>STUDY</th>
<th>N</th>
<th>Dose of Salbutamol</th>
<th>Mean initial K⁺ (mmol/L)</th>
<th>Peak reduction in K⁺ (mmol/L)</th>
<th>Time of max action</th>
<th>Duration of Effect (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allon⁶ 1989</td>
<td>10</td>
<td>10 mg</td>
<td>5.93</td>
<td>0.62</td>
<td>90</td>
<td>&gt;120</td>
</tr>
<tr>
<td>Allon⁶ 1996</td>
<td>8</td>
<td>10 mg</td>
<td>4.29</td>
<td>0.53</td>
<td>60</td>
<td>&gt;60</td>
</tr>
<tr>
<td>Liou⁴ 1994</td>
<td>17</td>
<td>10 mg</td>
<td>5.8</td>
<td>0.88</td>
<td>90</td>
<td>&gt;60</td>
</tr>
<tr>
<td>Montoliu¹¹ 1990</td>
<td>10</td>
<td>15 mg</td>
<td>6.5</td>
<td>0.9</td>
<td>30</td>
<td>&gt;360</td>
</tr>
<tr>
<td>Kim⁸ 1997</td>
<td>9</td>
<td>15 mg</td>
<td>5.99</td>
<td>0.57</td>
<td>60</td>
<td>&gt; 60</td>
</tr>
<tr>
<td>Allon⁶ 1989</td>
<td>10</td>
<td>20 mg</td>
<td>5.81</td>
<td>0.98</td>
<td>90</td>
<td>&gt;120</td>
</tr>
<tr>
<td>Allon⁹ 1990</td>
<td>12</td>
<td>20 mg</td>
<td>5.56</td>
<td>0.66</td>
<td>60</td>
<td>&gt;60</td>
</tr>
<tr>
<td>McClure¹² 1994</td>
<td>11</td>
<td>2.5/ 5 mg*</td>
<td>5.9</td>
<td>0.61</td>
<td>30</td>
<td>&gt;300</td>
</tr>
<tr>
<td>Mandelberg¹⁰ 1999</td>
<td>17</td>
<td>1200µg (via MDS-I)</td>
<td>5.5</td>
<td>0.4</td>
<td>60</td>
<td>ns</td>
</tr>
</tbody>
</table>

Table 25: Studies investigating efficacy of nebulised salbutamol in hyperkalaemia.

*children (aged 5-18 years)
ns – not stated

Salbutamol may be ineffective in some patients with hyperkalaemia. Non-selective beta-blockers may prevent the hypokalaemic response to salbutamol.¹⁴ Up to 40% of patients with end stage renal disease do not respond to salbutamol and the mechanism for this resistance is unknown.⁶,⁹ Given its variable efficacy, salbutamol should therefore not be used as monotherapy for treatment of hyperkalaemia.⁴

References


**Guideline 16.5 Hyperkalaemia: STEP2 –Shift K into cells; Sodium bicarbonate**

We suggest that intravenous sodium bicarbonate infusion is not used routinely for the acute treatment of hyperkalaemia. (2C)

**Rationale (Guideline 16.5)**

There is currently insufficient evidence to support the routine use of intravenous sodium bicarbonate for the acute treatment of hyperkalaemia. Almost all of the available evidence comes from studies performed in stable chronic haemodialysis patients. When compared with other K⁺-lowering regimens, sodium bicarbonate monotherapy failed to lower serum K⁺ acutely. 1-5 Although, some studies have suggested bicarbonate may increase the efficacy of other therapies, such as insulin-glucose and salbutamol, 6 others have not demonstrated any additional benefit from bicarbonate administration when added to insulin-glucose 1 or salbutamol 1-6. The combination of all three treatments was the most effective strategy in one study. 5

Prolonged administration of sodium bicarbonate may lower K⁺, but at the expense of a sodium load. 3 A randomised controlled trial conducted by Jaber et al assessed the effect of using hypertonic sodium bicarbonate (4.2%) in critically ill patients with severe metabolic acidosis (pH < 7.2). 7 There was no difference in the primary outcome (composite of death from any cause by day 28 or 1 organ failure at day 7), however the bicarbonate group had significantly lower K⁺ levels and a lower requirement for renal replacement therapy. A recent retrospective study of the use of bicarbonate infusion in
patients with sepsis reported improved survival in the sub-group of patients with severe acidosis
associated with AKI stage 2 or 3.\textsuperscript{8}

There is no evidence to suggest that sodium bicarbonate is more effective at lowering serum $K^+$ as the
severity of metabolic acidosis increases. Changes in serum $K^+$ did not correlate with basal values of
plasma bicarbonate or blood pH.\textsuperscript{3,9} There is also no evidence to suggest that sodium bicarbonate is
more effective in patients as the severity of hyperkalaemia increases.\textsuperscript{5} Nevertheless, a recent report
advocates the administration of hypertonic sodium bicarbonate (100-250ml 8.4% solution) in patients
with metabolic acidosis (pH < 7.2) or in patients in whom intravenous calcium is deemed to be
contraindicated (e.g. hypercalcaemia).\textsuperscript{10}

Overall, the available evidence is limited and may not reflect the clinical response in patients with
hyperkalaemia in the context of acute kidney injury. The use of sodium bicarbonate comes with the
risk of sodium and fluid overload and the risks may outweigh any potential (unproven) benefits in this
patient group. The use of sodium bicarbonate in hyperkalaemic cardiac arrest is discussed in
Guideline 24.3.

References

1. Allon, M. and N. Shanklin, \textit{Effect of bicarbonate administration on plasma potassium in dialysis
p. 508-514.

2. Blumberg, A., et al., \textit{Effect of Various Therapeutic Approaches on Plasma Potassium and Major

3. Blumberg, A., P. Weidmann, and P. Ferrari, \textit{Effect of Prolonged Bicarbonate Administration on


5. Kim, H.J., et al., \textit{The acute therapy of hyperkalemia with the combined regimen of bicarbonate and

transcellular gradient in patients with renal failure: Effect of various therapeutic approaches}. East

7. Jaber, S., et al., \textit{Sodium bicarbonate therapy for patients with severe metabolic acidemia in the
intensive care unit (BICAR-ICU): a multicentre, open-label, randomised controlled, phase 3 trial}. The

8. Zhang, Z., et al., \textit{Effectiveness of sodium bicarbonate infusion on mortality in septic patients with

297-302.

Guideline 16.6.1 – Hyperkalaemia: STEP 3 – Remove $K^+$ from body; Potassium binders

We recommend that Sodium Zirconium Cyclosilicate is used in the emergency management of acute life-threatening hyperkalaemia (serum $K^+ \geq 6.5$ mmol/l). (1A)

Audit Measures

1. The proportion of patients with acute severe hyperkalaemia (serum $K^+ \geq 6.5$ mmol/l) treated with Sodium Zirconium Cyclosilicate [Audit Standard; 100%].

Rationale (Guideline 16.6.1)

Until recently, there had been no new advances in treatment of acute hyperkalaemia for decades. Sodium Zirconium Cyclosilicate (SZC) is a non-absorbed potassium binder that preferentially exchanges $H^+$ and $Na^+$ for $K^+$ and ammonium ions throughout the entire gastrointestinal tract.\(^1\) The $K^+$-binding capacity of SZC is up to 9 times greater than that of SPS.\(^2\)

The SZC clinical trials have been discussed in detail in Guidelines 10.1-10.3 and include three RCTs\(^3-5\) and one open label clinical trial.\(^6\) Major limitations are that all studies were performed in the stable out-patient setting and the threshold for treatment was lower than standard practice with few patients having a serum $K^+ \geq 6.0$ mmol/l.

### Table 26: Proportion of patients taking SZC 10g three times daily achieving restoration of normokalaemia ($K 3.5-5.0$ mmol/l) during acute phase.

<table>
<thead>
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</thead>
<tbody>
<tr>
<td>24 hours</td>
<td></td>
<td>66%</td>
<td>66%</td>
</tr>
<tr>
<td>48 hours</td>
<td>86.4%</td>
<td>88%</td>
<td>75%</td>
</tr>
<tr>
<td>72 hours</td>
<td></td>
<td></td>
<td>78%</td>
</tr>
</tbody>
</table>

SZC provides a potential option for severe acute hyperkalaemia for several reasons. It has a rapid onset of action within 1 hour.\(^1\) The median time to normalisation of serum $K^+$ is 2.2 hours and SZC lowers serum $K^+$ by 1.1 mmol/l within 48 hours.\(^5\) The ZS-003 and ZS-004 trials also demonstrated a greater $K^+$-lowering effect with increasing severity of hyperkalaemia.\(^4,5\) In patients with a serum $K^+ > 6.0$ mmol/l, SZC lowers serum $K^+$ by 1.5 mmol/l within 48 hours. The efficacy of SZC over the first 24-72 hours (Table 26), demonstrates that 66% of patients achieved normokalaemia within 24 hours.\(^5,6\) In contrast, the other oral $K^+$-lowering drugs (i.e. calcium resonium and Patiromer) are not recommended for acute management as they are too slow in onset or poorly tolerated.
NICE has approved the use of SZC as an option in the treatment acute life-threatening hyperkalaemia alongside standard care in hospitalised patients.

1 NICE has approved SZC as an option in the treatment of acute life-threatening hyperkalaemia alongside standard care in hospitalised patients.7 Given the lack of evidence of SZC in the acute setting, NICE assessed its efficacy in patients with clinically relevant hyperkalaemia. The number of patients with a serum K⁺ of 5.5-5.9 mmol/l was 38.8% in ZS-004 and 45% in ZS-005. The number of patients with K⁺ ≥ 6.0mmol/l was 15.1% in ZS-004 and 16.8% in ZS-005.7 A post-hoc analysis of the sub-group of patients with K⁺ ≥ 6.0 mmol/l in the ZS-004 and ZS-005 studies showed that most patients treated with SZC achieved a serum K⁺ between 4.0-6.0 mmol/l.7

2 The treatment threshold for ‘life-threatening’ hyperkalaemia is a serum K⁺ ≥ 6.5 mmol/l. SZC 10g three times daily can be used for up to 72 hours (correction phase), but if hyperkalaemia is not controlled by this time, it should be discontinued. NICE concluded that randomised evidence demonstrating improved survival was not needed in the context of treating life-threatening hyperkalaemia in emergency circumstances.7 The cost-effectiveness analysis suggested that SZC for acute hyperkalaemia is a good use of NHS resources.

3 Following the correction phase, the pharmaceutical company marketing authorisation suggests maintenance therapy with SZC. The starting dose of 5g daily may be up-titrated to a maximum dose of 10g daily or down-titrated to 5g alternate days with the aim of preventing recurrence.1 However, maintenance treatment is not consistent with current clinical practice and there is no evidence for this in the acute setting at present. Treatment with SZC beyond the first 72 hours (correction phase) will be guided by clinical circumstances.

4 Further research in the acute setting is required to demonstrate the need for maintenance therapy.

5 ENERGIZE is an ongoing Phase 2 (NCT03337477), multi-centre randomised, double-blind placebo controlled study to evaluate SZC as an adjunct to insulin-glucose in treatment of acute hyperkalaemia for normalisation of serum K⁺.8 The study includes patients with a serum K⁺ ≥ 5.8 mmol/l, although this is below the current treatment threshold (K⁺ ≥ 6.0 mmol/l) for insulin-glucose. Patients will receive SZC 10g three times daily over 10 hours (at 0, 4, and 10 hrs) during the treatment period of 24 hours. Patients will also receive standard care with insulin (0.1 units/kg) and glucose 25g.

6 The primary end-point is the mean absolute change in serum K⁺ from baseline until 4 hours after dosing with SZC/ placebo to assess the effect of SZC when added to standard care. Secondary end-points include serial K⁺ measurements, proportion of patients who achieved a serum K⁺ < 6.0 mmol/l and < 5.0 mmol/l at 4 hours without additional therapy and the proportion of patients requiring additional K⁺-lowering therapy within 4 hours of treatment.

7 The ENERGIZE trial may also help to address the role for SZC in treatment of moderate hyperkalaemia (K⁺ 6.0 – 6.4 mmol/l) alongside standard care (insulin-glucose). Further study is also warranted to determine whether SZC could be an alternative to insulin-glucose in this patient group. The main advantage of this strategy would be reducing the risk of hypoglycaemia in patients who are at a lower risk of arrhythmias.
Guideline 16.6.2 – Hyperkalaemia: STEP 3 – Remove K⁺ from body; Cation-exchange resin

We suggest that calcium resinum is not used in the emergency management of severe hyperkalaemia, but may be considered in patients with moderate hyperkalaemia. (2B)

Audit Measures

1. The frequency of bowel complications with the use of cation-exchange resins.

Rationale (Guideline 16.6.2)

Cation-exchange resins, sodium polystyrene sulfonate (SPS) or calcium polystyrene sulfonate (CPS) are cross-linked polymers with negatively charged structural units which entraps K⁺ in the distal colon in exchange for Ca²⁺. The most common resin used in hospitals in the UK is CPS, Calcium resinum®. The onset of action is slow (> 4 hours) and efficacy is unpredictable excluding its use in emergencies. It is also poorly tolerated due to taste and constipation. The most serious adverse effect of resins is intestinal necrosis.

Evidence in support for the use of cation-exchange resins in the treatment of hyperkalaemia is very limited and these drugs were approved before evidence-based practice was established. It is unclear whether the resins have a K⁺-lowering effect in isolation or whether this is caused by the induction of diarrhoea by cathartics. Multiple doses are required over several days, with the effect on lowering the serum K⁺ noted over 1 to 5 days. The Cochrane Review for the acute management of hyperkalaemia included no studies on resins. Resins play no role in the emergency management of severe hyperkalaemia.
Resins may be considered in patients with moderate hyperkalaemia in the acute setting (with no or mild ECG changes) where slower reduction in serum K⁺ may not compromise the patient. Nasir et al demonstrated equal efficacy of SPS and CPS in lowering serum K⁺ over a 3-day period in patients with CKD. Resins may also be used in combination with other strategies (i.e. insulin-glucose, low K⁺ diet), as an alternative to treating patients who are poor candidates for dialysis, or when dialysis is delayed.

The use of resins in chronic hyperkalaemia is discussed in the Community Section - Guideline 8.1. Another potassium binder, Patiromer, is licensed for the management of hyperkalaemia in European, but the outcome of the appraisal by NICE is awaited. Patiromer has been discussed in the Community section – Guideline 9.1.

References

Hyperkalaemia in Hospitalised Patient (Guidelines Hyperkalaemia 17.1 – 17.2) Blood monitoring

(Guidelines 17.1 – 17.2)

Guideline 17.1.1 – Hyperkalaemia: STEP 4 - Blood monitoring; serum potassium
We recommend that the serum K+ is monitored closely in all patients with hyperkalaemia to assess efficacy of treatment and to monitor for rebound hyperkalaemia after the initial response to treatment wanes. (1B)

Guideline 17.1.2 – Hyperkalaemia: STEP 4 - Blood monitoring; serum potassium
We suggest that serum K+ is assessed at least 1, 2, 4, 6 and 24 hours after identification and treatment of moderate or severe hyperkalaemia. (2C)

Audit measures
1. The proportion of patients in whom serum K+ was measured at least once within 2 hours of treatment for severe hyperkalaemia [Audit Standard: 100%].
2. The proportion of patients in whom a serum K+ was not performed within 6 hours of identification of hyperkalaemia [Audit Standard: 0%].

Rationale (Guidelines 17.1.1 – 17.1.2)
Insulin-glucose infusion and nebulised salbutamol are the most effective treatments in reducing serum K+ levels in current practice. The time to peak effect with insulin-glucose ranges from 30-60 minutes1,2,5 and for nebulised salbutamol from 30-90 minutes1,2,5-9. Therefore, the combined effect of these drugs can be assessed between 30-90 minutes after treatment. Their effects last for up to 4-6 hours. Sodium zirconium cyclosilicate (SZC) is now recommended in the treatment of severe hyperkalaemia (Guideline 16.6.1). The onset of action is within 1 hour and the median time to normalisation of serum K+ is 2.2 hours.11

The aim of treatment is to achieve rapid control with a serum K+ < 6.0 mmol/L within 2 hours of initiation of treatment. The peak efficacy of all three K+ -lowering drugs can be assessed at 1-2 hours. Therefore, measure serum K+ at 1 and 2 hours after initial treatment to determine if the K+ level has decreased sufficiently.
Further monitoring at 4 and 6 hours is required to assess for any rebound in serum K+ as the effects of drug therapy wears off.12-16 Measure the serum K+ at 24 hours to ensure that control of hyperkalaemia has been maintained.

References


**Guideline 17.2 – Hyperkalaemia: STEP 4 - Blood monitoring: blood glucose**

We recommend that the blood glucose concentration is monitored at regular intervals (0, 15, 30, 60, 90, 120, 180, 240, 360, 480 and 720 minutes) up to 12 hours after administration of insulin-glucose infusion in all patients with hyperkalaemia. (1C)

**Audit measure**

1. The proportion of patients who have at least one blood glucose test performed within 1 hour of completion of insulin-glucose infusion [Audit Standard: 100%].

2. The frequency of hypoglycaemia occurring in patients receiving treatment with insulin-glucose for hyperkalaemia.

**Rationale (Guideline 17.2)**

Hypoglycaemia, defined as a blood glucose of < 4.0 mmol/L, is the most common adverse event following insulin-glucose infusion for the treatment of hyperkalaemia. Even mild hypoglycaemia is associated with an increased risk of mortality in hospitalised patients. Severe hypoglycaemia, is defined as a blood glucose of < 2.8 mmol/L.
The clinical manifestations of hypoglycaemia tend to be progressive, but the early signs are not always
detected. Mild hypoglycaemia often presents with sweating, palpitations, tremor and hunger. Severe
hypoglycaemia results in more serious symptoms including confusion, coma or even death.\(^7\) The impact of
hypoglycaemia is independent of diabetic status and adverse outcomes have been shown in patients with
diabetes mellitus or without diabetes.\(^7,8\) One mechanism by which hypoglycaemia may be detrimental is by
reducing myocardial blood flow and this has been shown in patients with diabetes and in healthy adults.\(^9,10\)

Iatrogenic hypoglycaemia is a significant patient safety event, therefore should be anticipated with regular
blood glucose monitoring. Risk factors for hypoglycaemia are shown in Table 22, Guideline 17.3. The
incidence of hypoglycaemia appears to be lower in patients treated with 50g vs 25g glucose as initial
treatment as discussed in Guideline 16.3.\(^11\)

The majority of hypoglycaemic events occur between 2.0 to 3.5 hours after insulin-glucose infusion (Table
16, Guideline 16.3).\(^1,4,5,12\) Apel et al demonstrated that 75% of hypoglycaemic episodes occurred within 3
hours of insulin administration (median 2 hours) and persist for a median of 2 hours.\(^4\) However, in patients
without diabetes, hypoglycaemia may occur within 1 hour.\(^11\) The risk of hypoglycaemia persists for as late as
6 hours after administration of IV insulin.\(^1,4,5,12,13\) The Joint British Diabetes Societies for inpatient care has
advised blood glucose monitoring for 12 hours after insulin-glucose infusion for treatment of hyperkalaemia:
at least 3 times in the first hour followed by at least 6 further measurements over the subsequent 11 hours.
Recent studies suggest that variables related to treatment (dose of insulin, dose of glucose) and the baseline
clinical parameters (e.g. pre-treatment glucose) have a greater influence on the rate of hypoglycaemia than
non-modifiable baseline patient characteristics.\(^2,5\) Therefore, this is a potentially preventable adverse event.
The current guideline recommendation provides an increased glucose dose to the patients anticipated to be
at the greatest risk of hypoglycaemia (i.e. pre-treatment blood glucose < 7.0 mmol/l). This criteria will likely
overlap with other patient groups at risk including patients with low body weight, advanced age or renal
failure. Frequent blood glucose monitoring remains the cornerstone of preventing hypoglycaemia.

References

1. Schafer, S., et al., Incidence of hypoglycemia following insulin-based acute stabilization of
2. Scott, N.L., et al., Hypoglycemia as a complication of intravenous insulin to treat hyperkalemia in
5. Coca, A., et al., Hypoglycemia following intravenous insulin plus glucose for hyperkalemia in
6. Bruno, A., et al., Normal glucose values are associated with a lower risk of mortality in hospitalized
and association with glycemia medication usage: Secondary analysis of the ACCORD clinical trial
8. Wei, M., et al., Low fasting plasma glucose level as a predictor of cardiovascular disease and all-


**Hyperkalaemia in Hospitalised Patient (Guidelines Hyperkalaemia 18.1 – 18.6) Referral to specialist services and escalation of care (Guidelines 18.1 – 18.6)**

**Guideline 18.1 - Hyperkalaemia: Specialist Referral**
We suggest that patients with severe hyperkalaemia (serum K+ ≥ 6.5 mmol/L) be referred to their local renal or critical care team for an urgent opinion, guided by the clinical scenario and its persistence after initial medical treatment. (2C)

**Guideline 18.2 - Hyperkalaemia: Referral to critical care services**
We recommend that for patients with severe hyperkalaemia, and where there is no provision of renal services on site, referral is made to the local critical care team in the first instance, guided by the clinical scenario and established local policies. (1C)

**Guideline 18.3 - Hyperkalaemia: Escalation of care**
We recommend that patients are referred to the critical care team by a senior member of the referring team if escalation of care is required from the outset or if the patient fails to respond to initial treatment. (1B)

**Guideline 18.4 - Hyperkalaemia: Treatment facilities - Critical care**
We recommend that patients with severe hyperkalaemia and problems with airway, breathing, circulation and/or conscious level, be referred to the local critical care team in the first instance. (1C)

**Guideline 18.5 – Hyperkalaemia: Treatment facilities – Ward or High dependency area**
We recommend that stable patients with severe hyperkalaemia be admitted to an area with facilities for continuous cardiac monitoring which are sufficiently staffed to support clinical monitoring and treatment, including an acute medical unit, renal unit, coronary care unit, HDU or ICU depending on local facilities or practice. (1C)

**Guideline 18.6 – Hyperkalaemia: RRT in treatment of hyperkalaemia**
We recommend that the decision on timing, suitability and modality for initiation of RRT in patients with life-threatening hyperkalaemia, either from the outset or resistant to initial medical therapy, is taken urgently by a nephrologist or critical care specialist. (1C)
Audit measures
1. The incidence of patients requiring emergency dialysis for severe hyperkalaemia.
2. The frequency of hospital transfer to facilitate emergency dialysis for treatment of severe hyperkalaemia.

Rationale (Guidelines 18.1 – 18.6)
Hyperkalaemia may be present on hospital admission or develop during the course of admission due to acute illness or alterations in medications. It may be feasible to manage most cases of mild to moderate hyperkalaemia on a non-renal ward. In many of these cases, hyperkalaemia resolves after treating the precipitant (e.g. discontinuing a RAASi drug).

Patients with moderate hyperkalaemia who are at risk of further rise (e.g. oliguria, rhabdomyolysis) and those with severe hyperkalaemia should be assessed by a senior clinician (i.e. registrar or consultant grade). Referral to the renal or critical care team should be guided by the cause of hyperkalaemia, condition of the patient, response to initial medical treatment and availability of services locally.¹

To facilitate specialist referral, information on the patient history, haemodynamic status, NEWS2, medication, biochemistry and ECG findings should be readily available. Urine output in patients with AKI is very valuable if available. A history of advanced kidney disease or dialysis-dependency will allow appropriate triage to an area with dialysis facilities. Use the Hyperkalaemia Algorithm (Appendix 7) to assist specialist referral.

Given the risk of arrhythmias, patients with severe hyperkalaemia require continuous cardiac monitoring and need to be triaged to an area with these facilities.² Patient triage is guided by the need for basic or advanced organ support. For patients who can be cared for within a renal unit, the need for escalation of care (Guidelines 18.3) and safety of patient transfer if required (Guidelines 19.1 – 19.2) must also be considered. The management plan, ceiling of care (i.e. ward, HDU or ICU) and resuscitation status should be documented early in the course of admission for all patients. Patients requiring acute renal replacement therapy (e.g. haemodialysis or haemofiltration) meet the criteria for Level 2 care, and this can be delivered in a renal unit or critical care unit. Patients receiving a minimum of two organ support (e.g. renal and cardiovascular or respiratory support) meet the criteria for Level 3 care.³

The decision to refer for escalation of care should take place after the initial resuscitation measures are underway, the response to treatment has been assessed and after consultation with senior medical staff. This decision should take into account the likelihood of survival (e.g. reversible illness), extent of comorbidity, accurate assessment of pre-morbid functional status, and the patient’s wishes. Inappropriate admission to a critical care area may create false hope and unrealistic expectations for patients and their families.

Postoperative patients, especially after major surgery, may exhibit acidosis and/or fluid and electrolyte shifts. Significant haemorrhage and need for massive blood transfusion may increase risk of hyperkalaemia, among other abnormalities, and these patients are best cared for in a higher care level area.⁴ Rhabdomyolysis may be associated with significant metabolic acidosis and hyperkalaemia, warranting care of these patients in a critical care environment.
Severe hyperkalaemia can cause abrupt cardiac arrest, sometimes without warning ECG changes. It is a key indication for emergency RRT. Where a decision has been taken to treat with RRT, it should be performed with due regard for potential deterioration. The provision of RRT in renal units and ICUs varies across the country with respect to the timing of initiation, prescribed dose, and modality of RRT available. Conventional intermittent haemodialysis (IHD) is thought to be the most effective method for K⁺ removal, but continuous venovenous haemofiltration (CVVH) and continuous venovenous haemodiafiltration (CVVHDF) are more frequently available in ICUs in the UK. Nearly 90% of UK ICUs have facilities for RRT.

Traditionally, it has been thought that CVVH is not as efficient as IHD at removing K⁺ and therefore was not generally recommended as the first line extracorporeal therapy in hyperkalaemic patients. However, CVVH and CVVHDF are acceptable RRT techniques for management of hyperkalaemia, albeit with a slower initial reduction in serum K⁺ than with IHD, but followed by sustained correction of electrolyte abnormalities. Potassium removal with IHD decreases after 2 hours and rebound occurs after dialysis is stopped.

The main advantages of continuous methods are their potential benefits in haemodynamically unstable patients, lower risk of rebound hyperkalaemia (given the continuous nature and kinetics of solute removal), ability to tailor K⁺ removal according to serum K⁺ measurements and, importantly, the wide availability in ICUs.

References

4 **Guideline 19.1 - Hyperkalaemia: Transfer to renal services**
We suggest that transfer to renal services be considered in clinically stable patients in whom hyperkalaemia cannot be controlled (i.e. serum $K^+ < 6.5$ mmol/L) using medical measures, particularly in the presence of advanced or oliguric renal failure (either AKI or CKD). (2C)

**Guideline 19.2 - Hyperkalaemia: Minimum standards for safe patient transfer**
We suggest that any inter- or intra-hospital patient transfer is coordinated by senior clinicians and follows national guidelines. (2B)

**Rationale (Guidelines 19.1 – 19.2)**
The most important aspect of patient transfer is ensuring safety. There are three key steps in optimising patient transfer - firstly, to decide if transfer is absolutely necessary; secondly, to optimise the patient prior to transfer; and thirdly, to coordinate and perform the transfer itself.\(^1\)

The decision to transfer the patient with hyperkalaemia will be guided by the availability of renal services locally. Intra-hospital patient transfer from a ward or emergency department to a high dependency area, renal unit or ICU within the referring hospital is less complicated, but still requires good communication and coordination. Cardiac monitoring and resuscitation equipment are essential for the transfer of patients with hyperkalaemia, either within or between hospitals.

Inter-hospital transfer to the nearest renal unit or ICU may be required for definitive management. This decision must be made by the responsible consultant, in conjunction with consultant colleagues from relevant specialities in both the referring and receiving hospitals.\(^2\) The timing and urgency of transfer will be decided by the nephrologist and/or intensivist. The decision to accept a transferred patient should be made by a consultant in the receiving unit.

Pre-transfer stabilisation is essential for all patients.\(^{1,3}\) Following appropriate medical therapy for hyperkalaemia, the response to treatment should be assessed with repeat observations, biochemistry, blood glucose and ECG prior to transfer. We suggest that a patient should not, in general, be transferred between hospitals if the serum $K^+$ is $\geq 6.5$ mmol/L, though other factors (in particular, the location of intensive care and dialysis facilities) will occasionally over-ride this consideration. Critical care review is essential for patients with any concern regarding oxygenation, ventilation or haemodynamic instability.
The organisation of the patient transfer itself requires a coordinated approach and liaison with the receiving team to ensure that they are prepared for the patient’s arrival. The use of a transfer checklist, protocols and skilled staff reduce mortality. The clinical risk of the transfer and the level of competence required by escorting staff will be guided by the patient’s condition. Every hospital should have suitable arrangements in place for providing patient transfer including trained personnel, equipment, and drugs to treat the specific problem. Hospitals should form transfer networks to co-ordinate and manage clinically indicated transfers. Record keeping is a legal requirement for all patient transfers. Clear records should be maintained at all stages of transfer including the patient’s condition, reason for transfer, names of referring and accepting consultants, clinical status prior to transfer, during transfer and on arrival. Arrangements should be in place for the return of staff and equipment after transfer. The procedure for safe patient transfer is summarised in Table 27.

Prompt clinical re-assessment by the receiving medical team is required following transfer, including observations, bloods and ECG. The K⁺-lowering effect of medical treatment for hyperkalaemia is temporary (<6 hours), therefore repeat bloods to assess for rebound hyperkalaemia is important (Guideline 18.1). The potential for hypoglycaemia up to 6 hours after administration of insulin-glucose should be considered and blood glucose checked on arrival.

### Table 27: Minimum standards for safe patient transfer.


<table>
<thead>
<tr>
<th>Requirement</th>
<th>Details</th>
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<tbody>
<tr>
<td>1. Decision regarding need for patient transfer</td>
<td></td>
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<tr>
<td>2. Review of investigations and treatment and ensure clear management plan</td>
<td></td>
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<tr>
<td>3. Pre-transfer assessment and stabilisation</td>
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<tr>
<td>4. Good communication between referring team, critical care and receiving teams</td>
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<tr>
<td>5. Arrangement of ambulance for inter-hospital transfer</td>
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<tr>
<td>6. Consider staff (medical &amp; nursing), drugs (iv calcium, salbutamol neules, 20% dextrose in event of hypoglycaemia) and equipment (cardiac monitor/ defibrillator, blood glucose monitor) required for safe transfer</td>
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<tr>
<td>7. Ensure medical and nursing records are complete and are kept confidential, as governed by the Data Protection Act 2018</td>
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<tr>
<td>8. Inform patient’s relatives of transfer</td>
<td></td>
</tr>
<tr>
<td>9. Provide ongoing treatment and care as necessary during transfer, including maintaining clinical appropriate records</td>
<td></td>
</tr>
<tr>
<td>10. Maintaining patient dignity</td>
<td></td>
</tr>
<tr>
<td>11. Hand-over to receiving team</td>
<td></td>
</tr>
<tr>
<td>12. Return of transfer staff and equipment</td>
<td></td>
</tr>
</tbody>
</table>

Prompt clinical re-assessment by the receiving medical team is required following transfer, including observations, bloods and ECG. The K⁺-lowering effect of medical treatment for hyperkalaemia is temporary (<6 hours), therefore repeat bloods to assess for rebound hyperkalaemia is important (Guideline 18.1). The potential for hypoglycaemia up to 6 hours after administration of insulin-glucose should be considered and blood glucose checked on arrival.

Hyperkalaemia in Hospitalised Patient (Guidelines Hyperkalaemia 20.1 – 20.3) Prevention (Guidelines 20.1 – 20.3)

Guideline 20.1 – Hyperkalaemia: Prevention of hyperkalaemia in hospitalised patients
We recommend that the need for prescribed medication which can cause hyperkalaemia are reviewed in the context of the current illness and level of renal function both on and during hospital admission. (1B)

Guideline 20.2 – Hyperkalaemia: Prevention of hyperkalaemia in hospitalised patients
We recommend that community blood monitoring is arranged on discharge for all patients who have required treatment for hyperkalaemia during hospital admission. (1B)

Guideline 20.3 – Hyperkalaemia: Prevention of hyperkalaemia in hospitalised patients
We recommend that the risk of recurrence of hyperkalaemia is considered before reinstating previous medication that may have contributed to the episode. (1B)

Audit Measures
1. The frequency of hyperkalaemia developing beyond 24 hours of hospital admission.
2. The frequency of prescribed drugs potentially contributing to hyperkalaemia.

Rationale (Guideline 20.1 – 20.3)
The NCEPOD Report (2009), ‘Adding Insult to Injury’, highlighted the risk of AKI in acute hospital admissions.¹ Acute illness (e.g. sepsis, diarrhoea and vomiting) with systemic hypotension can result in reduced renal blood flow and ultimately AKI with hyperkalaemia. Patients may present with hyperkalaemia at the time of hospital admission or it may develop after hospital admission in patients in whom the K⁺ level was normal on arrival. Clinicians should be alert to the potential development of hyperkalaemia in the context of intercurrent illness in patients receiving drugs known to exacerbate hyperkalaemia. Early recognition and treatment of AKI can reduce morbidity and mortality.
Hyperkalaemia often occurs after hospital admission. A study of in-patients with hyperkalaemia showed that 33.3% of cases developed after hospital admission. Most cases were mild, but 15.4% were moderate or severe ($K^+ \geq 6.0$ mmol/l). AKI was present in 73% of cases with a pre-renal cause in 50% of these. The aetiology was often multifactorial, but hyperkalaemia was more common in the elderly and patients with diabetes and/or CKD. Prescribed medication was implicated in 76% of patients receiving potentially hyperkalaemia-inducing drugs (e.g. RAASi) and 55% of these patients were taking two or more of such medications. Furthermore, this study demonstrated that the severity of hyperkalaemia was found to be significantly correlated ($p<0.01$) with the number of potentially hyperkalaemia-inducing drugs used concurrently. Medications frequently implicated in hyperkalaemia are summarised in Table 28.

Hospital acquired hyperkalaemia is common in the elderly, aged 75 years or more. Robert et al investigated the factors predisposing to the development of hyperkalaemia occurring 3 or more days after hospital admission.

### Table 28: Drugs commonly associate with hyperkalaemia (Adapted from 2,3)

#### Drugs that affect aldosterone secretion
- ACE inhibitors
- Angiotensin Receptor Blockers
- Non-steroidal anti-inflammatory drugs
- Calcineurin inhibitors
- Heparins
- Antifungals (e.g.: ketoconazole, fluconazole and itraconazole)

#### Drugs that block aldosterone binding to mineralocorticoïd receptor (MRA)
- Spironolactone
- Eplerenone
- Drospirenone

#### Drugs that inhibit activity of epithelial sodium channel
- Potassium sparing diuretics (e.g. amiloride and triamterene)
- Trimethoprim
- Pentamidine

#### Drugs that alter transmembrane potassium movement
- $\beta$-blockers
- Digoxin
- Intravenous cationic amino acids
- Hyperosmolar solutions (e.g. mannitol, glucose)
- Suxamethonium

#### Potassium containing agents
- Potassium supplements (e.g. Sando-K®, Kay-Cee L Liquid ®)
- Salt substitutes
- Herbal medicines (e.g. alfalfa, dandelion, horsetail, milkweed and nettle)
- Stored red blood cells
admission in an elderly cohort.\textsuperscript{5} Hyperkalaemia developed during 4.5% of hospital admissions and 27% of episodes were considered severe (K\textsuperscript+ ≥ 6.0 mmol/l). AKI was present in 51% of cases and hyperkalaemia-inducing drugs were implicated in 80.5% of cases.\textsuperscript{5} Overall, 79.9% of hyperkalaemic events were potentially avoidable.

Hyperkalaemia is particularly common in patients with CKD. Furuland et al reported hyperkalaemia (K\textsuperscript+ > 5.0 mmol/l) in 48.4% of patients admitted with renal impairment with multiple episodes occurring in 28.8% of patients with CKD Stage 3-5.\textsuperscript{6} The main risk factors for recurrence were decline in renal function, diabetes and treatment with RAASI drugs. Patients with hyperkalaemia were shown to have a longer duration of hospital stay and higher mortality risk than those without hyperkalaemia.\textsuperscript{6}

Pharmacists can also play a role in the prevention of hospital-acquired hyperkalaemia during medicines reconciliation. Reviewing drug therapy and dosage early in the course of hospital admission, especially in patients at risk of AKI, allows time to consider if any medications should be withheld.\textsuperscript{7,8}

Patients may also be at risk of hyperkalaemia after hospital discharge. Amongst patients who were normokalaemic and prescribed a RAAS inhibitor on discharge from hospital, 12.3% of patients have been shown to develop hyperkalaemia during the early period after discharge.\textsuperscript{9} Risk increases in the presence of impaired renal function, use of drug combinations that can exacerbate hyperkalaemia or in patients with a higher baseline K\textsuperscript+ level.\textsuperscript{9} Patient education and community monitoring should be in place before hospital discharge.

Re-instating RAASI or other medication following an acute illness associated with hyperkalaemia is another important consideration. This decision balances the risk-benefit ratio and original indication of the drug (e.g. heart failure).\textsuperscript{10} It is reasonable to consider re-introduction and re-titration of the drug, on recovery, in patients who previously had stable renal function and K\textsuperscript+ levels prior to the acute illness.\textsuperscript{9} Whether treatment is re-started in hospital or intended in the community, clear communication with primary care or specialist clinic (e.g. Heart Failure service) is required on hospital discharge.

References

12(9): p. e0184402.


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**Hyperkalaemia in Hospital (Guidelines 21.1) Treatment algorithm: Hospital (Guideline 21.1)**

**Guideline 21.1 – Hyperkalaemia; Algorithm in Hospital**

We recommend that hyperkalaemia in hospitalised patients is managed using the treatment algorithm which provides guidance on the medical therapies and the need for initiation of renal replacement therapy. (1C)

**Rationale (Guideline 21.1)**

Treatment algorithms provide a systematic approach for managing medical emergencies and can improve consistency in clinical practice. This strategy has been utilised in resuscitation for decades and the provision of clear user-friendly instructions is helpful in stressful and time-critical situations. Algorithms may also be used as an aide memoire and as a teaching tool.

The response to hyperkalaemia in hospitalised patients is guided by its severity and ECG appearances. The algorithm provides actions to be taken at different time intervals (i.e. first 15-30 minutes, next 30-60 minutes) to avoid delay. It follows the 5-step approach in treating hyperkalaemia to ensure that each priority is addressed as shown in Appendix 7.

The 2019 algorithm provides guidance for the new treatment recommendations:

- 10% glucose infusion following insulin-glucose for patients with a pre-treatment blood glucose < 7.0 mmol/l
- Sodium zirconium cyclosilicate for life-threatening hyperkalaemia
Section 3

Management of Hyperkalaemia in Resuscitation
Introduction

Hyperkalaemia is an uncommon, but potentially reversible cause of cardiac arrest.\textsuperscript{1,2} It most often occurs in patients with pre-existing renal disease or in the context of an acute kidney injury. Patients receiving long-term haemodialysis (HD) are most at risk of hyperkalaemia. Cardiac arrest can occur in hospital, within an out-patient dialysis unit or out of hospital, but hyperkalaemia should be considered in all settings in patients at risk. Patients on long-term HD are one of the highest risk groups for out-of-hospital cardiac arrest, occurring 20 times more frequently than in the general population.\textsuperscript{3}

The reported incidence of in-hospital hyperkalaemic cardiac arrest is variable. Wallmuller et al found hyperkalaemia as the primary aetiology in only 1% of in-hospital cardiac arrests (n=1041) although it was the most common metabolic cause (47%).\textsuperscript{4} In contrast, Wang et al\textsuperscript{5} reported an incidence of 12% (n=1114) and Saarinen et al\textsuperscript{6} reported an incidence of 13% (n=104) in patients with PEA as the initial rhythm following in-hospital cardiac arrest (IHCA).

Patients with all stages of CKD have a higher prevalence of cardiovascular disease, but the mortality risk is estimated to be 57% higher in patients with eGFR < 60 ml/min per 1.73 m\textsuperscript{2}\textsuperscript{7} compared with the general population without CKD.\textsuperscript{7} Cardiovascular disease is also highly prevalent in the dialysis population. The added insult of hyperkalaemia in patients with pre-existing heart disease may contribute to sudden death in dialysis patients, presumably from cardiac arrest.

Several studies have reported a high incidence of sudden cardiac death (SCD) in haemodialysis patients.\textsuperscript{8-10} There is no consistent definition of SCD, but in a systematic review, it was defined as death due to cardiac arrest occurring suddenly within 1 hour of witnessed symptom onset or within 24 hours of the patient last being well.\textsuperscript{11} In the Dialysis Outcomes and Practice Patterns Study (DOPPS) assessing modifiable practices associated with sudden death among HD patients, sudden death was defined as death due to arrhythmia, cardiac arrest and/ or hyperkalaemia.\textsuperscript{12} The US Renal Data System (USRDS), the largest dialysis registry, has reported an increase in SCD from 25% in 2012 to 37% in 2015.\textsuperscript{13} Three clinical trials in patients with ESRD (4D,\textsuperscript{14} HEMO\textsuperscript{15} and EVOLVE\textsuperscript{16}), have reported an incidence of SCD ranging from 22-26% consistent with the findings from the USRDS database. SCD is also the commonest cause of death in children on HD, reported to be as high as 25%, suggesting that the aetiology of SCD may include factors other than the traditional cardiovascular risk factors.\textsuperscript{10} Potential risk factors for SCD in HD patients are summarised in Table 29.\textsuperscript{8,12,17-24}
Table 29: Potential risk factors for sudden cardiac death in patients with ESRD.

<table>
<thead>
<tr>
<th>Risk Factors for Sudden death in Haemodialysis Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrolyte disturbances: Hyperkalaemia, hypokalaemia</td>
</tr>
<tr>
<td>Excess volume shifts during dialysis</td>
</tr>
<tr>
<td>2-day inter-dialytic interval (i.e. Mondays for patients dialysing on Mon/Wed/ Fri schedule)</td>
</tr>
<tr>
<td>Low potassium dialysate fluid (0 or 1 mmol solutions)</td>
</tr>
<tr>
<td>Non-compliance with diet and dialysis attendance or regimen</td>
</tr>
<tr>
<td>Low calcium dialysate</td>
</tr>
<tr>
<td>Dialysis treatment time &lt; 210 minutes</td>
</tr>
<tr>
<td>Venous catheter for vascular access</td>
</tr>
<tr>
<td>Patient factors – age, comorbidities, poor nutritional status</td>
</tr>
<tr>
<td>Cardiac factors – left ventricular hypertrophy, systolic and diastolic dysfunction, vascular stiffness</td>
</tr>
</tbody>
</table>

Pre-dialysis hyperkalaemia and hypokalaemia have both been shown to be associated with higher all-cause mortality. Pun et al demonstrated a 49% increase in risk of cardiac arrest with each 1 mmol/l decrease in serum K⁺ below 5.1 mmol/l and a 38% increased risk with each 1 mmol/l increase above 5.1 mmol/l. There was no advantage of using a low K⁺ dialysate. The intermittent nature of HD treatment is a further consideration. Bleyer et al demonstrated that HD patients are susceptible to SCD in the first 12 hours from start of the HD session, but the highest risk period is the last 12 hours of the 2-day inter-dialytic interval. In this study, hyperkalaemia (K⁺ ≥ 6.0 mmol/l) was present in 6.5% of patients with SCD.

Optimising and controlling K⁺ levels in dialysis patients is challenging. Kovesdy et al demonstrated greater survival in maintenance HD patients with a pre-dialysis serum K⁺ of 4.6 – 5.3 mmol/l. The conventional thrice-weekly HD schedule is difficult to overcome, but evidence suggests that careful dialysis prescription with the avoidance of low K⁺ dialysates and fistula access reduces the risk of cardiac arrest. Other factors associated with a favourable outcome after cardiac arrest in dialysis patients were the use beta-blockers, RAASi and calcium channel blockers at the time of the event.

This section will cover the epidemiology and special considerations of resuscitation in patients receiving dialysis. An overview of resuscitation in dialysis patients provides a foundation for developing practice in patients with hyperkalaemic cardiac arrest.
References


Hyperkalaemia in Resuscitation (Guideline 22.1) Hyperkalaemic cardiac arrest – special circumstance (Guideline 22.1)

Guideline 22.1 – Hyperkalaemia; Cardiac Arrest - special circumstance

We recommend that hyperkalaemia is considered in all patients who have a cardiac arrest, as part of identifying and treating a reversible cause using the ‘4 Hs and 4 Ts’ approach. (1A)

Audit Measure

1. All cardiac arrests should be audited – hospital participation in the National Cardiac Arrest Audit is encouraged as part of quality improvement and benchmarking.

Rationale (Guidelines 22.1)

Hyperkalaemia is an important and potentially reversible cause of cardiac arrest, therefore should be considered in all patients, particularly in the presence of renal failure. Recognition of hyperkalaemia as the aetiology cardiac arrest may be pre-arrest or during the resuscitation attempt. Early detection of hyperkalaemia before cardiac arrest provides a window of opportunity to prevent arrhythmias or cardiac arrest, but delays in treatment are well recognised.

The National Patient Safety Alert resource for hyperkalaemia (2018) highlighted 35 cases of cardiac arrest in patients with hyperkalaemia which were reported due to concerns related to treatment and/or monitoring.\(^1\) Wang et al (2016) reported that 20% (5/25) of dialysis patients who suffered a hyperkalaemia cardiac arrest did not receive either intravenous calcium or sodium bicarbonate.\(^2\) Saarinen et al (2011) investigated the impact of appropriate treatment in cases where a reversible cause of cardiac arrest was identified and found that no patients received appropriate treatment when the aetiology was hyperkalaemia.\(^3\)

The ECG may be helpful in assessing the risk of cardiac arrest in patients with hyperkalaemia. Severe hyperkalaemia causes a progressive decrease in myocardial conductivity and excitability, thereby blocking cardiac conduction globally and maintaining cardiac standstill.\(^4\) However, the progressive ECG changes frequently described may not be present and the first sign of hyperkalaemia may be cardiac arrest. An et al reported that approximately 20% of patients presented with cardiac arrest at the time of diagnosis of hyperkalaemia.\(^5\) Durfei et al demonstrated that arrhythmias or cardiac arrest...
occurred within 6 hours of the presenting ECG in 15% of patients with serum K⁺ ≥ 6.5 mmol/l before IV calcium was administered and before K⁺-lowering treatment was initiated in all but one patient. The probability of cardiac arrest is likely to correlate with the severity of hyperkalaemia, but the threshold for VF in hyperkalaemia appears to vary from patient to patient. For these reasons, arrhythmias should be anticipated and cardiac monitoring is essential for all patients with severe hyperkalaemia or in the presence of ECG changes. Prompt treatment of hyperkalaemia can avoid arrhythmias and cardiac arrest. Avoid delays in treatment and seek specialist help early.

References


Rationale (Guidelines 23.1 – 23.3)

The incidence of cardiac arrest in dialysis patients is higher than in the general population, therefore vigilance and training is essential. The incidence of cardiac arrest in the out-patient setting ranges from 3.4 – 7.8 / 100,000 HD sessions as shown in Table 30. Little data is available on the incidence of in-hospital cardiac arrest in patients on long-term HD. Wong et al reported a rate of 1.4 events per 1000 in-hospital days with a survival to hospital discharge of 22%. An early study of in-hospital CPR in patients with ESRD showed a survival to hospital discharge of only 8%.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of HD sessions</th>
<th>Number of cardiac arrests</th>
<th>Incidence of CPR /100,000 dialysis sessions</th>
<th>Survival to Hospital Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karnik 2001¹</td>
<td>5,744,708</td>
<td>400</td>
<td>7</td>
<td>NA</td>
</tr>
<tr>
<td>La France 2006³</td>
<td>307,553</td>
<td>24</td>
<td>7.8</td>
<td>75%</td>
</tr>
<tr>
<td>Davis 2008²</td>
<td>2,611,119</td>
<td>110</td>
<td>3.4</td>
<td>24%</td>
</tr>
</tbody>
</table>

Table 30: Incidence and outcome of cardiac arrest in out-patient dialysis units.

NA – not available.

Within the out-patient setting, most cardiac arrests occur during the dialysis session as shown in Table 31. Karnik et al reported that the mean time into dialysis at cardiac arrest was 123 ± 77 minutes. The mean time to cardiac arrest was shorter in patients with central venous catheters compared with arteriovenous fistulas. Electrolyte and fluid shifts may also play a role in the timing of events.

<table>
<thead>
<tr>
<th>Study</th>
<th>N=</th>
<th>Before HD</th>
<th>During HD</th>
<th>After HD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karnik 2001¹</td>
<td>400</td>
<td>7%</td>
<td>81%</td>
<td>12%</td>
</tr>
<tr>
<td>Davis 2008²</td>
<td>152</td>
<td>10%</td>
<td>70%</td>
<td>20%</td>
</tr>
<tr>
<td>La France 2006³</td>
<td>38</td>
<td>8%</td>
<td>78%</td>
<td>14%</td>
</tr>
</tbody>
</table>

Table 31: Timing of cardiac arrest during dialysis in out-patient centres.

HD – haemodialysis

Shockable cardiac arrest rhythms (pulseless VT or VF), have been reported to be more common in the dialysis population than non-shockable rhythms (PEA or asystole). Davis et al demonstrated a shockable primary arrest rhythm in 65% of arrests. Karnik et al reported the arrest rhythm in only 16% of cases but of these, the initial rhythm was VF in 42%, VT in 20% and asystole in 15%. LaFrance et al reported data on the first cardiac arrest rhythm in only 12 patients - VF/VT (6/12 patients), PEA/asystole (6/12 patients).
### Table 32: Outcome of cardiac arrest in patients receiving haemodialysis (HD) in an outpatient dialysis facility versus all in-hospital cardiac arrests.

<table>
<thead>
<tr>
<th>Study</th>
<th>PEA/Asystole</th>
<th>VF/VT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events (%)</td>
<td>ROSC Achieved (%)</td>
</tr>
<tr>
<td><strong>Davis 2008</strong>&lt;sup&gt;2&lt;/sup&gt;</td>
<td>35</td>
<td>37</td>
</tr>
<tr>
<td>HD patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Out-patient HD unit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n= 152</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>La France 2006</strong>&lt;sup&gt;3&lt;/sup&gt;</td>
<td><em>50</em></td>
<td>NA</td>
</tr>
<tr>
<td>HD patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Out-patient HD unit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n= 24</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Meaney 2010</strong>&lt;sup&gt;6&lt;/sup&gt;</td>
<td>76</td>
<td>42</td>
</tr>
<tr>
<td>US gen pop IHCA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n= 51,919</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nolan 2014</strong>&lt;sup&gt;7&lt;/sup&gt;</td>
<td>72</td>
<td>26</td>
</tr>
<tr>
<td>UK gen pop IHCA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n= 23,554</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PEA – pulseless electrical activity; VF – ventricular fibrillation; VT – ventricular tachycardia; ROSC – return of spontaneous circulation; IHCA – In hospital cardiac arrest

* Data available for primary cardiac arrest rhythm in only 12/24 patients

Shockable cardiac arrest rhythms are associated with a higher incidence of return of spontaneous circulation (ROSC) and survival to hospital discharge in the general population as well as in patients with ESRD as shown in Table 32. Non-shockable cardiac arrest rhythms are associated with a poor outcome. Registry data in the general population in the UK and USA demonstrate survival to hospital discharge of 11% in patients presenting with PEA/ asystole.<sup>6,7</sup> In contrast, Wang et al reported a non-shockable rhythm in 92.7% of IHCA in hyperkalaemic patients which in part accounts for the survival to hospital discharge of only 3.7% in this study.<sup>6</sup>

Shockable cardiac arrest rhythms are more common in haemodialysis patients than in the general population.

Survival after cardiac arrest is better with shockable rhythms.
Modifications to ALS in Renal Failure

The universal ALS algorithm applies to all patients and the initial steps of recognition of cardiac arrest, initiating high-quality CPR with minimal interruption, and attempting defibrillation if required, are independent of the cause of cardiac arrest.

During CPR, reversible causes should be considered and treated. If the serum potassium is ≥ 6.5 mmol/L before or early in the resuscitation attempt, hyperkalaemia should be considered to be the potential cause of the cardiac arrest. Hyperkalaemia occurring late in the resuscitation attempt may be the consequence of progressive acidosis and hypoxia, and may not be the precipitant of the cardiac arrest or require specific intervention.

Special considerations during resuscitation in dialysis patients is shown in Table 33. The cardiac arrest team may have little knowledge of these considerations in dialysis patients, therefore expert help is essential for optimising care and safety.

The practice of defibrillation in HD units is variable across the UK and many staff are unaware of the safety considerations. The ERC Guidelines (2015) recommends disconnection from dialysis equipment prior to defibrillation, unless defibrillator-proof, in keeping with the International Electrotechnical Committee (IEC) standards 60601-2-4.
Automated external defibrillators (AED) are now widely available for non-expert use worldwide to facilitate early defibrillation. Many dialysis centres are predominantly nurse-led. For this reason, the National Kidney Foundation KDOQI Guidelines (2005) has recommended that all dialysis facilities should have on-site capability of defibrillation and the use of AEDs is the simplest and most cost effective device.\textsuperscript{11} The implementation of AEDs within dialysis facilities was mandated within one year of this guideline. Shortly thereafter, Lehrich et al investigated the use of AEDs in dialysis centres and reported that the presence of AEDs alone did not independently improve survival and suggested that further measures are required to affect outcome.\textsuperscript{12}

The impact of dialysis unit staff initiating resuscitation before arrival of paramedics has recently been reported to assess outcomes of staff-led CPR and AED use. In this study of OHCA in out-patient dialysis clinics (n=398 events), dialysis staff initiated CPR in 81% of events, but applied an AED before paramedics arrived in only 52.3%.\textsuperscript{13} The timing of events in relation to dialysis is not available. When dialysis staff were the first to apply the AED, there was a greater proportion of shockable rhythms (41% vs 25%), reinforcing early application of AED. The odds of survival to hospital discharge was 3-
fold higher with staff-initiated CPR, but there was only a non-significant trend towards improved survival to discharge with staff-initiated AED. This may be explained by the low usage of AED by nursing staff.

Cardiac arrest in dialysis centres are witnessed events.

CPR should be initiated by nursing staff.

First responders require regular training in use of an AED.

Within out-patient dialysis centres, cardiac arrest occurs most often during dialysis thereby are witnessed events. A shockable rhythm is more common, therefore early defibrillation using safe practice should be attempted. Patients with a shockable rhythm have the best chance of survival, therefore prompt and effective action by first responders is crucial.

References
Hyperkalaemia in Resuscitation (Guidelines 24.1 – 24.4) Treatment: Calcium chloride (Guideline 24.1)

Guideline 24.1 – Cardiac Arrest: Treatment - Intravenous calcium

We recommend that intravenous calcium chloride is administered if hyperkalaemia is known or suspected to be the cause of cardiac arrest. (1A)

Audit measures

1. The proportion of patients treated with intravenous calcium for hyperkalaemic cardiac arrest.

Rationale (Guidelines 24.1)

This guideline extrapolates from management in the non-arrested patient, recognising the sparsity of evidence for the use of specific medical interventions in hyperkalaemic cardiac arrest. Intravenous calcium is widely recommended for treatment of hyperkalaemia in the context of toxic ECG changes, arrhythmias and cardiac arrest. However, in the absence of hyperkalaemia or other specific indication, IV calcium can have deleterious effects in cardiac arrest with coronary vasospasm and worsening cerebral hypoxic damage.

The quality of evidence for the general use of IV calcium in cardiac arrest was reviewed using the 2010 International Liaison Committee on Resuscitation (ILCOR) evidence evaluation process. Only 10 studies were adequate for inclusion and only two studies had a blinded randomised design. The analysis was further limited by the wide variation in sample size, reported data and outcomes. The conclusion was that there is no evidence that IV calcium during CPR improves survival after cardiac arrest. Its role in specific settings of hyperkalaemia, calcium channel blocker intoxication, hypocalcaemia and hypermagnesaemia remain unclear due to limited data.

More recently, Wang et al (2016) have reported the outcome of IV calcium in hyperkalaemic IHCA. In this study, 56% of patients received IV calcium either alone (4/109; 4%) or more frequently in combination with sodium bicarbonate (57/109; 52%). ROSC was achieved in only one patient who received IV calcium alone (1/4; 25%), but this patient did not survive > 24 hours. In comparison, ROSC was achieved in a higher proportion of patients who received both drugs (12/57; 21%).

Despite the limited evidence-base, IV calcium has become standard practice for preventing and treating arrhythmias in hyperkalaemia. Its effect is evidenced by the improvement in the ECG changes in the non-arrested patient. Its effects last only 30-60 minutes, therefore further doses may be required if hyperkalaemia persists.
References


Treatment: Insulin-glucose (Guideline 24.2)

Guideline 24.2.1 – Cardiac Arrest: Treatment – Insulin-glucose

We suggest that 10 units soluble insulin and 25g glucose is administered if hyperkalaemia is known or suspected to be the cause of cardiac arrest. (2C)

Guideline 24.2.2 – Cardiac Arrest: Treatment – Insulin-glucose

We suggest 10% glucose infusion be initiated if the blood glucose is < 7.0 mmol/l at any stage during the resuscitation attempt.

Audit measure

1. The proportion of patients treated with insulin-glucose for hyperkalaemic cardiac arrest.

Rationale (Guidelines 24.2.1 – Guideline 24.2.2)

Insulin and glucose is the most effective treatment for hyperkalaemia in the non-arrested patient as discussed in Guideline 16.3. The onset of action is within 15 minutes with a peak reduction in serum K+ ranging from 0.65 – 1.0 mmol/l by 60 minutes. The main adverse effect is hypoglycaemia, therefore blood glucose monitoring is essential.

International resuscitation guidelines have historically recommended the use of insulin-glucose for hyperkalaemic cardiac arrest based on treatment in the non-arrested patient. The efficacy of insulin-glucose is augmented with the use of salbutamol and SZC in the non-arrested patient. In cardiac arrest, the use of adrenaline has an analogous effect to salbutamol and will likely enhance K+-lowering, but unfortunately there are no clinical trials to confirm this.

Cardiac arrest is induced to facilitate cardiopulmonary bypass. The standard technique for induction of cardiac arrest includes the delivery of a high concentration of K+ to the myocardium. Therefore, hyperkalaemia frequently occurs after cardioplegia. This scenario is essentially an iatrogenic hyperkalaemic cardiac arrest. The 2019 European Guidelines on cardiopulmonary bypass in adult cardiac surgery suggests treatment with IV calcium and insulin-glucose if the serum K+ exceeds 6.5 – 7.0 mmol/l.

Given the sparsity of evidence for insulin-glucose in cardiac arrest, it is relevant to assess their effects on the ischaemic heart. The ischaemic heart is an energy-depleted organ. Glucose assumes a central role for energy production in the ischaemic heart and the relative contribution of glucose to energy production is highly dependent on the severity of ischaemia. Myocardial glucose extraction is inversely related to coronary blood flow. During prolonged severe myocardial ischaemia, the decline of glucose uptake may be attenuated by an increase of extracellular glucose concentration or the addition of insulin thereby protecting the heart against ischaemic injury. This theory has been applied during cardiac surgery with the administration of insulin and glucose to induce a state of ‘hyperinsulinaemic normoglycaemia’, thereby promoting myocardial glucose uptake/ utilisation, augmenting myocardial efficiency and increasing cardiac output.

The optimal dose of insulin and glucose during cardiac surgery is unclear. Morgan et al suggested 30-50g per 10 units of insulin. Davis et al suggested that if the glucose dose is 0.5 – 2g/kg, then the appropriate ratio is 1 unit insulin to 4g glucose. Kocoglu et al suggested 2g of glucose for 1 unit of insulin, but hypoglycaemia was common and required treatment with 10% glucose. These regimens were intended for cardiac protection during cardioplegia (given in high doses) rather than treatment of hyperkalaemia, but suggests
that a glucose dose > 25g (with 10 units insulin) is needed to reduce risk of hypoglycaemia. Given the importance of glucose to myocardial function, hypoglycaemia would compound the effects of ischaemia during cardiac arrest.

The ERC recommendation for insulin-glucose during cardiac arrest has changed over the past two decades. The ERC Resuscitation Guidelines (2000, 2005) for managing life-threatening electrolyte abnormalities recommended 10 units insulin with 50g glucose. Subsequent ERC guidelines (2010, 2015) altered the dose of glucose to 25g based on the available evidence and the Cochrane review on the emergency interventions for hyperkalaemia published in 2005.

The current RA Hyperkalaemia guideline (2019) recommends 10 units insulin with 25g glucose for treating acute hyperkalaemia following a comprehensive review in Guideline 16.3. Although several recent studies investigating the risk of iatrogenic hypoglycaemia appear to show equivalent efficacy with low-dose insulin (5 units), Garcia et al found a trend towards greater efficacy with 10 units insulin compared with 5 units in treating patients with a serum K ≥ 6.0 mmol/l. An analysis of the K⁺-lowering efficacy in studies using 10 units insulin also showed a trend towards greater efficacy with worsening hyperkalaemia (Figure 6). These findings warrant further investigation before a reduction in the dose of insulin can be recommended given the potential consequences for patients with life-threatening hyperkalaemia.

This review also found that the most consistent risk factor for iatrogenic hypoglycaemia after insulin-glucose was a pre-treatment blood glucose < 7.0 mmol/l. On this basis, an infusion of 10% glucose (50ml/hr for 6 hours) was suggested to avoid hypoglycaemia. The data provided above for cardiac surgery also suggested that 25g glucose was insufficient to prevent hypoglycaemia when administered with 10 units insulin and in one study 10% glucose infusion was required.

Hyperkalaemic cardiac arrest usually requires prolonged resuscitation and often occurs in patients with other risk factors for iatrogenic hypoglycaemia including renal failure. Preventing hypoglycaemia is also important in cardiac arrest. The baseline blood glucose may not be available, therefore initiation of a 10% glucose infusion should be considered if the blood glucose is < 7.0 mmol/l at any stage during the resuscitation attempt.

References


Guideline 24.3 – Hyperkalaemia; Cardiac Arrest – Sodium bicarbonate Treatment: Sodium bicarbonate (Guideline 24.3)

We suggest that sodium bicarbonate is administered if hyperkalaemia is known or suspected to be the cause of cardiac arrest. (2C)

Audit measure

The proportion of patients treated with sodium bicarbonate for hyperkalaemic cardiac arrest.

Rationale (Guidelines 24.3)

The use of sodium bicarbonate in cardiac arrest has evolved over the past few decades. The rationale for using sodium bicarbonate (SB) is to counteract the worsening metabolic acidosis in cardiac arrest as a result of hypoxia, poor perfusion and increased lactate production. The potential deleterious effects of using sodium bicarbonate in cardiac arrest are an increase in intracellular acidosis, reduced cardiac output and worsening tissue acidosis. Sodium bicarbonate was commonly used in the early resuscitation guidelines in the 1970’s – 1980’s, but use declined in the 1990’s in light of concerns related to potential harm. A review by Adgey et al in 1998 recommended that treatment with sodium bicarbonate should be reserved for cardiac arrest in one of four settings: 1) severe acidosis (pH < 7.1), 2) prolonged cardiac arrest (> 10-20 minutes), 3) hyperkalaemia and 4) overdose of tricyclic antidepressants. More recently, Weng et al (2013) showed no benefit of sodium bicarbonate during prolonged CPR. Velissaris et al (2016) conducted a comprehensive review of the literature and found that there was little evidence to support the routine use of sodium bicarbonate during CPR. Clinical practice is guided by international resuscitation guidelines. The 2010 ACLS Guidelines for adults published by the American Heart Association stated that ‘the routine use of sodium bicarbonate is not recommended for patients in cardiac arrest’, but supported its use in hyperkalaemia and tricyclic overdose with or without cardiac arrest. Similarly, the European Resuscitation Council (ERC) guidelines (2015) have also recommended the use of sodium bicarbonate for these specific indications.

Although there is little evidence that sodium bicarbonate lowers serum K+, the rationale for its use in hyperkalaemia cardiac arrest is to mitigate the effects of metabolic acidosis which exacerbates hyperkalaemia. The largest study of hyperkalaemic cardiac arrest undertaken by Wang et al (2016) demonstrated that approximately 82% of patients received SB either alone (32/109; 29%) or in combination with intravenous calcium (57/ 109; 52%). SB was administered early in the course of resuscitation (within 10 minutes) and ROSC was achieved in 47% of patients who received SB alone and 21% who received both drugs.

The treatment of hyperkalaemic cardiac arrest is multi-modal and both American and European resuscitation guidelines recommend the use of sodium bicarbonate in the setting of hyperkalaemic cardiac arrest.

References

Guideline 24.4 – Hyperkalaemia; Cardiac Arrest – Initiation of dialysis during CPR  
Treatment: Initiation of dialysis during cardiac arrest (Guideline 24.4)

We suggest that renal replacement therapy with ongoing CPR is considered for hyperkalaemic cardiac arrest, if hyperkalaemia is resistant to medical therapy. (2C)

Audit measure

The proportion of patients with refractory hyperkalaemic cardiac arrest treated with dialysis initiation during CPR.

Rationale (Guidelines 24.4)

Survival after hyperkalaemic cardiac arrest is dependent on urgent control of the serum K⁺ level. Intravenous calcium does not alter serum K⁺ level and there is little evidence that sodium bicarbonate significantly lowers serum K⁺. Therefore, the only drugs administered during CPR which may lower the serum K⁺ are insulin-glucose and adrenaline.

In the largest study of hyperkalaemic cardiac arrest (n=109), dialysis was not instituted during CPR.¹ Patients were analysed by the severity of hyperkalaemia - K⁺ 6.5 – 7.9 mmol/l (72/ 109; 66%), K⁺ 7.9 – 9.4 mmol/l (30/109; 28%) and K⁺ > 9.4 mmol/l (7/ 109; 6%). Overall, ROSC > 20 minutes was achieved in 37% of patients, but only 4 patients (3.7%) survived to hospital discharge. The incidence of ROSC declined with increasing severity of hyperkalaemia and was achieved in: 32 patients with a serum K⁺ 6.5 – 7.9 mmol/l (44%), 7 patients with a serum K⁺ 7.9 – 9.4 mmol/l (23%) and in only one patient with a serum K⁺ > 9.4 mmol/l (14%). No patients with a K⁺ > 9.4 mmol/l survived beyond 24 hours. The authors suggested that there might be a threshold for medical therapies and beyond this level, dialysis may be an alternative option.

There have been numerous case reports of successful resuscitation following hyperkalaemic cardiac arrest in adults and children as shown in Table 34.²⁻¹⁴ Survival after both pulseless VT or VF and asystole or PEA cardiac arrest has been reported. In many of these reports, patients were refractory to defibrillation until the potassium was controlled. Resuscitation efforts were frequently prolonged, and in some published cases, extra-corporeal membrane oxygenation (ECMO) support was used to augment systemic perfusion.⁶¹¹¹⁴ There were no neurological sequelae in most of these cases despite prolonged resuscitation attempts, although this may reflect publication bias.
Success has been reported using all modes of RRT: haemodialysis (HD), haemofiltration (CVVH), haemodiafiltration (HDF), as well as peritoneal dialysis (PD). Dialysis has also been used successfully for re-warming in accidental hypothermia without cardiac arrest\textsuperscript{15-17} and in cardiac arrest.\textsuperscript{18,19} In one of these cases, manual CPR was performed for 5.5 hours and CVVH was achieved with no technical difficulties for over 3 hours.\textsuperscript{18} This patient made a full neurological recovery, returned to work within 6 weeks and has become a parent.

The severity of hyperkalaemia is a good indicator of the likelihood of achieving and sustaining ROSC. Analysis of the case reports shown above in Table 34 reveals that the mean serum $K^+$ at the time of cardiac arrest was 9.2 mmol/l (range 8.3-10.2 mmol/l). The mean serum $K^+$ at ROSC was 6.1 mmol/l (range 4.2-7.6 mmol/l) in patients who received a haemodialysis modality. Therefore, the mean reduction in $K^+$ required to achieve ROSC was 3.01 mmol/l (range 1.3-5.0 mmol/l) and this would be difficult to achieve with drugs alone.

The term ‘extreme hyperkalaemia’ has been used in the literature.\textsuperscript{[20-22]} It has been defined as a serum $K^+$ > 9.0 mmol/l.\textsuperscript{[23]} Wang et al reported no survivors in patients with a serum $K^+$ > 9.4 mmol/l treated without dialysis during CPR.\textsuperscript{1} In contrast, in the series of patients treated with dialysis during CPR (Table 34), 9/15 (60%) had a serum $K^+$ > 9.0 mmol/l and 7/9 (78%) survived with full neurological recovery. This would suggest that dialysis during CPR can improve the outcome for patients with extreme hyperkalaemia.
The ERC Guidelines (2015) suggest considering dialysis initiation for hyperkalaemic cardiac arrest resistant to medical therapy. This recommendation was based on several considerations:

- Firstly, the reports of successful outcomes of hyperkalaemic cardiac arrest have demonstrated that it is technically feasible to dialyse during CPR. With the aid of the blood pump, a blood flow rate of up to 200 ml/min can be achieved with a chest compression rate of 100/min.
- Secondly, it seems logical to utilise the most effective intervention for the most serious complication of hyperkalaemia, particularly when unresponsive to medical therapies.

### Table 34: Outcome of hyperkalaemic cardiac arrest with RRT during CPR.

<table>
<thead>
<tr>
<th>Study</th>
<th>Age (yrs)</th>
<th>Arrest Rhythm</th>
<th>[K] at arrest (mmol/L)</th>
<th>CPR pre-RRT (min)</th>
<th>Dialysis modality</th>
<th>Dialysis duration (min)</th>
<th>[K] at ROSC (mmol/L)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gomez-Arnau 1981</td>
<td>36</td>
<td>Asystole</td>
<td>9.7</td>
<td>70</td>
<td>HD</td>
<td>75</td>
<td>6.6</td>
<td>Full recovery</td>
</tr>
<tr>
<td>Torrecilla 1989</td>
<td>53</td>
<td>Asystole</td>
<td>10.2</td>
<td>15</td>
<td>HD</td>
<td>90</td>
<td>6.5</td>
<td>Full recovery</td>
</tr>
<tr>
<td>Lin 1994</td>
<td>27</td>
<td>VT</td>
<td>9.6</td>
<td>55</td>
<td>HD</td>
<td>25</td>
<td>7.6</td>
<td>Full recovery</td>
</tr>
<tr>
<td></td>
<td>58</td>
<td>VF</td>
<td>8.5</td>
<td>35</td>
<td>HD</td>
<td>30</td>
<td>7.2</td>
<td>Full recovery</td>
</tr>
<tr>
<td></td>
<td>77</td>
<td>VT</td>
<td>8.5</td>
<td>155</td>
<td>HD</td>
<td>25</td>
<td>5.2</td>
<td>Died</td>
</tr>
<tr>
<td>Costa 1994</td>
<td>57</td>
<td>Asystole</td>
<td>9.6</td>
<td>15</td>
<td>HD</td>
<td>95</td>
<td>7.2</td>
<td>Survived (3 days)</td>
</tr>
<tr>
<td>Lee 1994</td>
<td>11</td>
<td>Asystole</td>
<td>10.2</td>
<td>140</td>
<td>HF on CPB</td>
<td>ns</td>
<td>ns</td>
<td>Full recovery</td>
</tr>
<tr>
<td>Jackson 1996</td>
<td>16</td>
<td>Asystole</td>
<td>9.8</td>
<td>165</td>
<td>PD</td>
<td>60</td>
<td>4.3</td>
<td>Full recovery</td>
</tr>
<tr>
<td>Kao 2000</td>
<td>68</td>
<td>VT</td>
<td>8.3</td>
<td>150</td>
<td>HD</td>
<td>40</td>
<td>5.1</td>
<td>Full recovery</td>
</tr>
<tr>
<td>Schummer 2000</td>
<td>68</td>
<td>ns</td>
<td>9.0</td>
<td>ns</td>
<td>HDF</td>
<td>15</td>
<td>ns</td>
<td>Full recovery</td>
</tr>
<tr>
<td>Iwanczuk 2008</td>
<td>53</td>
<td>ns</td>
<td>8.5</td>
<td>ns</td>
<td>HD</td>
<td>40</td>
<td>5.4</td>
<td>Full recovery</td>
</tr>
<tr>
<td>Chiu 2014</td>
<td>66</td>
<td>VF</td>
<td>8.6</td>
<td>ns</td>
<td>CVVH on VA-ECMO</td>
<td>ns</td>
<td>ns</td>
<td>Full recovery</td>
</tr>
<tr>
<td>Tijssen 2017</td>
<td>17</td>
<td>Asystole</td>
<td>8.3</td>
<td>ns</td>
<td>CRRT on ECMO</td>
<td>ns</td>
<td>ns</td>
<td>Full recovery</td>
</tr>
<tr>
<td>Kim 2019</td>
<td>13</td>
<td>Sine wave</td>
<td>9.6</td>
<td>90</td>
<td>HF on VA-ECMO</td>
<td>ns</td>
<td>ns</td>
<td>Full recovery</td>
</tr>
<tr>
<td>Klingkowski 2019</td>
<td>5</td>
<td>VF</td>
<td>9.2</td>
<td>ns</td>
<td>CVVH and ECMO</td>
<td>25 (ECMO prolonged)</td>
<td>4.2</td>
<td>Full recovery</td>
</tr>
</tbody>
</table>

(ns = not specified)
Thirdly, other invasive procedures are recommended for other special circumstances of cardiac arrest - cardiopulmonary bypass for hypothermia, chest drain insertion for tension pneumothorax and pericardiocentesis for cardiac tamponade. ECMO has also become increasingly utilised in resuscitation, including in hyperkalaemic cardiac arrest. Therefore, there is a clear rationale to considering dialysis in refractory hyperkalaemia.

Fourthly, survival in patients with extreme hyperkalaemia is very low without the initiation of dialysis during CPR.

Lastly, the evidence base for other interventions for hyperkalaemia, particularly calcium salts, is also limited, but has become standard medical practice.

The practical approach to resuscitation for refractory hyperkalaemic cardiac arrest is not included in renal specialist training programs, therefore most renal physicians may be reluctant to consider this largely because of inexperience and the expectation of technique failure. However, the resuscitation team will be even less knowledgeable about dialysis and the management of hyperkalaemia in cardiac arrest and will look to the renal team for guidance. Given the sparsity of information available, a review of the modifications in advanced life support in dialysis patients was previously reported. An update and summary of the procedure is outlined in Table 35.

Once CPR is underway, initiate medical treatment for hyperkalaemia and seek expert help early during the resuscitation attempt. If hyperkalaemia is suspected (e.g. dialysis patient or pre-arrest ECG changes), treat even before the serum $K^+$ is known. Monitor serum $K^+$ (using blood gas analyser) every 15 minutes to assess response to treatment. Monitor blood glucose to assess for hypoglycaemia and start an infusion of 10% glucose if blood glucose level falls below 7.0 mmol/l.

Next, consider if medical treatment alone is likely to be effective. Ultimately, the severity of hyperkalaemia, the initial response to medical therapy, the suitability of the patient and the availability of dialysis facilities provide the best guide for considering dialysis in cardiac arrest.

Next, plan ahead and consider the timing for initiation of dialysis. Analysis of the case reports suggest that the mean duration of CPR before initiation of dialysis was 89 minutes (range 15-165 minutes). The mean duration of dialysis to achieve ROSC was 50 minutes (range 15-95 minutes). There appeared to be an inverse relationship between duration of CPR and duration of dialysis required to achieve ROSC. Given that dialysis initiation will require some planning, it is reasonable to start preparations early and to consider initiation if ROSC is not achieved within 15 minutes.

Anticipate that the resuscitation attempt will be prolonged. Therefore the use of mechanical devices to perform chest compressions (e.g. LUCAS2, Autopulse) should be considered. Where available, ECMO should be considered, as this has been used effectively to permit initiation of RRT to correct severe hyperkalaemia whilst optimising perfusion. There is growing evidence over the last three decades that chest compression can support adequate blood flow for RRT during CPR. The increasing availability of ECMO also offers greater opportunities for prolonged cardiac arrest management and these modalities can be used simultaneously. Given that defibrillation is frequently unsuccessful until the serum $K^+$ is controlled, analogous to rewarming for hypothermic cardiac arrest, RRT should be considered for refractory hyperkalaemic cardiac arrest.

"Like most things in life, you may not always succeed, but failure is usually guaranteed if you do not try."
Table 35: Summary of procedure for initiation of dialysis during CPR.

<table>
<thead>
<tr>
<th><strong>Initial Approach</strong></th>
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<tbody>
<tr>
<td>- Follow ALS Algorithm</td>
</tr>
<tr>
<td>- Give medical treatment for hyperkalaemia during CPR as per Hyperkalaemic Cardiac Arrest Algorithm</td>
</tr>
<tr>
<td>- Refer for Expert Help</td>
</tr>
<tr>
<td>- Use mechanical device for chest compressions</td>
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<table>
<thead>
<tr>
<th><strong>Preparation for Dialysis Initiation</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- If ROSC not achieved within 15 minutes consider initiating dialysis</td>
</tr>
<tr>
<td>- Choose RRT modality depending on local availability</td>
</tr>
<tr>
<td>- Use renal trained nurse (preferably two) to deliver dialysis treatment</td>
</tr>
<tr>
<td>- Prepare dialysis machine with a low K⁺ dialysate</td>
</tr>
<tr>
<td>- Get vascular access (if necessary) whilst machine is being prepared - use femoral vein with ultrasound guidance; easy access and away from CPR</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Initiation of Dialysis during CPR</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Give fluid bolus (250ml) once connected to dialysis machine and record starting time</td>
</tr>
<tr>
<td>- Started with pump speed of 100ml/min and gradually increase aiming for 200ml/min</td>
</tr>
<tr>
<td>- Give anticoagulation unless contraindicated (e.g. history of trauma)</td>
</tr>
<tr>
<td>- Check K⁺ level every 15 min using arterial blood gas analyser and monitor blood glucose</td>
</tr>
<tr>
<td>- Give further IV Calcium Chloride if resuscitation is prolonged</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Defibrillation</strong></th>
</tr>
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<tbody>
<tr>
<td>- When serum K⁺ &lt; 7.0 mmol/L, consider attempting defibrillation if shockable rhythm</td>
</tr>
<tr>
<td>- Do not perform defibrillation during dialysis unless machine is defibrillation-proof</td>
</tr>
<tr>
<td>- Disconnect patient from dialysis machine just before defibrillation, then immediately reconnect</td>
</tr>
<tr>
<td>- If ROSC achieved, resume dialysis until serum K⁺ &lt; 6.5 mmol/L to maintain ROSC</td>
</tr>
<tr>
<td>- If ROSC not achieved, resume dialysis until serum K⁺ &lt; 6.5 mmol/L and attempt defibrillation again if shockable rhythm</td>
</tr>
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<table>
<thead>
<tr>
<th><strong>Post-resuscitation care</strong></th>
</tr>
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<tbody>
<tr>
<td>- Re-assess serum K⁺, blood glucose and ECG when ROSC achieved</td>
</tr>
<tr>
<td>- Terminate dialysis when serum K⁺ controlled (K⁺ &lt; 6.5 mmol/L) and cardiac rhythm stable</td>
</tr>
<tr>
<td>- Record time of termination of dialysis and serum K⁺ at ROSC</td>
</tr>
<tr>
<td>- Transfer to ICU</td>
</tr>
</tbody>
</table>
References


Hyperkalaemia in Resuscitation (Guidelines 25.1 – 25.2) Prevention (Guidelines 25.1 – 25.2)

Guideline 25.1 – Hyperkalaemia; Prevention of Cardiac Arrest in Hyperkalaemia

We recommend that hyperkalaemia is treated urgently in patients with severe hyperkalaemia (K+ ≥ 6.5 mmol/l) and in those with ECG changes suggestive of severe hyperkalaemia. (1C)

Guideline 25.2 – Hyperkalaemia; Prevention of Cardiac Arrest in Hyperkalaemia

We recommend continuous cardiac monitoring for patients with severe hyperkalaemia (K+ ≥ 6.5 mmol/l) in a setting appropriate for the level of care required. (1C)

Audit Measure

1. Number of patients with a serum K+ ≤ 6.0 mmol/l within 2 hours of treatment for severe hyperkalaemia.

Rationale (Guidelines 25.1 – 25.2)

The outcome of hyperkalaemic cardiac arrest is generally poor and unpredictable, therefore efforts to avoid its occurrence is the best approach. Primary measures to prevent the development of hyperkalaemia in patients at risk is a key step. Patients with renal failure, heart failure and/or diabetes have a high risk, particularly when treated with RAASi drugs. Cautious prescribing and blood monitoring is essential in these patients.

Preventing cardiac arrest in patients who have become hyperkalaemic is dependent on prompt recognition and treatment. The initial clinical presentation may be overshadowed by the acute illness, but severe
hyperkalaemia is likely to be more immediately life-threatening. Limb weakness is an ominous sign. Look for toxic ECG changes which may precede cardiac arrest - wide QRS complex, bradycardia or sine wave (Figure 4), but some patients may have a normal ECG despite severe hyperkalaemia. The rationale for cardiac monitoring is to detect arrhythmias before cardiac arrest ensues, therefore a higher level of care is required.

Delays in treatment are well recognised and has resulted in patient harm. The potential for clinical deterioration may not be appreciated by medical or nursing staff prior to cardiac arrest. Time is frequently lost whilst awaiting repeat bloods to confirm hyperkalaemia even in the presence of renal failure and ECG changes. Refer for specialist advice early in patients with severe hyperkalaemia with ECG changes, end-stage renal disease, oliguric AKI, and in patients who do not respond to medical treatment.

Treat severe hyperkalaemia as a medical emergency.

IV calcium is a crucial step in the prevention of arrhythmias and cardiac arrest in hyperkalaemia. It is important to re-assess the ECG after administration of IV calcium as a further dose may be necessary if toxic changes persist. Continuous cardiac monitoring is essential. Vigilance is also required as toxic ECG changes may recur when the effects of the drug have worn off after approximately 30-60 minutes. IV calcium may buy time, but does not lower the serum K⁺. Therefore, other therapeutic measures should not be delayed.

Adverse events related to severe hyperkalaemia has been evaluated to determine if the ECG is helpful in risk stratification. Durfey et al retrospectively assessed the initial ECG, laboratory values, patient demographics and adverse events within 6 hours of the presenting ECG. The study included 188 patients with a serum K⁺ ≥ 6.5 mmol/l (mean K⁺ 7.1 mmol/l). Adverse events occurred in 15% of patients including symptomatic bradycardia (n=22), VT (n=2), CPR (n=2) and death (n=4). All of these events occurred prior to administration of IV calcium and all but one occurred before administration of K⁺-lowering medication. This highlights the importance of timely treatment to prevent arrhythmias and cardiac arrest.

Another common pitfall in the treatment of hyperkalaemia is the lack of blood monitoring after initiating medical treatment. If the serum K⁺ is not repeated at approximately one hour after treatment when the drugs have taken its maximum effect, then the efficacy of treatment cannot be assessed. Patients who are refractory to medical treatment are potentially at risk of cardiac arrest. Furthermore, there is a tendency for rebound hyperkalaemia once the effects of insulin-glucose and salbutamol have worn off. Failure to repeat the serum K⁺ at 4-6 hours will miss this rebound and could result in arrhythmias or cardiac arrest. Rebound also occurs after dialysis and may be exaggerated if temporising drugs have been used.

There are a few fallacies related to hyperkalaemia that require clarification:

- Patients with pacemakers are not protected from hyperkalaemic cardiac arrest. Indeed, pacemaker failure has been well documented in this circumstance.
- The presence of a normal ECG in the context of severe hyperkalaemia is not protective against arrhythmias.
• Severe hyperkalaemia can occur in the presence of near normal renal function, but may be assumed to be spurious. An urgent ECG and repeat blood sample using a blood gas analyser should confirm the presence of hyperkalaemia.

• Patients receiving longterm haemodialysis do not have a ‘tolerance’ to severe hyperkalaemia and are also at risk of cardiac arrest. Medical treatment will only temporarily lower the serum $K^+$, therefore urgent dialysis is indicated.

References


Hyperkalaemia in Resuscitation (Guidelines 26.1) Treatment algorithm: Resuscitation (Guideline 26.1)

Guideline 26.1 – Hyperkalaemia; Algorithm in Cardiac Arrest
We recommend that cardiac arrest attributable to hyperkalaemia is managed using the treatment algorithm which provides guidance on the medical therapies and the need for initiation of renal replacement therapy during CPR. (1C)

Rationale
Hyperkalaemia is a potentially reversible cause of cardiac arrest, but achieving and sustaining ROSC is dependent on controlling the serum $K^+$ level. In this way, this special circumstance is analogous to hypothermic cardiac arrest. There are fewer drug therapy options for controlling hyperkalaemia during cardiac arrest (Guidelines 24.1 - 24.3) and the degree of $K^+$-lowering required to achieve ROSC may not be achievable with drugs alone (Guideline 24.4). The hyperkalaemia algorithm outlines the modifications to ALS and the specific interventions to address hyperkalaemia as illustrated in Appendix 8.
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Appendices

1. Stages of Chronic Kidney Disease

2. Oral potassium lowering drugs.

3. Trials of oral potassium lowering drugs

4. Drug administration and safety
   A. Intravenous Calcium – Chloride and Gluconate solutions
   B. Insulin-glucose infusion
   C. Salbutamol
   D. Patiromer
   E. Sodium zirconium cyclosilicate
   F. Calcium resonium

5. ECG in Hyperkalaemia – sine wave.

6. Algorithm – Management of Hyperkalaemia in the Community.

7. Algorithm – Management of Hyperkalaemia in Hospital.

Appendix 1: Stages of CKD (KDOQI Guidelines)\(^1\)

<table>
<thead>
<tr>
<th>Stage</th>
<th>eGFR</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≥ 90</td>
<td>Kidney damage with normal or ↑GFR</td>
</tr>
<tr>
<td>2</td>
<td>60-89</td>
<td>Kidney damage with mild ↓GFR</td>
</tr>
<tr>
<td>3</td>
<td>30-59</td>
<td>Moderate ↓GFR</td>
</tr>
<tr>
<td>4</td>
<td>15-29</td>
<td>Severe ↓GFR</td>
</tr>
<tr>
<td>5</td>
<td>&lt;15 (or dialysis)</td>
<td>Kidney failure</td>
</tr>
</tbody>
</table>

eGFR – estimated glomerular filtration rate.

Notes
Patients in stages 1 and 2 must have evidence of kidney damage identified on imaging studies (e.g. structural abnormality) or abnormalities in blood or urine (e.g. haematuria and/or proteinuria).

Reference
### Appendix 2: Oral potassium lowering drugs.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Calcium resonium</th>
<th>Patiromer</th>
<th>SZC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>Entraps $K^+$ in exchange for $Ca^{2+}$</td>
<td>Non-specific binding of $K^+$ in exchange for $Ca^{2+}$</td>
<td>Selective $K^+$ binding in exchange for $Na^+$</td>
</tr>
<tr>
<td><strong>Site of action</strong></td>
<td>Distal Colon</td>
<td>Distal colon</td>
<td>Entire intestinal tract</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>Oral or rectal</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>15-60g/day</td>
<td>8.4-25.2 g/day</td>
<td>2.5-30 g/day</td>
</tr>
<tr>
<td><strong>Onset of effect</strong></td>
<td>&gt;4 hours</td>
<td>4-7 hours</td>
<td>1 hour</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td>Unpredictable and variable</td>
<td>$-1.01 \text{ mmol/l in 4 weeks [OPAL-HK]}$</td>
<td>$-1.1 \text{ mmol/l in 48 hours [ZS-003, ZS-004]}$ Median time to normalisation of serum $K^+$ is 2.2 hours [ZS-004]</td>
</tr>
<tr>
<td><strong>Common adverse effects</strong></td>
<td>Gastrointestinal disorders Hypokalaemia</td>
<td>Gastrointestinal disorders Hypokalaemia Hypomagnesaemia</td>
<td>Gastrointestinal disorders Hypokalaemia Oedema</td>
</tr>
<tr>
<td><strong>Serious adverse effects</strong></td>
<td>Colonic necrosis</td>
<td>No episodes of colonic perforation or necrosis reported</td>
<td>No episodes of colonic perforation or necrosis reported</td>
</tr>
<tr>
<td><strong>FDA Approval</strong></td>
<td>1958</td>
<td>2015</td>
<td>2018</td>
</tr>
<tr>
<td><strong>NICE Appraisal status</strong></td>
<td>N/A</td>
<td>Pending</td>
<td>Approved</td>
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</table>

Comparison between potassium-binding agents for treatment of hyperkalaemia.
## Appendix 3: Trials of oral potassium lowering drugs

<table>
<thead>
<tr>
<th>STUDY</th>
<th>N=</th>
<th>INTERVENTION</th>
<th>CKD (eGFR &lt;60)</th>
<th>DIABETES</th>
<th>HEART FAILURE</th>
<th>RAASi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lepage 2015 RCT</td>
<td>33</td>
<td>SPS</td>
<td>100%</td>
<td>72%</td>
<td>9%</td>
<td>76%</td>
</tr>
<tr>
<td>Nasir 2014 RCT</td>
<td>97</td>
<td>CPS SPS</td>
<td>100%</td>
<td>65%</td>
<td>NA</td>
<td>0% (excluded)</td>
</tr>
<tr>
<td>Gruy-Kapral 1998 RCT</td>
<td>6</td>
<td>SPS</td>
<td>HD</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Ash 2015 Phase II RCT</td>
<td>90</td>
<td>SZC</td>
<td>100%</td>
<td>56%</td>
<td>NA</td>
<td>62%</td>
</tr>
<tr>
<td>Packman 2015 Phase III RCT</td>
<td>753</td>
<td>SZC</td>
<td>75%</td>
<td>60%</td>
<td>40%</td>
<td>67%</td>
</tr>
<tr>
<td>Kosiborod 2014 Phase III RCT</td>
<td>258</td>
<td>SZC</td>
<td>66%</td>
<td>66%</td>
<td>36%</td>
<td>70%</td>
</tr>
<tr>
<td>Fishbane 2017 Phase II RCT</td>
<td>751</td>
<td>SZC</td>
<td>73%</td>
<td>62%</td>
<td>38%</td>
<td>64%</td>
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<tr>
<td>Pitt 2011 PEARL-HF (RCT)</td>
<td>104</td>
<td>Patiromer</td>
<td>27%</td>
<td>32%</td>
<td>100%</td>
<td>NA</td>
</tr>
<tr>
<td>Bakris 2015 AMETHYST-DN (RCT)</td>
<td>222</td>
<td>Patiromer</td>
<td>87%</td>
<td>100%</td>
<td>35%</td>
<td>71%</td>
</tr>
<tr>
<td>Bushinsky 2015 Phase I Trial</td>
<td>25</td>
<td>Patiromer</td>
<td>100%</td>
<td>60%</td>
<td>28%</td>
<td>100%</td>
</tr>
<tr>
<td>Weir 2015 OPAL-HK (RCT)</td>
<td>243</td>
<td>Patiromer</td>
<td>100%</td>
<td>57%</td>
<td>42%</td>
<td>100%</td>
</tr>
<tr>
<td>Pergola 2017 TOURMALINE (RCT)</td>
<td>112</td>
<td>Patiromer</td>
<td>76%</td>
<td>82%</td>
<td>9%</td>
<td>59%</td>
</tr>
<tr>
<td>Pitt 2018 Open-label</td>
<td>63</td>
<td>Patiromer</td>
<td>100%</td>
<td>43%</td>
<td>100%</td>
<td>98%</td>
</tr>
</tbody>
</table>

Trials of oral potassium lowering drugs, representative comorbidities and use of RAASi drugs.

NA – not available
### Appendix 4A: Drug administration and safety - IV calcium preparations

#### Calcium Chloride

<table>
<thead>
<tr>
<th>Available as</th>
<th>Calcium chloride 10% pre-filled syringe 10mL (contains 6.8mmol of calcium in 10mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preparation</td>
<td>Can be used undiluted</td>
</tr>
</tbody>
</table>
| Flush solutions | • Flush well with sodium chloride 0.9% to reduce vein irritation.  
• Incompatible with many solutions (including sodium bicarbonate and phosphate). |
| Administration | • Give by intravenous injection over 3-5 minutes.  
• Give as a bolus injection during resuscitation.  
• Preferably administer via a central venous device (if already in-situ).  
• For peripheral administration, choose a large vein and monitor closely for phlebitis.  
• Ensure patient is supine and closely observed during injection.  
• Monitor ECG and blood pressure. |
| Specialist technical information | • Extravasation can cause tissue damage because of the high osmolarity. |
| Cautions and side effects | • **Cautions**: Hypercalcaemia. Digoxin.  
• **Side Effects**: Too rapid administration may lead to symptoms of hypercalcaemia and may cause cardiac arrhythmias or arrest, hypotension and vasomotor collapse, sweating, hot flushes, nausea and vomiting. |

#### Calcium Gluconate

<table>
<thead>
<tr>
<th>Available as</th>
<th>Calcium gluconate 10% ampoules (contains 2.2mmol of calcium in 10mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preparation</td>
<td>Can be used undiluted.</td>
</tr>
</tbody>
</table>
| Flush solutions | • Flush well with sodium chloride 0.9% or glucose 5% to avoid vein irritation.  
• Incompatible with many solutions (including sodium bicarbonate and phosphate). |
| Administration | • The rate of administration should not exceed 2mL per minute (equivalent to 10mL of undiluted injection over 5 minutes).  
• For peripheral administration, choose a large vein and monitor closely for phlebitis.  
• Ensure patient is supine and closely observed during injection.  
• Monitoring ECG and blood pressure. |
| Specialist technical information | • Extravasation can cause tissue damage because of the high osmolarity. |
| Cautions and side effects | • **Cautions**: Hypercalcaemia. Digoxin.  
• **Side-Effects**: Administer slowly to minimise peripheral vasodilation, cardiac depression and circulatory collapse. |
References


### Appendix 4B: Drug administration and safety – Insulin-glucose infusion

<table>
<thead>
<tr>
<th><strong>10 units of Soluble Insulin in 50mL Glucose 50% (25g)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Available as</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Preparation</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Concentration of final solution</strong></td>
</tr>
<tr>
<td><strong>Dilution/flush solutions</strong></td>
</tr>
<tr>
<td><strong>Administration</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Storage and handling</strong></td>
</tr>
<tr>
<td><strong>Specialist technical information</strong></td>
</tr>
<tr>
<td><strong>Cautions and side effects</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
Alternative Glucose preparations

<table>
<thead>
<tr>
<th>20% Glucose</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Available as</strong></td>
<td>100 ml bottle</td>
</tr>
<tr>
<td><strong>Volume required for 25g glucose</strong></td>
<td>125 ml (two bottles required)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>10% Glucose</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Available as</strong></td>
<td>500 ml bag</td>
</tr>
<tr>
<td><strong>Volume required for 25g glucose</strong></td>
<td>250 ml</td>
</tr>
</tbody>
</table>

References


Appendix 4C: Drug administration and safety - Salbutamol

<table>
<thead>
<tr>
<th>Salbutamol Nebulised Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Available as</strong></td>
</tr>
<tr>
<td>• 2.5mg/2.5mL nebuliser solution</td>
</tr>
<tr>
<td>• 5mg/2.5mL nebuliser solution</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
</tr>
<tr>
<td>• 10mg DOSE</td>
</tr>
<tr>
<td>= 10ml of 2.5mg/2.5mL nebuliser solution.</td>
</tr>
<tr>
<td>= 5ml of 5mg/2.5mL nebuliser solution.</td>
</tr>
<tr>
<td>• 20mg DOSE</td>
</tr>
<tr>
<td>= 10ml of 5mg/2.5mL nebuliser solution.</td>
</tr>
<tr>
<td>• Use a face mask or T-piece.</td>
</tr>
<tr>
<td><strong>Cautions and side effects</strong></td>
</tr>
<tr>
<td>• <strong>Cautions:</strong></td>
</tr>
<tr>
<td>- Consider only giving 10mg in patients with ischaemic heart disease.</td>
</tr>
<tr>
<td>- Tachyarrhythmia</td>
</tr>
<tr>
<td>- Open angle glaucoma</td>
</tr>
<tr>
<td>• <strong>Side-Effects:</strong></td>
</tr>
<tr>
<td>- Tremor</td>
</tr>
<tr>
<td>- Tachycardia</td>
</tr>
<tr>
<td>- Headache</td>
</tr>
</tbody>
</table>

References
## Appendix 4D: Drug administration and safety – Patiromer

### Patiromer

<table>
<thead>
<tr>
<th>Available as</th>
<th>8.4g, 16.8g and 25.2g sachets</th>
</tr>
</thead>
</table>
| Preparation  | • The dose should be poured into a glass containing approximately 40mL of water and then stirred.  
• Another approximately 40mL of water should be added, and the suspension stirred again thoroughly. The powder will not dissolve.  
• More water may be added to the mixture as needed. |
| Administration| • Apple juice or cranberry juice can be used instead of water to prepare the mixture (be aware of potential interactions with cranberry juice). Other liquids should be avoided due to potential potassium content.  
• Should be taken with food.  
• **Administration should be separated by 3 hours from other medicines.** |
| Storage and handling | • The reconstituted mixture should be taken within 1 hour of initial suspension.  
• Unopened storage and transportation should be refrigerated (2°C-8°C). Patients may store below 25°C for up to 6 months. |
| Cautions and side effects | • **Cautions** – Hypercalcaemia, hypomagnesaemia, GI disorders, contains sorbitol.  
• **Side-effects** – Hypomagnesaemia, constipation, diarrhoea, abdominal pain and flatulence |

*Black label medicine subject to additional monitoring to allow quick identification of new safety information. Report all suspected adverse reactions.*

### References


Appendix 4E: Drug administration and safety – Sodium zirconium cyclosilicate

**Sodium Zirconium Cyclosilicate**

<table>
<thead>
<tr>
<th>Available as</th>
<th>5g, 10g sachets (powder oral suspension)</th>
</tr>
</thead>
</table>
| **Preparation**    | • The contents of the sachet should be emptied into a glass containing approximately 45mL of water and stirred well. The powder will not dissolve.  
                      • Advise patient to drink the tasteless liquid while still cloudy.  
                      • If the suspension settles - it should be stirred again. |
| **Administration** | • The suspension can be taken with or without food.  
                      • Administer at least 2 hours before or 2 hours after oral medications with clinically meaningful gastric pH dependent bioavailability. |
| **Treatment: Correction Phase** | • SZC 10g three times daily until normokalaemia (serum K⁺ 4.0 – 5.0 mmol/l) achieved.  
                      • Usually duration is 24 – 48 hours, maximum duration 72 hours.  
                      • Discontinue after 72 hours if normokalaemia not achieved. |
| **Treatment: Maintenance Phase** | • SZC 5g daily starting dose (after normokalaemia achieved)  
                      • Titrate up to 10g once daily or down to 5g alternate days guided by serum K⁺ levels.  
                      • Monitor serum K level regularly.  
                      • Discontinue of hypokalaemia develops (serum K⁺ < 4.0 mmol/l) |
| **Cautions and side effects** | • **Cautions** – can cause QT interval lengthening as a result of a reduction in serum potassium. May be opaque to X-rays – consider if having abdominal X-rays.  
                      • **Side effects** – Hypokalaemia, oedema, gastrointestinal disorders. |

*Black label medicine subject to additional monitoring to allow quick identification of new safety information. Report all suspected adverse reactions.*

**References**

## Appendix 4F: Drug administration and safety – Calcium resonium

### Calcium Resonium

<table>
<thead>
<tr>
<th>Available as</th>
<th>Calcium Resonium Powder (99.934%)</th>
</tr>
</thead>
</table>

#### Preparation
- **Oral administration:**
  - Each 1g of resin should be mixed with 3 to 4mL of water or syrup (not fruit juices). This corresponds to 45 to 60mL of liquid for a 15g dose.
- **Rectal administration**
  - 30g of resin should be mixed with 150mL of water or glucose 10% as a daily retention enema.

#### Administration
- For oral administration, administer at least 3 hours before, or 3 hours after other medication. In patients with gastroparesis consider a 6-hour separation.
- For rectal administration, the enema should be retained for at least 9 hours then the colon should be irrigated to remove the resin.

#### Cautions and side effects
- Contra-indicated in hypercalcaemia or in obstructive bowel disease.
- Concomitant use with sorbitol is not recommended due to gastrointestinal stenosis and intestinal ischaemia.

### References
Appendix 5 – Sine wave ECG
Appendix 6 – Hyperkalaemia Algorithm - Community

Management of Hyperkalaemia in the Community

Exclude pseudohyperkalaemia

K⁺ 5.5 – 5.9 mmol/l

Medication review:
RAASI
Potassium supplements
Trimethoprim/co-trimoxazole
NSAID
Non-selective beta-blockers
‘lo-salt’ substitute

Low K⁺ diet
Treat metabolic acidosis
Consider Diuretic

K⁺ < 5.5 mmol/l

No treatment required

K⁺ 6.0 – 6.4 mmol/l

ACUTELY ILL OR AKI PRESENT

NO

STOP RAASI

YES

STOP RAASI

K⁺ 6.5 mmol/l

MONITOR SERUM K⁺

PREVENT RECURRENT OF HYPERKALAEMIA

* Sodium Zirconium Cyclosilicate (SZC)
Starting dose: 10g three times daily for maximum 72 hours
Maintenance dose: 5g once daily
Titrate up to 10g daily
Or Down to 5g alternate days

CKD 3b or Heart Failure

YES

K⁺ persistently ≥ 6.0 mmol/l, Sub-optimal RAASI therapy, AND Not on dialysis

NO

Secondary care only

Start SZC (*see text box)

Sodium Zirconium Cyclosilicate (SZC)

Publication date: 1.12.2019
Review Date: 1.12.2024
The Renal Association UK
Appendix 7 – Hyperkalaemia Algorithm – Hospital

**Emergency Management of Hyperkalaemia in Adults**

- **Assess using ABCDE approach**
- 12-lead ECG and monitor cardiac rhythm if serum potassium (K⁺) ≥ 6.5 mmol/L
- Exclude pseudo-hyperkalaemia
- Give empirical treatment for arrhythmia if hyperkalaemia suspected

### MILD

K⁺ 5.5 - 5.9 mmol/L

- Consider cause and need for treatment

### MODERATE

K⁺ 6.0 - 6.4 mmol/L

- Treatment guided by clinical condition, ECG and rate of rise

### SEVERE

K⁺ ≥ 6.5 mmol/L

- Emergency treatment indicated

**ECG Changes?**

- Peaked T waves
- Flat/absent P waves

**Shift K⁺ into cells**

- Insulin–Glucose IV Infusion
  - Give 10 units soluble insulin in 25 g glucose
  - Give 10% glucose @ 50ml/hr for 5 hrs (25g) if pre-treatment blood glucose < 7.0 mmol/L

**Protect the Heart**

- Calcium resorcin 15g tds orally OR 30g bd per rectum

**Remove K⁺ from body**

- Sodium zirconium cyclosilicate 30g tds for 72 hrs (max)

**Monitor K⁺ and blood glucose**

- Consider Dialysis
  - K⁺ ≥ 6.5 mmol/L despite medical therapy

**K⁺: potassium; Na⁺: sodium; Creat: creatinine; Bicarb: bicarbonate; BM: blood glucose; max - maximum**

Publication Date: 1.12.2019  
Review Date: 1.12.2024  
The Renal Association UK
Appendix 8 – Hyperkalaemia Algorithm – Resuscitation

**Treatment of Hyperkalaemic Cardiac Arrest**

1. Follow ALS Algorithm
2. Identify and treat reversible causes
3. Hyperkalaemia (K⁺ ≥ 6.5 mmol/l)
   - Seek expert help

**First 15 min**

- **Calcium Chloride or Calcium Gluconate IV bolus**
  - Consider repeating dose if ROSC not achieved within 5-10 min, or if resuscitation attempt is prolonged

- **Insulin – Glucose IV bolus**
  - Start 10% glucose infusion if BMI < 7.0 at any time during CPR
  - Risk of hypoglycaemia

- **Sodium Bicarbonate IV bolus**

**15 min onwards**

- **Dialysis**
  - Plan early
  - Use existing dialysis access OR
  - Insert femoral line with US guidance
  - CVVH: Use K⁺-free dialysate fluid
  - HD/HD: Use 0 or 1 mmol/L K⁺ dialysate fluid

**Blood Monitoring:**

- Baseline
- 15 min
- 30 min
- 60 min
- 90 min
- 120 min
- 180 min
- 240 min
- 360 min


Publication date: 1.12.2019 Review Date: 1.12.2024 The Renal Association UK
Abbreviations

1. AAGBIG: Association of Anaesthetists of Great Britain and Ireland Guideline
2. ABCDE: Airway – Breathing – Circulation – Disability – Exposure
3. ACC: American College of Cardiology
4. ACE-i: Angiotensin converting enzyme inhibitor
5. AED: Automated External Defibrillator
6. AHA: American Heart Association
7. AKI: Acute Kidney Injury
8. ALS: Advanced Life Support
9. ARB: Angiotensin II receptor blocker
10. ARDS: Adult respiratory distress syndrome
11. AUC: Area under the curve
12. AV: Arterio-venous
13. AVPU: Alert – Verbal – Pain - Unresponsive
14. BGA: Blood gas analyser
15. BM: Blood glucose
16. BP: Blood pressure
17. Ca²⁺: Calcium ion
18. CKD: Chronic kidney disease
19. CPR: Cardiopulmonary resuscitation
20. CPS: Calcium polystyrene sulphonate
21. CV: Cardiovascular
22. CVVH: Continuous veno-venous haemofiltration
23. CVVHDF: Continuous veno-venous haemodiafiltration
24. DM: Diabetes Mellitus
25. DNACPR: Do Not Attempt Cardiopulmonary Resuscitation
26. DOPPS: Dialysis Outcomes and Practice Patterns Study
27. ECG: Electrocardiogram
28. ECMO: Extra-corporeal membrane oxygenation
29. eGFR: Estimated glomerular filtration rate
30. EMA: European Medicines Agency
<table>
<thead>
<tr>
<th>No.</th>
<th>Acronym</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ERC</td>
<td>European Resuscitation Council</td>
</tr>
<tr>
<td>2</td>
<td>ESC</td>
<td>European Society of Cardiology</td>
</tr>
<tr>
<td>3</td>
<td>ESRD</td>
<td>End-stage renal disease</td>
</tr>
<tr>
<td>4</td>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>5</td>
<td>FICM</td>
<td>Faculty of Intensive Care Medicine</td>
</tr>
<tr>
<td>6</td>
<td>GCS</td>
<td>Glasgow coma scale</td>
</tr>
<tr>
<td>7</td>
<td>GFR</td>
<td>Glomerular filtration rate</td>
</tr>
<tr>
<td>8</td>
<td>HBP</td>
<td>Hypertension</td>
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<tr>
<td>9</td>
<td>HD</td>
<td>Haemodialysis</td>
</tr>
<tr>
<td>10</td>
<td>HDF</td>
<td>Haemodiafiltration</td>
</tr>
<tr>
<td>11</td>
<td>HDU</td>
<td>High dependency unit</td>
</tr>
<tr>
<td>12</td>
<td>HF</td>
<td>Haemofiltration</td>
</tr>
<tr>
<td>13</td>
<td>HFrEF</td>
<td>Heart failure with reduced ejection fraction</td>
</tr>
<tr>
<td>14</td>
<td>HK</td>
<td>Hyperkalaemia</td>
</tr>
<tr>
<td>15</td>
<td>HR</td>
<td>Hazard ratio</td>
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<td>16</td>
<td>Hypo</td>
<td>Hypoglycaemia</td>
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<tr>
<td>17</td>
<td>ICS</td>
<td>Intensive Care Society</td>
</tr>
<tr>
<td>18</td>
<td>ICU</td>
<td>Intensive Care Unit</td>
</tr>
<tr>
<td>19</td>
<td>IEC</td>
<td>International Electrotechnical Committee</td>
</tr>
<tr>
<td>20</td>
<td>IHCA</td>
<td>In-hospital cardiac arrest</td>
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<tr>
<td>21</td>
<td>IHD</td>
<td>Intermittent haemodialysis</td>
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<tr>
<td>22</td>
<td>ILCOR</td>
<td>International Liaison Committee on Resuscitation</td>
</tr>
<tr>
<td>23</td>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>24</td>
<td>K⁺</td>
<td>Potassium ion</td>
</tr>
<tr>
<td>25</td>
<td>KDOQI</td>
<td>Kidney Disease Outcomes Quality Initiative</td>
</tr>
<tr>
<td>26</td>
<td>MET</td>
<td>Medical emergency team</td>
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<td>27</td>
<td>Mg⁺</td>
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<td>28</td>
<td>MHRA</td>
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<td>32</td>
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<td>6</td>
<td>OHCA</td>
<td>Out-of-hospital cardiac arrest</td>
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<tr>
<td>7</td>
<td>OR</td>
<td>Odds ratio</td>
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<td>8</td>
<td>PEA</td>
<td>Pulseless electrical activity</td>
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<td>10</td>
<td>RAASI</td>
<td>Renin-Angiotensin-Aldosterone-System inhibitor</td>
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<td>11</td>
<td>RCT</td>
<td>Randomised controlled trial</td>
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<td>12</td>
<td>ROSC</td>
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<td>14</td>
<td>SB</td>
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<td>VF</td>
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