CLINICAL PRACTICE GUIDELINES

TREATMENT OF ACUTE HYPERKALAEMIA IN ADULTS

UK Kidney Association (UKKA)

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Purpose of Guideline Update

An update of the UKKA Hyperkalaemia Guideline (2020) was prompted following enquiries related to the administration of Calcium Gluconate and to provide new guidance related to the use of oral potassium binders and blood glucose monitoring. Therefore, the main changes to treatment recommendations are within the Hospital Section of this update.

The MHRA have recently commissioned a review of the clinical indications, dosage, rate and method of administration of Calcium Gluconate following which a patient safety alert and prescribing guidance has been issued pertaining to the treatment of hyperkalaemia.

Feedback was also received that suggested greater emphasis was required to highlight the 2-stage Insulin-glucose regimen in the original hospital treatment algorithm (2020). In response, an amendment was issued in August 2022. This has been included in the update as there is now new evidence to support the proposed threshold (blood glucose < 7 mmol/l) for administering a 5-hour infusion of 10% glucose following Insulin-glucose.

We have also reviewed blood glucose monitoring in light of growing evidence that a 6 hour period may be adequate. This change reverts to the 2014 protocol and may help to improve adherence in clinical practice. There remains insufficient evidence to alter the insulin dosing regimen.

Clinical experience is growing for the use of the novel potassium binders, Sodium Zirconium Cyclosilicate and Patiromer. Further studies have been undertaken in the acute setting and have been included in this update. There now appears to be no role for Calcium Resonium in the acute setting.

The Hyperkalaemia Algorithm (Hospital) has been updated to reflect all changes outlined in this update including the rate of administration of IV calcium salts, the wider scope for use of the novel potassium binders to include both moderate and severe hyperkalaemia, the removal of calcium resonium and the modified blood glucose monitoring regimen.

The Community and Resuscitation sections have also been reviewed and updated, although there are no major changes to clinical practice.

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Summary of key changes to Hyperkalaemia Guideline – HOSPITAL SECTION

GUIDELINE	TREATMENT	ORIGINAL	CHANGE
16.2a	**IV Calcium salts**	10ml 10% Calcium Chloride over 5 min	**10ml 10% Calcium Chloride over 5 min (*unchanged*)**
		30 ml 10% Calcium Gluconate over 5 min	**30 ml 10% Calcium Gluconate over 10 min (*as per 2014 UKKA guideline and MHRA*)**
16.2b	**IV Calcium salts**	Not included in original guideline	**Give Calcium Chloride in resuscitation setting and Calcium Gluconate for all other patients**
16.3.3	**Insulin-Glucose (Avoiding Hypoglycaemia)**	Algorithm – 2-stage protocol appeared unclear (2020)	**Algorithm updated to highlight 2-stage protocol (Version 2 – Aug 2022)**
16.6.1a	**Sodium Zirconium Cyclosilicate (SZC)**	Give SZC 10g tds for 72hrs	**Give SZC 10g tds for up to 72hrs for severe HK ($K^+ \geq 6.5$ mmol/l)**
16.6.1b	**Sodium Zirconium Cyclosilicate (SZC)**	Not included in original guideline	**Consider SZC 10g tds for up to 72hrs for moderate HK (K^+ 6.0 - 6.4 mmol/l)**
16.6.2	**Patiromer**	Consider Patiromer 8.4g once daily for severe HK ($K^+ \geq 6.5$ mmol/l)	**Consider Patiromer 8.4g for moderate or severe HK ($K^+ > 6.0$ mmol/l) (*does not apply in Scotland*)**
16.6.3	**Calcium resonium**	Consider Calcium resonium 15g tds orally or 30g bd per rectum for moderate HK (K^+ 6.0 - 6.4 mmol/l)	**Calcium resonium is no longer routinely recommended in treatment of acute HK**
17.2	**Blood glucose monitoring**	Monitor blood glucose for 12 hours post treatment	**Monitor blood glucose for 6 hours post treatment**
22.1	**Algorithm (Hospital)**	IV Calcium	**Rate of administration of Calcium Gluconate amended**
		Sodium Zirconium Cyclosilicate	**Give for severe HK and consider for moderate HK**
		Patiromer	**Consider in moderate or severe HK (*does not apply in Scotland*)**
		Calcium resonium	**Removed from acute treatment protocol**
		Blood glucose monitoring	**Monitor for 6 hours**
Appendix 3A	**Calcium Gluconate**	Give 30ml over 15 min IV	**Give 30ml over 10 min IV**

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GUIDELINE DEVELOPMENT

Purpose

This guideline provides an updated version of the 2020 UKKA Hyperkalaemia guideline. 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.

Scope

The original Hyperkalaemia Guideline (2014) focussed on the management of hyperkalaemia in secondary care. The 2020 Guideline provided a comprehensive overview of the detection and treatment of hyperkalaemia in the community, hospital and resuscitation settings. The 2023 Guideline provides an update of treatment recommendations in the acute hospital setting.

Review of Evidence

The literature was reviewed using multiple databases - PubMed (1960-2023), Ovid MEDLINE (1946-2023), EMBASE (1974-2023), Science Direct (1995-2023), The Cochrane Library (1995-2023), Web of Knowledge (2001-2023) for all studies pertaining to treatment of hyperkalaemia in adults. Websites searches included National Institute for Health and Care Excellence, Scottish Medicines Consortium, Healthcare Improvement Scotland, Medicines and Healthcare products Regulatory Agency and European Medicines Agency.

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 writing process followed the Renal Association Guideline development manual. The 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).

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INTRODUCTION

There is no universally accepted definition of hyperkalaemia. This guideline has adopted the European Resuscitation Council (ERC) Guideline definition with a threshold serum potassium (K^+) level of ≥ 5.5 mmol/l, established in 2005[1] and maintained to current date.[2] It is further classified by severity into mild (5.5-5.9 mmol/l), moderate (6.0-6.4 mmol/l) or severe (≥ 6.5 mmol/l). Hyperkalaemia is a common medical emergency when it presents acutely. The presence of persistent hyperkalaemia in the community is often regarded as chronic, usually in the context of drugs that exacerbate the condition.

The incidence of hyperkalaemia in the hospital setting ranges from 1.1% and 10%.[3-5] The incidence in the community varies dependent on the case mix of the population studied. The Chronic Kidney Disease Prognosis Consortium study showed that the prevalence of hyperkalaemia (K^+ > 5.5 mmol/l) was 0.49% in the general population, but was more prevalent in patients with CKD (4.2%).[6] The prevalence of chronic hyperkalaemia in patients with CKD rises significantly with declining renal function.[7]

In-hospital mortality is significantly higher in patients with hyperkalaemia (18.1%) compared to those with hypokalaemia (5.0%) or normokalaemia (3.9%).[3] A U-shaped association between serum K^+ and mortality has been shown, including in patients with CKD and in patients receiving longterm haemodialysis.[8] Patients with severe hyperkalaemia (K^+ > 6.5 mmol/l) are most at risk and > 30% in-hospital mortality has been reported.[9, 10]

The treatment of hyperkalaemia is still evolving as clinical experience is gained using new drugs and novel treatment approaches are developed. The key focus remains patient safety. Clinical decisions on when to treat and how aggressively to treat require a patient centred approach guided by the clinical setting and rate of change in serum K^+ level. Patients with moderate levels of hyperkalaemia pose the greatest dilemma, especially when acuity is low, but warrant intervention to avoid deterioration. Severe hyperkalaemia risks arrhythmias and cardiac arrest, therefore prompt recognition and intervention is required.

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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, or as soon as feasible, if an episode of mild hyperkalaemia (K^+ 5.5 – 5.9 mmol/l) is 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 ($K^+ \geq 6.5$ 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 urea and electrolytes 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 or eGFR < 30 ml/min. (1B)

Guideline 2.3 – Monitoring of patients after initiation of ACE-I and ARB.

We recommend that urea and electrolytes should be assessed at 1 – 2 weeks after initiation of ACE-I or ARB and after every dose titration. (1A)

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Guideline 2.4 – Monitoring of patients after initiation of MRAs.

We recommend that urea and electrolytes 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 $K^+ \geq 6$ mmol/l who do not meet the criteria for treatment with patiromer or 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 $K^+ \geq 5.5$ mmol/l. (1B)

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

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

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

We suggest hospital assessment 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 persistent hyperkalaemia with a serum $K^+ > 5.5$ mmol/l. (1B)

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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 option to treat chronic hyperkalaemia in non-hospitalised patients who do not meet the criteria for Patiromer or Sodium Zirconium Cyclosilicate. (2C)

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

We recommend that Patiromer is an option in the management of persistent hyperkalaemia with a confirmed serum $K^+ \geq 6.0$ mmol/l in out-patients with CKD Stage 3b-5 (not on dialysis) or heart failure receiving a sub-optimal dose or not receiving RAASi therapy due to hyperkalaemia. (1A)

Guideline 9.2 – Patiromer for the management of Hyperkalaemia

We recommend that treatment with Patiromer is discontinued if RAASi therapy is stopped. (1A)

Guideline 9.3 – Patiromer for the management of Hyperkalaemia

We recommend that Patiromer is initiated in secondary care only. (1A)

Guideline 10.1 – Sodium Zirconium Cyclosilicate for the management of Hyperkalaemia

We recommend that Sodium Zirconium Cyclosilicate (SZC) is an option in out-patients for the management of persistent hyperkalaemia with a confirmed serum $K^+ \geq 6.0$ 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)

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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)

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. (1B)

SECTION II: HOSPITAL

Guideline 13.1 – 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 13.2 – Hyperkalaemia: Clinical Assessment; NEWS

We recommend that all patients with known or suspected hyperkalaemia undergo urgent clinical assessment using an early warning scoring system to assess level of acuity. (1C)

Guideline 14.1 – Hyperkalaemia: ECG

We recommend that all hospitalised 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)

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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)

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 follow a logical 5-step approach. (1B)

Guideline 16.2a – Hyperkalaemia: STEP 1 – Protect the heart; intravenous calcium salts; dose and rate of administration

We recommend that an equivalent dose (6.8 mmol) of IV calcium is given to patients with hyperkalaemia in the presence of ECG changes at a dose and rate of 30ml 10% Calcium Gluconate over 10 minutes OR 10ml 10% Calcium Chloride over 5 minutes guided by the clinical setting. (1C)

Guideline 16.2b – Hyperkalaemia: STEP 1 – Protect the heart; intravenous calcium salts; choice guided by clinical setting

We recommend that IV Calcium Chloride is the preferred calcium salt in resuscitation (cardiac arrest or peri-arrest) and IV Calcium Gluconate should be used for all other patients in the presence of ECG signs of hyperkalaemia. (1C)

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 ($K^+ \geq 6.5$ 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)

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

We recommend initiation of an infusion of 10% glucose at a rate of 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. (2B)

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 ($K^+ \geq 6.5$ 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)

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)

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

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

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

We suggest that Sodium Zirconium Cyclosilicate is considered in the acute management of moderate hyperkalaemia (serum K^+ 6.0 – 6.4 mmol/l). (1B)

Guideline 16.6.2 – Hyperkalaemia: STEP 3 – Remove K^+ from body; Potassium binders

We suggest that Patiromer is an option for the emergency management of acute hyperkalaemia (serum $K^+ \geq 6.0$ mmol/l). (1C)

Guideline 16.2 – Hyperkalaemia: STEP 3 – Remove K^+ from body; Cation-exchange resin

We recommend that calcium resonium should no longer be routinely used in the management of acute hyperkalaemia. (2B)

Guideline 17.1.1 – Hyperkalaemia: STEP 4 - Blood monitoring; serum K^+

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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 K^+

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)

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 and 360 minutes) after administration of insulin-glucose infusion in all patients with hyperkalaemia. (1C)

Guideline 18.1 - Hyperkalaemia: Treatment in haemodialysis patients

We recommend that haemodialysis patients with severe hyperkalaemia (serum $K^+ \geq 6.5$ mmol/L) receive dialysis treatment urgently. (1A)

Guideline 18.2 - Hyperkalaemia: Treatment in haemodialysis patients

We recommend that haemodialysis patients with severe hyperkalaemia (serum $K^+ \geq 6.5$ mmol/L) and toxic ECG changes be treated with intravenous calcium salt to reduce risk of arrhythmias even when dialysis is immediately available. (1C)

Guideline 18.3 - Hyperkalaemia: Treatment in haemodialysis patients

We recommend that haemodialysis patients with severe hyperkalaemia (serum $K^+ \geq 6.5$ mmol/L) be treated with standard medical therapies to lower serum potassium if dialysis is not immediately available. (1B)

Guideline 18.4 - Hyperkalaemia: Treatment in haemodialysis patients

We suggest that potassium binders may be considered to reduce the risk of hyperkalaemia during the inter-dialytic period. (1B)

Guideline 19.1 - Hyperkalaemia: Specialist Referral

We suggest that patients with severe hyperkalaemia (serum $K^+ \geq 6.5$ 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 19.2 - Hyperkalaemia: Referral to critical care services

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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 19.3 - 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 19.4 - 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 19.5 – Hyperkalaemia: Treatment facilities – Ward, Enhanced Care or Critical Care 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, enhanced care area, or critical care unit (HDU or ICU) depending on local facilities or practice. (1C)

Guideline 19.6 – Hyperkalaemia: RRT in treatment of hyperkalaemia in acutely unwell patients.

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 20.1 - 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 20.2 - 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)

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Guideline 21.1 – 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 21.2 – Hyperkalaemia: Prevention of hyperkalaemia in hospitalised patients

We recommend a low potassium diet for hospitalised patients with moderate or severe hyperkalaemia. (1C)

Guideline 21.3 – 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 21.4 – 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 22.1 – 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. (1B)

SECTION III: RESUSCITATION

Guideline 23.1 – 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)

Guideline 24.1 – Hyperkalaemia; Cardiac Arrest – Resuscitation strategy in haemodialysis patients

We recommend that standard ALS practice in cardiac arrest be applied to patients requiring dialysis. (1A)

Guideline 24.2 – Hyperkalaemia; Cardiac Arrest – Defibrillation practice in haemodialysis patients

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

Guideline 25.1 – 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. (1C)

Guideline 25.2.1 – Cardiac Arrest: Treatment – Insulin-glucose

We recommend that 10 units soluble insulin and 25g glucose is administered if hyperkalaemia is known or suspected to be the cause of cardiac arrest. (1B)

Guideline 25.2.2 – Cardiac Arrest: Treatment – Insulin-glucose

We suggest 10% glucose infusion be initiated if the blood glucose is < 7.0 mmol/l at the time of cardiac arrest. (2C)

Guideline 25.3 – 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 25.4 – Hyperkalaemia; Cardiac Arrest – Initiation of dialysis during CPR

We suggest that renal replacement therapy with ongoing CPR may be considered for hyperkalaemic cardiac arrest, if hyperkalaemia is resistant to medical therapy and appropriate staff and facilities are available. (2C)

Guideline 26.1 – 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 26.2 – 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 – 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)

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Figure 4: There are five key steps in the treatment of hyperkalaemia (*never walk away without completing all of these steps*).

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Figure 6: Incidence of post-treatment hypoglycaemia with glucose above and below 7 mmol/l. Reproduced with permission from *Tee et al, Clin Endocrinol (Oxf) 2021; 94: 176-182.*

Figure 7: Time to development of hypoglycaemia following Glucose-Insulin (GwI) infusion. Reproduced with permission from *Tee et al, Clin Endocrinol (Oxf) 2021; 94: 176-182*

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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. Frequency of hospital admission for severe hyperkalaemia (serum K^+ > 6.5 mmol/l) detected on routine blood test in the community.
2. Frequency of blood monitoring for patients receiving RAASi drugs in the community.
3. Proportion of patients admitted to hospital with severe hyperkalaemia detected in the community who subsequently did not warrant emergency treatment on repeat testing.
4. Proportion of patients with moderate hyperkalaemia who have received dietary potassium advice in the renal out-patient setting.
5. The proportion of out-patients with moderate hyperkalaemia (serum K^+ 6.0 - 6.4 mmol/l) treated with patiromer who achieved a serum $K^+ \leq 5.0$ mmol/l within 1 week.
6. The proportion of out-patients who achieve maximal dose RAASi therapy whilst taking patiromer.
7. The proportion of out-patients with moderate hyperkalaemia (serum K^+ 6.0 - 6.4 mmol/l) treated with SZC who achieved a serum $K^+ \leq 5.0$ mmol/l within 48 hours.
8. The proportion of out-patients who achieve maximal dose RAASi therapy whilst taking SZC.
9. Proportion of patients with severe hyperkalaemia (Serum $K^+ \geq 6.5$ mmol/l) on admission to hospital who had been provided with 'Sick Day Rules' advice.
10. Length of hospital stay and in-hospital mortality of patients admitted with hyperkalaemia.
11. Proportion of patients with a serum K^+ level ≥ 6.0 mmol/L who had a 12-lead ECG recorded before and after treatment for hyperkalaemia.
12. The frequency of ECG changes in patients treated with intravenous calcium salts.
13. The proportion of patients with severe hyperkalaemia ($K^+ \geq 6.5$ mmol/L) treated with insulin-glucose infusion.
14. The proportion of patients with acute severe hyperkalaemia (serum $K^+ \geq 6.5$ mmol/l) treated with Sodium Zirconium Cyclosilicate.

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15. The proportion of hospitalised patients with moderate hyperkalaemia (serum K^+ 6.0-6.4 mmol/l) treated with Sodium Zirconium Cyclosilicate.
16. The proportion of hospitalised patients with acute hyperkalaemia (serum K^+ > 6.0 mmol/l) treated with Patiromer.
17. The proportion of patients in whom serum K^+ was measured at least once within 2 hours of treatment for severe hyperkalaemia [Audit Standard: 100%].
18. 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%].
19. The frequency of hypoglycaemia occurring in patients receiving treatment with insulin-glucose for hyperkalaemia.
20. The incidence of patients requiring emergency dialysis for severe hyperkalaemia.
21. The frequency of hyperkalaemia developing beyond 24 hours of hospital admission.
22. The frequency of prescribed drugs potentially contributing to hyperkalaemia.
23. All cardiac arrests should be audited – hospital participation in the National Cardiac Arrest Audit is encouraged as part of quality improvement and benchmarking.
24. The proportion of patients treated with intravenous calcium for hyperkalaemic cardiac arrest.
25. The proportion of patients treated with sodium bicarbonate for hyperkalaemic cardiac arrest.
26. The number and outcome of patients with refractory hyperkalaemic cardiac arrest treated with dialysis initiation during CPR.

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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 in Prospective studies.
2. The efficacy of potassium binders (patiromer and sodium zirconium cyclosilicate) in combination with insulin-glucose infusion in the treatment of severe hyperkalaemia in hospitalised patients.
3. The efficacy of sodium bicarbonate in the treatment of severe hyperkalaemia in patients with AKI.
4. The incidence and outcome of hyperkalaemic cardiac arrest.

Future Developments:

Development of ready-to-use preparations of 10% (250ml) and 20% (125ml) glucose solutions in volumes appropriate for the treatment of hyperkalaemia.

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

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SECTION I

MANAGEMENT OF HYPERKALAEMIA

IN THE

COMMUNITY

&

OUT-PATIENT CLINIC

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I. Hyperkalaemia in the Community (Guidelines 1.1 – 12.1)

Introduction

The term 'chronic hyperkalaemia' generally refers to persistent mild-moderate hyperkalaemia in clinically well patients in the community. There is no consensus on the magnitude, duration and frequency of elevated K^+ levels that define chronicity.[1] Chronic hyperkalaemia is clinically important as it can interfere with the management of many medical conditions.

Mechanisms contributing to hyperkalaemia in patients with CKD include reduced aldosterone effect, reduced potassium cell uptake, and reduced delivery of sodium and water in the distal tubules.[1, 2] Risk factors for community-acquired hyperkalaemia as shown in Table 1.

Patient groups most at risk are those with CKD, diabetes mellitus and heart failure.[3] 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.[4] The presence of multiple co-morbidities or other risk factors further increase the risk of hyperkalaemia.[5-8]

The management of patients with heart failure is challenging given the high prevalence of renal impairment. In clinical trials of RAASi monotherapy, the incidence of hyperkalaemia ranges from 3 – 7%.[9] The overall incidence of hyperkalaemia was generally higher in clinical trials involving aldosterone antagonists.[9] Combination therapy of RAASi and aldosterone antagonist increases the risk of hyperkalaemia and hospitalisation.[10]

Risk Factor for Hyperkalaemia	Odds Ratio [Turgutalp] [5]	Odds Ratio [Sarafidis] [6]	Odds Ratio [Nakhoul] [7]	Odds Ratio [Horne] [8]
Renal Failure	5.55	2.06 (eGFR < 15)	1.25 (/5ml/min decrease)	1.04
Diabetes			1.53	0.95
Heart Failure			0.95	
≥2 Co-morbidities	2.22			
Serum bicarbonate < 25		1.30		
ARB	2.68	1.85	1.4	15.89
ACE-I	2.24	1.85	1.4	13.63
Spironolactone	2.53	2.10		7.77
NSAIDS	2.68			
Beta blocker	2.14		1.06	

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

Incidence of hyperkalaemia in the Community

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.[5, 8, 11-15] The prevalence of hyperkalaemia in patients with an eGFR > 60 ml/min is shown in Table 2. In a large UK primary care study, the overall incidence rate of a hyperkalaemic event was 2.9 per 100 person years.[8] In this study, the use of RAASi was strongly associated with hyperkalaemia with an odds ratio of 13.6 - 15.9.

Study	Country	Setting	N=	eGFR ml/min	Definition of HK mmol/l	Prevalence of HK %	Mortality risk with HK
Liamis 2013 [11]	Netherlands	General population (age > 55)	5179	>60	≥6.0	0.3	#OR 2.08
Chang 2016 [12]	USA	Health care system – HBP (age ≥ 18)	155,695	>60	>5	10.8	NA
					>5.5	2.3	
Hughes-Austin 2017 [13]	USA	Multi-ethnic general population (age ≥65)	9651	>60	≥5.0	2.8	+HR 1.41
Horne 2019 [8]	UK	General population (age ≥ 18)	195,178	>60	5.0 – 5.4	91.2	^2.51
					5.5 – 6.0	7.2	^3.83
					>6	1.6	^12.57

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

#OR- Odds Ratio; +HR- Hazard Ratio; ^All-cause mortality; HBP – hypertensive; NA – not available

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Hyperkalaemia is more common in patients with CKD and the incidence increases with declining renal function.[2] Sarafadis et al found that over 30% of patients experienced hyperkalaemia (K^+ > 5.5 mmol/l) in the pre-dialysis setting (eGFR < 15 ml/min).[6] A summary of the prevalence of hyperkalaemia in patients with CKD is shown in Table 3.

Study	Country	Setting	N=	eGFR ml/min	Definition of HyperK mmol/l	Prevalence HyperK %	Mortality by K^+ level
Korgaonkar 2010 [16]	USA	Renal Clinic	820	25.4	≥5.5	7.9	$^+$HR 1.57
Sarafidis 2012 [6]	UK	Low Clearance clinic	238	14.5	5.0 – 5.4	22.7	NA
					5.5 – 5.9	23.1	NA
					≥6.0	8.4	NA
Nakhoul 2015 [7]	USA	CKD Registry (USA)	36,359	47	5.0 – 5.4	11	$^\#$OR 1.12
					>5.5	3.3	$^\#$OR 1.65
Turgutalp 2016 [5]	Turkey	Elderly population (age > 65)	40,092	23-35	≥5.5	2.9	AUC values by age p< 0.001
Luo 2016 [15]	USA	Health care system (age ≥ 18)	55,266	< 60	5.0 – 5.4	14.9	*IRR 1.01
					5.5 – 5.9	3.9	*IRR 1.11
					≥6.0	1.1	*IRR 3.08
Furuland 2018 [14]	UK	Health care database	191,964	50.9	5.0 – 5.4	45.1	*IRR 1.1
					5.5 – 5.9	15.9	*IRR 1.60
					≥6.0	4.9	*IRR 2.88

Table 3: Prevalence of hyperkalaemia and mortality rate in patients with CKD.

NA – not available; $^+$HR – Hazard Ratio; $^\#$OR - Odds Ratio; AUC- Area Under Curve; *IRR- Incident rate ratio

Impact of chronic hyperkalaemia

Hyperkalaemia is associated with interruptions to medical therapies (i.e. RAASi and MRA), increased hospitalisation, prolongation of hospital stay, increased healthcare costs, and increased mortality.[2, 3, 17] Horne et al showed the incidence rates for all-cause hospitalisation in adults was 14.1 per 100 person years.[8] Turgutalp et al demonstrated a higher incidence of

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hospitalisation for hyperkalaemia in the elderly population: age 65-74 years (46%), age 75-84 years (44%) and ≥ 85 years (74%).[5]

Mortality increases with worsening severity of hyperkalaemia in the general population and in patients with CKD.[7, 8, 14, 15] Mortality in patients with heart failure has been shown to increase significantly 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).[18]

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.

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I. Hyperkalaemia in the Community (Guidelines Hyperkalaemia 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, or as soon as feasible, if an episode of mild hyperkalaemia (K^+ 5.5 – 5.9 mmol/l) is 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 ($K^+ \geq 6.5$ mmol/l) detected in the community are admitted for immediate assessment and treatment. (1B)

Audit measure:

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27. 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)

Blood monitoring of patients with CKD and those at risk of hyperkalaemia is now standard practice. Monitoring is also essential after an episode of hyperkalaemia. Good communication with the patient and Primary Care is essential.

Blood monitoring in patients with CKD

Patients with CKD are at risk of hyperkalaemia and progression of their underlying kidney disease, therefore require regular blood monitoring in the community. Several observational studies have reported the frequency of blood monitoring in patients with CKD in relation to detection of hyperkalaemic events. Chang et al (2016) 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%).[1] In patients with an eGFR < 30ml/min who had ≥4 tests per year, hyperkalaemia was found in 30%.

Luo et al (2016) reported the frequency of blood monitoring stratified by level of renal function and level of serum K^+.[2] 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. Detection of hyperkalaemia increased with increased 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 NICE CKD Guideline (2021) suggests that the frequency of monitoring should be tailored to the level of renal function, underlying cause of CKD, rate of decline in renal function, degree of proteinuria and other risk factors (e.g. diabetes, heart failure) as shown in Table 4.[3]

NICE – CKD GUIDANCE [3]	**ACR category A1:** (< 3 mg/mmol)	**ACR category A2:** (3 – 30 mg/mmol)	**ACR category A3:** (> 30 mg/mmol)
GFR category G1:	0 - 1	1	≥ 1

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(≥ 90ml/min/1.73 m^2)			
GFR category G2: (60-89ml/min/1.73 m^2)	0 - 1	1	≥ 1
GFR category G3a: (45-59ml/min/1.73 m^2)	1	1	2
GFR category G3b: (30-44ml/min/1.73 m^2)	1-2	2	≥ 2
GFR category G4: (15-29ml/min/1.73 m^2)	2	2	3
GFR category G5: (<15ml/min/1.73 m^2)	4	≥ 4	≥ 4

Table 4: NICE CKD Guideline (2021) – Minimum number of monitoring visits per year.[4]

Blood monitoring after a hyperkalaemic episode

More frequent monitoring is indicated during acute illness and following an episode of AKI or hyperkalaemia. Blood monitoring *after* a hyperkalaemic event in the community or after hospital discharge is essential.

Furuland et al (2018) utilised data from primary care records for approximately 7% of the UK population to assess the interval between hyperkalaemic episodes in patients with CKD.[5] 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 recurrent episodes (1^{st}-2^{nd}, 2^{nd}-3^{rd}, and 3^{rd}-4^{th}) in patients with serum K^+ 5.5 – 5.9 mmol/l was 0.84, 0.59 and 0.48 years respectively. The interval between recurrent episodes was shorter in patients with serum K^+ ≥ 6 mmol/l (0.65, 0.41 and 0.30 years respectively).

Horne et al (2019) demonstrated that only 5.8% of patients had a repeat serum K^+ performed within 14 days of the hyperkalaemic event, but a large number of patients had a serum K^+ < 5.5 mmol/l which may have been perceived to be non-urgent.[6] 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.

Davis et al (2021) assessed in-patient management and post-discharge outcomes of hospitalised patients with hyperkalaemia.[7] Within 30 days of discharge, hyperkalaemia recurred in 13.3% of patients with mild, 15.4% of patients with moderate and 18.4% of patients with severe

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hyperkalaemia. Hospital re-admission was required within 30 days post-discharge in 19.7%, 21.5% and 19.6% respectively.

'Think Kidneys' have provided practical guidance for repeat testing after a hyperkalaemic episode.[8] The timing is guided by the level of hyperkalaemia and clinical context as shown in Table 5.

Severity of Hyperkalaemia	Clinically well (no AKI)	Unexpected result	Clinically unwell or AKI
MILD K^+ 5.5 – 5.9 mmol/l	Repeat within 14 days	Repeat within 3 days	*Consider if hospital referral is indicated
	Assess for cause (drugs, diet) and address in the community		
MODERATE K^+ 6.0 – 6.4 mmol/l	Repeat within 1 working day**	Repeat within 24 hours	Refer to hospital
	Assess for cause (drugs, diet) and address in the community or hospital		
SEVERE $K^+ \geq 6.5$ mmol/l	**Refer to hospital for immediate assessment and treatment**		
	Assess for cause and address during hospital admission		

Table 5: Interval for repeat blood monitoring following an episode of hyperkalaemia.

*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*)[6]

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I. Hyperkalaemia in the Community (Guidelines Hyperkalaemia 2.1 – 2.7)

Guideline 2.1 – Assessment of patients prior to initiation of ACE-I or ARB.

We recommend that urea and electrolytes 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 or eGFR < 30 ml/min. (1B)

Guideline 2.3 – Monitoring of patients after initiation of ACE-I and ARB.

We recommend that urea and electrolytes 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 urea and electrolytes 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.

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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 $K^+ \geq 6$ mmol/l who do not meet the criteria for treatment with patiromer or sodium zirconium cyclosilicate. (1B)

Audit measure:

1. Frequency of blood monitoring for patients receiving RAASi drugs in the community.

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, but has resulted in an increased frequency of hyperkalaemia.

Impact of hyperkalaemia on optimisation of RAASi/ MRA therapy

Hyperkalaemia frequently limits use or titration of RAASi drugs. Epstein et al conducted a large study (> 7 million patient records) to determine the impact of hyperkalaemia on the optimal vs 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 with patients who reached optimal doses.[3]

Discontinuation of RAASi therapy in patients with CKD after an episode of hyperkalaemia can result in an increased risk of cardiovascular events and death.[4] The balance between optimising treatment and compromising renal function poses a significant clinical dilemma.

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Strategies to maintain RAASi treatment after an episode of hyperkalaemia may improve clinical outcomes in the CKD population.[5]

Blood monitoring during RAASi therapy

The aim of blood monitoring of serum K^+ in patients receiving RAASi drugs is to reduce the risk of adverse events. Raebel et al demonstrated that patients with diabetes who underwent K^+ 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.[6]

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.[7]

Jun et al assessed the timing of onset of hyperkalaemia in hospitalised patients following recent initiation of an ACE-I or ARB and found that 50.9% of patients developed hyperkalaemia at a K^+ level up to 5.5 mmol/l and 47.6% of patients developed hyperkalaemia at a K^+ level up to 6 mmol/l within the first week.[8]

National/ International recommendations for blood monitoring during RAASi therapy:
The **Renal Association [RA] and the British Society for Heart Failure [BSH] (2019)** advise monitoring of renal function is mandatory during initiation and titration of RAASi treatment.[9]
The **NICE Guideline for CKD (2021)** recommends measuring serum K^+ level before starting, within 1 to 2 weeks of initiation of RAASi therapy and after every dose increment.[10]
The **KDIGO Guideline (2023)** recommends measuring BP, serum creatinine and serum K^+ level within 2-4 weeks of initiation or increase in the dose of a RAASi drugs depending on the current GFR and serum K^+.[11]

National recommendations are shown above. Adherence to guideline recommendations appears to be poor. In a large population-based study of new users of RAASi drugs, < 33% of

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patients had a K^+ measurement within 30 days of drug initiation and only 76% had at least one measurement within the first year of treatment.[12] In another study, Chang et al reported that 20% of patients had no serum K^+ monitoring within 3 years of initiation of antihypertensive medication that affect potassium levels.[13]

Two large population based cohort studies performed to assess whether follow-up testing reduces treatment-related adverse events showed that follow-up blood testing was associated with increased 30-day hospitalisation or ED attendances with AKI and hyperkalaemia, but did not lower 30-day all-cause mortality.[14]

When to reduce or stop RAASi drugs

RAASi drugs can cause a rise in serum K^+, creatinine or both after initiation or after a dose up-titration. Within acceptable parameters, no change in treatment is necessary, but outwith these parameters (see below), a dose reduction or drug cessation may be required.

- The NICE CKD Guideline (2021) recommends that RAASi drugs should be withdrawn if the serum K^+ is ≥ 6 mmol/l. If serum creatinine increases by > 30% above baseline (equivalent to fall in eGFR > 25%), reduce or stop RAASi unless alternative cause is found. [10]
- The KDIGO Guideline (2023) recommends continuation of RAASi unless serum creatinine rises by > 30% within 4 weeks following initiation of treatment or an increase in dose.[11]

When to temporarily withhold RAASi drugs

The sick day rules for patients with diabetes, kidney or cardiovascular disease provides guidance to temporarily stop some medications (RAASi, diuretics, metformin, SGLT2i) during acute dehydrating illness (e.g. diarrhoea and vomiting).[15]

The RA/ BSH (2019) advise withdrawal of RAASi at all severities of hyperkalaemia in the context of acute illness (sepsis, hypovolaemia and/or AKI).[9] However, in the context of decompensated heart failure, the continuation/ reduction of RAASi therapy was permitted in patients with mild or moderate hyperkalaemia, but withdrawn if serum K^+ ≥ 6.5 mmol/l.

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The KDIGO Guideline (2023) recommends reducing or discontinuing RAASi in the setting of either symptomatic hypotension or uncontrolled hyperkalaemia despite medical treatment or to reduce uraemic symptoms while treating kidney failure (eGFR < 15 ml/min).[11]

When to consider K^+ binders for chronic hyperkalaemia

NICE has approved the use of potassium binders (patiromer and sodium zirconium cyclosilicate) 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.[16, 17] RAASi should be withdrawn in all patients with serum K^+ is ≥ 6 mmol/l who do not meet the criteria for these novel potassium binders.

When to re-start RAASi drug after acute illness

An important consideration in the management of an episode of hyperkalaemia is the balance between the immediate risk vs 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.

The RA/ BSH (2019) advise RAASi re-introduction after recovery and when K^+ is < 5.5 mmol/l.[9] Patients receiving multiple RAASi drugs and/or MRA should re-start one drug at a time.[9]

Involvement of specialist services, renal and heart failure teams, may facilitate safer re-introduction of treatment.

MRAs

Mineralocorticoid receptor antagonists (MRAs) have significantly improved heart failure management, but their use alone or in combination with RAASi, may exacerbate hyperkalaemia.

The European Society of Cardiology [18] and American Heart Association (AHA)/ American College of Cardiology (ACC) [19] have provided guidance for the initiation, monitoring and titration of MRAs.

- Acceptable baseline parameters: serum K^+ < 5.0 mmol/l and an eGFR > 30ml/min.
- Monitor Urea & Electrolytes (U&Es) at 1, 4, 8 and 12 weeks following initiation.
- Thereafter, monitor U&Es every 3 months during 1st year

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- From 2nd year onwards, monitor U&Es every 3-4 months.

The approach to treating hyperkalaemia in patients with heart failure on MRA is shown in the text box below. In patients without heart failure, drug cessation is recommended if serum $K^+ \geq$ 6.0 mmol/l.

Strategies for Managing Hyperkalaemia in patients with Heart failure on MRA

- K^+ 5.5-5.9 mmol/l: Reduce dose by half and monitor U&Es
- K^+ > 6.0 mmol/l: Start potassium binder (Patiromer or SZC) and monitor U&Es

Combined treatment of RAASi and an aldosterone antagonist increase the risk of hyperkalaemia, but Sinnott et al reported <33% of patients taking a RAASi had biochemical monitoring within two weeks of initiation of an aldosterone antagonist.[20] This highlights the gap in knowledge and clinical practice.

Nonsteroidal MRAs

Finerenone is a novel nonsteroidal, selective MRAs which has been shown to improve cardio-renal outcomes in patients with CKD and Type 2 diabetes.[21, 22] However, Finerenone was associated with a 2-fold higher risk of hyperkalaemia compared with placebo in the FIDELIO-DKD Trial.[21]

The KDIGO CKD Guideline (2023) suggests a nonsteroidal MRA (e.g. Finerenone) may be used in patients with Type 2 diabetes with an eGFR > 25ml/min, normal serum K^+ level, and albuminuria > 3 mg/mmol, despite maximum tolerated dose of RAASi.[11] A nonsteroidal MRA may be added to a RAASi and an SGLT2i for treatment of Type 2 diabetes and CKD in adults. To mitigate the risk of hyperkalaemia, serum K^+ should be monitored regularly. If serum K^+ > 5.5 mmol/l, Finerenone should be withheld.

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I. Hyperkalaemia in the Community (Guidelines Hyperkalaemia 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 $K^+ \geq 5.5$ mmol/l. (1B)

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.

Approximately 20% of patients with moderate-severe CKD develop hyperkalaemia ($K^+ > 5.5$ mmol/l) and many have recurrent episodes.[1] Data from several studies performed in the general population and in patients with CKD show an increased mortality risk in patients with a serum $K^+ \geq 5.5$ mmol/l.[2-7] 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.

National guidance from the Renal Association and British Society for Heart Failure (2019) provides recommendations to manage hyperkalaemia when the serum K^+ rises to ≥ 5.5 mmol/l.[8] This includes cessation of drugs that potentiate hyperkalaemia (e.g. K^+ supplements, Trimethoprim, NSAIDs, amiloride), avoidance of over-diuresis and dietary advice. 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.

Similarly, the KDIGO Guideline (2023) have also stated a threshold of $K^+ > 5.5$ mmol/l for initiation of strategies to manage hyperkalaemia in the non-emergent setting.[9] They have described a 3-tier approach to address:

- Correctable factors: Optimise bicarbonate level, optimise glycaemic control and consider loop diuretic and SGLT2i.
- Dietary restrictions: Assess dietary K^+ intake and consider dietetic referral

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- Medications: Consider dose adjustment of K^+-elevating drugs and consider initiation of K^+-binder.

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II. Hyperkalaemia in the Community (Guidelines Hyperkalaemia 4.1 – 4.2)

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

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

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

We suggest hospital assessment 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:

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28. Proportion of patients admitted to hospital with severe hyperkalaemia detected in the community who subsequently did not warrant emergency treatment on repeat testing.

Rationale (Guidelines Hyperkalaemia 4.1 – 4.2)

There is substantial variability in clinical practice related to referral for hospital assessment for 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 6, can precipitate severe hyperkalaemia.[1, 2]

Drugs that potentiate risk of hyperkalaemia in patients receiving RAASi and/or MRAs
Trimethoprim/co-trimoxazole
Potassium sparing diuretics
Potassium supplements
NSAIDs
Non-selective beta-blockers
Salt substitutes (lo-salt)
Digoxin toxicity

Table 6: Drugs that pose an additive effect on risk of hyperkalaemia in patients receiving RAASi and MRAs.

Acute illness is another common antecedent to hyperkalaemia. The REVEAL-ED study examined treatment patterns for hyperkalaemia in the Emergency Department and found that 79% of visits resulted in hospitalisation.[3] A further study found that the average patient with hyperkalaemia is expected to have 0.44 in-patient admissions per year.[4] Severe hyperkalaemia has also been shown to be an independent predictor of hospitalisation, all-cause and in-hospital mortality.[5]

Several studies have reported increased in-patient mortality associated with hyperkalaemia.[6-8] Davis et al found that in-patient mortality correlated with the severity of hyperkalaemia:

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12.3% in patients with mild, 15.5% with moderate and 19.5% with severe hyperkalaemia.[9] This is higher than a previous report which showed an in-patient mortality of 8%.[8]

A defined threshold for triggering intervention in the community and for prompting referral to hospital could improve patient outcome. 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.

Patients in the community with a serum K^+ ≥ 6.5 mmol/l should be referred to hospital for urgent assessment and treatment.

The position statement for 'Think Kidneys' (2017), recommend hospital admission in all patients with severe hyperkalaemia (K^+ ≥ 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.[10] Hospital admission should be considered in patients with mild hyperkalaemia (K^+ 5.5-5.9 mmol/l) if acutely unwell or have an AKI.

The RA/ BSH (2019) guidance for patients with heart failure also advise hospital admission for patients with severe hyperkalaemia (K^+ ≥ 6.5 mmol/l).[2]

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I. Hyperkalaemia in the Community (Guidelines Hyperkalaemia 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 persistent hyperkalaemia with a serum $K^+ > 5.5$ mmol/l. (1B)

Audit measures:

1. Proportion of patients with moderate hyperkalaemia who have received dietary potassium advice in the renal out-patient setting.

Rationale (Guideline 5.1)

Chronic management of hyperkalaemia usually starts with dietary education and institution of a low-K^+ diet. Dietary potassium comes from a wide range of foods including fruit and vegetables, meat and meat products, cereals, drinks, milk and milk products. Fruit and vegetables accounts for approximately 33% dietary potassium intake.[1]

Dietary advice in adults without kidney disease:

WHO recommends an average dietary K^+ intake of approximately 3.9g/ day (100mmol).[2] The Institute of Medicine, Food and Nutrition Board recommend a higher daily K^+ intake of 4.7g/ day (120mmol/l).[3] There is some evidence that increased K^+ intake in the general population reduces systolic blood pressure in adults with hypertension[4] and may also reduce risk of stroke.[5]

Dietary advice in patients with CKD (non-dialysis):

A low K^+ diet is defined as a dietary intake of 2-3g/day (51-77 mmol/day)[6]. In patients with CKD with persistent hyperkalaemia (serum $K^+ \geq 5.5$mmol/l), a dietary K^+ restriction of < 3g/ day

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(< 77 mmol/l) [7] or 1 mmol/kg/IBW [8] is recommended. In reality, a step-wise reduction in potassium intake is usually undertaken. Excessive dietary restrictions can result in a poorer diet which may risk development of cardiovascular disease [9] and contribute to malnutrition, particularly in advanced CKD. 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 ultimate goal.

Borrelli et al (2021) studied the association between current therapeutic options and control of serum K^+ in non-dialysis CKD patients receiving nephrology care (n=562, eGFR 39.8 ml/min, RAASi 76.2%) during a 12-month period.[10] Patients were stratified into four groups based on the presence of a $K^+ \geq 5.0$ mmol/l at baseline and at 12-month. During the study period, patients in all cohorts received bicarbonate supplements, K^+-binders and diuretics. Approximately 34% of patients had either new onset or persistent hyperkalaemia despite a low-K^+ diet and increase use of K^+-lowering drugs.

There are several National and International guidelines on the management of nutrition in CKD.

The UKKA (2019) Clinical Practice Guideline on Under-nutrition in CKD provides guidance on screening for risk of undernutrition in patients with CKD stages 4 and 5. Assessment by a specialist renal dietitian is also advised when patients begin education about RRT and within one month of dialysis initiation.[11]

NICE (2021) recommend offering dietary advice about potassium, phosphate, calorie and salt intake appropriate to the severity of CKD.[12]

The International Society of Renal Nutrition and Metabolism and the National Kidney Foundation (2021) have collaborated to provide an update on the Clinical Practice Guidelines for nutrition in CKD.[13] The new guidelines recommend screening patients with CKD stages 3-5D for nutritional status bi-annually using composite scores rather than single biomarkers (e.g. albumin) and considering specialist dietetic assessment. Dietary K^+ intake is tailored to maintain an acceptable serum level.

KDIGO (2023) recommend the use of registered dieticians or accredited nutrition providers to provide information for patients with CKD G3-G5 with emergent hyperkalaemia about dietary adaptations for potassium intake tailored to individual needs, severity of CKD, other

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comorbidities and quality of life.[14] Some patients may also warrant pharmacological intervention.

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I. Hyperkalaemia in the Community (Guidelines Hyperkalaemia 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)

Rationale (Guideline 6.1)

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Epidemiological studies show a prevalence of metabolic acidosis of 15-19% in patients with CKD stages 3-5.[1] The prevalence of metabolic acidosis increases with worsening severity of kidney disease and has been found in 30-50% of patients with eGFR < 30 ml/min.[2, 3] In patients without diabetes, the adjusted prevalence of serum bicarbonate < 22 mmol/l was 6.7% in patients with Stage G3, A1, but rises to 35.9% in patients with CKD Stage 5, A3.[4] Similarly, in patients with diabetes, the adjusted prevalence of serum bicarbonate < 22 mmol/l was 7.7% in patients with Stage G3, A1, but rises to 38.9% in patients with CKD Stage 5, A3.[4] Furthermore, serum bicarbonate levels steadily decrease with age > 60 years.[5] 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.

Potential benefits to bicarbonate replacement in patients with CKD

The benefit of treating chronic acidosis goes beyond the management of hyperkalaemia. Metabolic acidosis is also associated with muscle wasting, bone disease, hyperkalaemia and more rapid progression of CKD.[6] Additionally, there is some evidence that metabolic acidosis contributes to the progression of CKD.[1, 7, 8] 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).[7, 9]

Evidence-base for bicarbonate replacement in patients with CKD

A meta-analysis of all published RCTs (2019) investigating the effect of oral bicarbonate therapy in adults with CKD showed a slightly higher eGFR and serum bicarbonate levels in patients treated with oral replacement compared with placebo and this positive effect was attenuated in studies reporting outcomes at one year.[10] This study did not assess potassium levels.

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The BiCARB Trial (2020) is the largest placebo-controlled trial of oral sodium bicarbonate and evaluated the benefits and adverse effects of sodium bicarbonate in older patients with CKD for a period of up to 2 years. It included 380 community-based patients in the UK aged ≥ 60 years with an eGFR < 30 ml/min and serum bicarbonate < 22 mmol/l.[11] In contrast to other longterm studies, this study found no significant reduction in serum K^+ level. The BiCARB trial also reported no improvement in physical function or renal function and a higher rate of adverse events compared with placebo.

A systematic review (2021) identified 15 trials with ≥3 months of follow-up in patients with CKD (eGFR < 60 ml/min) to compare the effects of oral sodium bicarbonate vs placebo or versus no study medication on kidney outcomes.[12] The meta-analysis was limited to the placebo controlled trials and did not confirm any important effect of sodium bicarbonate on the risk of kidney failure.

A further systematic review (2022) including 18 studies found no benefit of bicarbonate replacement in reducing all-cause mortality, cardiovascular events or a decline in renal function in patients with advanced CKD.[13]

Risk of bicarbonate replacement in patients with CKD

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.[8] 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.[9, 14, 15]

National and International recommendation for bicarbonate replacement in CKD

There remains a paucity of evidence from clinical trials on the efficacy and safety of bicarbonate therapy, therefore many existing guidelines are based on expert consensus opinion.

The NICE CKD Guideline (2021) suggests that oral sodium bicarbonate should be considered in patients with and eGFR < 30 ml/min (CKD G4 or G5) with a serum bicarbonate < 20 mmol/l.[16]

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The KDOQI CKD guideline (2023) suggests using dietary and/or pharmacological treatment to prevent severe acidosis (e.g. bicarbonate < 16 mmol/l) and care should be taken to avoid over-correction or an adverse effect on BP control, serum potassium or fluid status.[4] This recommendation has not been graded due to the lack of large-scale RCTs supporting its use.

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I. Hyperkalaemia in the Community (Guidelines Hyperkalaemia 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)

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.[1] Diuretics should be avoided in patients who are hypovolaemic or oliguric.

Role of Diuretics in chronic hyperkalaemia

Diuretic therapy has a place in the management of chronic hyperkalaemia in patients who are normovolaemic or hypervolaemic. 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. The Sick Day rules apply, therefore diuretics should be withheld during acute illness.[4, 5]

Patients with heart failure

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.[6, 7]

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.[6] This combination potentiates diuresis and should theoretically enhance K^+ excretion.

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I. Hyperkalaemia in the Community (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 option to treat chronic hyperkalaemia in non-hospitalised patients who do not meet the criteria for Patiromer or Sodium Zirconium Cyclosilicate. (2C)

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. CPS is approved for use in Europe and SPS approved for use in the USA.

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).

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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.

Evidence-base for CPS and SPS in chronic hyperkalaemia

Although these resins have been used in clinical practice for decades, there have been only 4 RCTs evaluating SPS to reduce potassium levels and only one of these studies showed a statistically significant reduction after seven days.[4-7]

Gruy-Kapral (1998) reported a placebo-controlled randomised study of SPS in normokalaemic patients with ESRD on HD (n=6) and failed to show any significant reduction in serum K^+. The size, design and insufficient baseline data renders this study weak.[6]

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.[5]

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 ($p=0.07$).[4]

Nakayama et al (2018) performed a randomised crossover study (n=20) in pre-dialysis patients with hyperkalaemia ($K^+ > 5$ mmol/l). Patients received either SPS or CPS therapy for 4 weeks to compare efficacy of these resins. There was no significant difference in serum K^+ from baseline between the two groups, but the authors suggested that CPS may be safer as it did not induce volume overload.[7]

A Cochrane review (2020) evaluated CPS and SPS in chronic hyperkalaemia and concluded there is insufficient high-quality evidence to recommend their use for chronic hyperkalaemia in patients with CKD.[8]

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Considerations when using Calcium resonium (CPS)

Tolerability and the risk of severe gastrointestinal adverse effects limit their longterm use.[9, 10] The risk of gastro-intestinal events is enhanced by the concomitant use of sorbitol.[10]

The availability of novel potassium binders (patiromer and sodium zirconium cyclosilicate) with a stronger evidence base for efficacy and more favourable side-effect profiles have already started to replace CPS and SPS in clinical practice.

Given that UK guidance from NICE and SMC have given restricted indications for the use of Patiromer and SZC for treating chronic hyperkalaemia (see Guideline 9.1 and 10.1), calcium resonium may still be an option for patients who do not meet the criteria. SPS and CPS are no longer recommended in the acute setting.

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I. Hyperkalaemia in the Community (Guideline 9.1)

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

We recommend that Patiromer is an option in the management of persistent hyperkalaemia with a confirmed serum $K^+ \geq 6.0$ mmol/l in out-patients with CKD Stage 3b-5 (not on dialysis) or heart failure receiving a sub-optimal dose or not receiving RAASi therapy due to hyperkalaemia. (1A)

Guideline 9.2 – Patiromer for the management of Hyperkalaemia

We recommend that treatment with Patiromer is discontinued if RAASi therapy is stopped. (1A)

Guideline 9.3 – Patiromer for the management of Hyperkalaemia

We recommend that Patiromer 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 patiromer who achieved a serum $K^+ \leq 5.0$ mmol/l within 1 week.
2. The proportion of out-patients who achieve maximal dose RAASi therapy whilst taking patiromer.

Rationale (Guideline 9.1 – 9.3)

Patiromer is a non-absorbed, sodium free, K^+-binding polymer.[1] Calcium is used, rather than sodium, as the counter ion 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.[1] 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.[1]

Until the availability of K^+-binders, the standard approach to treating chronic hyperkalaemia has been a dose reduction or cessation of cardioprotective medication along with the institution of a low K^+ diet. Dietary K^+-restriction was implemented in patiromer trials and K^+-lowering drugs are unlikely to replace a low K^+ diet although may allow a less restrictive intake.

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The definition of hyperkalaemia used in the patiromer trials to guide treatment differed from the Renal Association (2014) [2] and European Resuscitation Council (2015) [3] guidelines available at that time. 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.[4-9] Early studies included 3 Phase I clinical pharmacology studies and 12 single dose drug-drug interaction studies as summarised in Table 7.[10]

Evidence-base for Patiromer for chronic hyperkalaemia

In the PEARL-HF [11] and PEARL-HF extension [9] studies, all participants had a diagnosis of chronic heart failure. Fewer patients in OPAL-HK (42%)[5] and AMETHYST-DN (35%)[6] 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.

STUDY	N=	Study Duration	Mean Baseline K^+ (mmol/l)	Study Groups	CHANGE IN SERUM K^+ by PATIROMER DOSE (dose in g twice daily)				
					4.2g	8.4g	12.6g	15g	16.8g
PEARL – HF Pitt 2011 [11] Phase II trial	104	4 weeks	4.69	**Patiromer** N= 55				-0.22	
			4.65	**Placebo** N= 49				+0.23	
OPAL-HK Weir 2015 [5] Phase III trial	243	**Phase 1** ***Treatment*** 4 weeks	5.3	**Mild HK** 5.0-5.4 N= 92	-0.65				
			5.7	**Mod-Sev HK** 5.5-6.4 N= 151		-1.23			
	107	**Phase 2** ***Withdrawal*** 8 weeks	4.49	**Patiromer** N=55	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				
			4.45	**Placebo** N=52	+ 0.72				
AMETHYST-DN Bakris 2015 [6] Phase II trial	306	52 weeks	5.3	**Mild HK** 5.0-5.5 N=222	-0.35	-0.51	-0.55		

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				Mod HK 5.6-5.9 N=84		-0.87	-0.97		-0.92
Bushinsky 2015 [7] Prospective	25	48 hours	5.93	**All**		7hrs: -0.21 20hrs: -0.52 48hrs: -0.75			
TOURMALINE Pergola 2017 [8] Randomised Open label	112	4 weeks	5.34	**With Food** N=55	-0.65 median daily dose was 8.4g (8.4, 12.6)				
			5.44	**Without Food** N=57	-0.62 median daily dose was 8.4g (8.4, 14.1)				
PEARL-HF extension study Pitt 2018 [9] Open-label	63	8 weeks	4.78	**All**		-0.13			

1 **Table 7: Studies of efficacy of Patiromer in the treatment of hyperkalaemia.**

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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.

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)[6] and 13% of participants in the PEARL-HF extension study (8 weeks)[9]. 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.

A meta-analysis of the patiromer clinical trials (2015) showed that the mean reduction in serum K^+ at Day 3 was 0.36 mmol/l and at 4 weeks was 0.70 mmol/l.[12] Overall, 93% of patients could continue, start or titrate RAASi therapy during the maintenance phase of the studies.[12]

The AMBER trial was a Phase 2 RCT to investigate the efficacy of Patiromer vs placebo in patients with resistant hypertension and CKD (eGFR 25-45 ml/min).[13] At 12-weeks, 86% of patients treated with Patiromer compared with 66% treated with placebo remained on spironolactone ($p<0.0001$).

Haller et al (2022) performed a pooled analysis of three RCTS (AMETHYST-DN, OPAL-HK, and TUROMALINE) to determine the safety and efficacy of Patiromer in hyperkalaemic patients with CKD most of whom were receiving a RAASi.[14] Patients were stratified into two groups based on renal function: mild/ moderate (eGFR ≥ 45ml/min) and severe/ end-stage (eGFR < 45 ml/min) and data over a 4-week treatment period was assessed. The mean reduction in serum K^+ was 0.6 mmol/l and 0.84 mmol/l respectively. Patiromer discontinuation due to adverse effects was 2% and 6% respectively.

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Zhuo et al (2022) assessed the risk of hospitalisation for heart failure in patients with hyperkalaemia treated with Sodium Zirconium Cyclosilicate (SZC) vs Patiromer.[15] Although the incidence of hospitalisation was higher in the SZC vs Patiromer group (35.8/ 1000 vs 25.1/ 1000 person-years), it did not reach statistical significance.

The DIAMOND trial (2022) investigated the use of Patiromer for managing hyperkalaemia in patients with heart failure with reduced ejection fraction.[16] Patients with current or historic RAASi-related hyperkalaemia (n=1642) were enrolled in a placebo-controlled run-in phase of up to 12 weeks. Patiromer was used whilst concurrently optimising RAASi and MRA therapy to specified target doses which was achieved in 84.6% of patients. The risk of hyperkalaemia (K^+ > 5.5 mmol/l) and reduction of MRA dose was lower in the Patiromer group.

Recommendation for use of Patiromer for chronic hyperkalaemia

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.

NICE[17] and SMC[18] have approved the use of patiromer in the treatment of chronic hyperkalaemia. The key evidence for clinical effectiveness was derived from the OPAL-HK study which showed a reduction in serum K^+ by a mean of 1.01 mmol/l after 4 weeks (Phase 1).[5]

NICE and SMC criteria for use of Patiromer in the treatment of chronic hyperkalaemia:

- **CKD Stage 3b-5 OR Heart Failure**
  AND
- **Serum K^+ confirmed to be ≥ 6.0 mmol/l**
  AND
- **Receiving a sub-optimal dose or not taking RAASi due to hyperkalaemia**
  AND
- **Not on dialysis**

Patiromer should be initiated in secondary care.

Stop Patiromer if RAASi therapy is discontinued.

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The Cochrane review of potassium binders for chronic hyperkalaemia in people with CKD (2020) included 15 studies (n=1849 participants).[19] Three of these studies were among patients treated with haemodialysis. Binders included calcium polystyrene sulfonate, sodium polystyrene sulfonate, patiromer, and sodium zirconium cyclosilicate. The certainty of evidence for all outcomes was low and studies were not designed to measure clinical outcomes such as arrhythmias. Patiromer made little to no difference to death.

Blood monitoring for patients treated with Patiromer for chronic hyperkalaemia

The drug data sheet suggests that serum K^+ should be monitored as clinically indicated.[1] A reasonable approach would be weekly for the first month after every dose titration, and then monthly thereafter.

A rebound in serum K^+ occurs on cessation of patiromer, therefore withdrawal should be undertaken cautiously. The serum K^+ may rise as early as two days after cessation of patiromer, especially if RAASi therapy is continued,[1] therefore monitor serum K^+ within one week after drug cessation.

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I. Hyperkalaemia in the Community (Guidelines 10.1 – 10.3)

Guideline 10.1 – Sodium Zirconium Cyclosilicate for the management of Hyperkalaemia

We recommend that Sodium Zirconium Cyclosilicate (SZC) is an option in out-patients for the management of persistent hyperkalaemia with a confirmed serum $K^+ \geq 6.0$ 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)

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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 $K^+ \leq 5.0$ 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 Ca^{2+} or Mg^{2+} compared with SPS.[3] A comparison of the mechanism of action of all oral K^+ binders is shown in Appendix 2.

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 is described in Appendix 4E.

Evidence-base for SZC for chronic hyperkalaemia

Initial studies included three randomised controlled trials and one open label clinical trial. The first was a double-blind RCT (2015) 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] ZS-005 investigated efficacy of SZC over 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.

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STUDY	Study Design	N =	Study duration	Dose of SZC (x3/day)	Renal function eGFR (ml/min)	Mean Baseline K^+ (mmol/l)	K^+ Change (mmol/l)
ZS-002 [4] Ash 2015	Phase II RCT	90	48 hrs	Placebo 0.3g 3g 10g	58.1 ± 26.5 56.5 ± 24.0 57.1 ±22.1 51.6 ± 22.3	5.1 ± 0.4 5.2 ± 0.3 5.0 ± 0.3 5.1 ± 0.4	- 0.26 ± 0.4 - 0.39 ± 0.4 - 0.42 ± 0.4 - 0.92 ± 0.5
ZS-003 [5] Packman 2015	Phase III RCT	753	**Stage 1** 48 hrs	**Induction** (randomised) Placebo 1.25g 2.5g 5g 10g		 5.3 5.4 5.4 5.3 5.3	 - 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)
			Stage 2 Days 3-14	**Maintenance** (randomised) Placebo SZC 5g		3.5 – 4.9	 + 0.47%/ hr + 0.09%/ hr
				Placebo SZC 10g			+ 1.04%/ hr + 0.14%/ hr
ZS-004 [6] HARMONIZE Kosiborod 2014	Phase III RCT	258	**Stage 1** 48 hrs	**Induction** (open label) 10g	46.3 ± 30.5	5.6 ± 0.4	- 1.1 (1.0-1.1)
			Stage 2 28 days	**Maintenance** (randomised) Placebo 5g 10g 15g	 48.0 ± 28.8 48.0 ± 30.7 44.7 ± 30.7 44.9 ± 29.5	 4.6 ± 0.4 4.5 ± 0.4 4.4 ± 0.4 4.5 ± 0.4	 - 0.4 (0.3-0.6) - 0.8 (0.6-0.9) - 1.1 (0.9-1.3) - 1.2 (1.0-1.4)
ZS-004E [1]	Extension of ZS-004	123	11 mths	**Maintenance** (open label) 10g once daily	46.3 ± 30.5	4.6	88% of patients achieved K^+ < 5.1 mmol/l
ZS-005 [7] Spinowitz 2019	Phase III Open-label Prospective (single arm)	751	24-72 hrs	**Acute Phase** 10g	< 60: 73.5% ≥ 60: 25.3%	5.6	- 0.8
			12 mths	**Extended Phase** 5g once daily titrated to 10 or 15g/ day OR 5g alt days		5.6	- 1.0
HARMONIZE - GLOBAL [8] Zannad 2020	Phase III RCT	267	48 hrs	**Correction Phase** 10g tds		5.7 ± 0.5	-1.28
			28 days	**Maintenance** (randomised) Placebo 5g 10g		3.5 – 5.0	Geometric LSM 5.32 (5.16, 5.49) 4.81 (4.69, 04.94) 4.38 (4.27, 4.50)

1 **Table 8: Studies of the efficacy of SZC in treatment of Hyperkalaemia**

2 SZC – Sodium zirconium cyclosilicate; hrs – hours; mths – months; LSM – least squares mean

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The key clinical trials for SZC in the treatment of hyperkalaemia are summarised in Table 8. These studies 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).

These clinical trials have demonstrated the efficacy of SZC. 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.[1] The median time to normalisation of serum K^+ was 2.2 hours.[6] SZC lowers serum K^+ by 1.1 mmol/l within 48 hours.[6] The ZS-003 and ZS-004 clinical trials also demonstrated a greater K^+-lowering effect with increasing severity of hyperkalaemia.[5, 6] In patients with a serum $K^+ > 6.0$ mmol/l, SZC lowers serum K^+ by 1.5 mmol/l within 48 hours.[6] In the longterm study conducted over 12 months, 87% of patients were able to continue RAASi or increase the dose and only 11% discontinued RAASi therapy.[7]

A meta-analysis of the SZC trials (2017) have shown that it lowers serum K^+ by 0.17 mmol/l at 1 hour and 0.67 mmol/l at 48 hours after administration.[9] In a subgroup analysis of patients with a baseline serum K^+ ranging from 6.1 – 7.2 mmol/l, SZC lowered serum K^+ by a mean of 0.4 mmol/l at 1 hour after administration of 10g dose.[10] In the HARMONIZE-Global study, significantly more patients achieved normokalaemia with SZC 5mg (58.6%) and SZC 10mg (77.3%) compared with placebo (24%).[8]

Roger et al (2021) conducted a Phase 3 study (n=751) to assess the longterm safety and efficacy of SZC in patients with mild-moderate vs severe-end-stage CKD.[11] During the correction phase, 82% of patients achieved normokalaemia in both eGFR groups within 24 hours. By 72 hours, 100% of patients with a baseline eGFR < 30ml/min and 95% of patients with a baseline eGFR ≥ 30 ml/min achieved normokalaemia suggesting equivalent efficacy across CKD stages.

The OPTIMIZE I Study (2023) evaluated RAASi modifications among patients (n=589) who initiated SZC for hyperkalaemia.[12] Most patients optimised RAASi dosage (77.4%). Overall, 69.6% maintained the same dose, and 7.8% had up-titration of dose after initiating SZC. A similar rate of optimisation was found in patients with CKD (78.9%) and those with CKD + diabetes (78.1%). At 1 year, 73.9% of all patients who optimised RAASi were still on therapy.

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Recommendations for use of SZC for chronic hyperkalaemia

NICE [13] and SMC [14] have approved SZC for restricted use as indicated below. The key evidence is that SZC reduces serum K^+ in two- and four-week studies. Safety and efficacy have also 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.

NICE and SMC criteria for use of SZC in the treatment of chronic hyperkalaemia:

- **CKD Stage 3b-5 OR Heart Failure**
  AND
- **Serum K^+ confirmed to be ≥ 6.0 mmol/l**
  AND
- **Receiving a sub-optimal dose or not taking RAASi due to hyperkalaemia**
  AND
- **Not on dialysis**

SZC should be initiated in secondary care.

Stop SZC if RAASi therapy is discontinued.

Cochrane review of potassium binders for chronic hyperkalaemia in people with CKD (2020) included 15 studies (n=1849 participants).[15] Three of these studies were among patients treated with haemodialysis. Binders included calcium polystyrene sulfonate, sodium polystyrene sulfonate, patiromer, and sodium zirconium cyclosilicate. The certainty of evidence for all outcomes was low. SZC made little to no difference to death.

Blood monitoring for patients treated with SZC for chronic hyperkalaemia

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).[1] Dose titration or cessation will be led by secondary care. In real-world practice, blood

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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.[7] Serum K^+ should also be assessed one week after drug cessation.[7]

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I. Hyperkalaemia in the Community (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. Proportion of patients with severe hyperkalaemia (Serum $K^+ \geq 6.5$ mmol/l) on admission to hospital who had been provided with 'Sick Day Rules' advice.

Rationale (Guideline 11.1 - 11.3)

Given the potential consequences of hyperkalaemia, preventing its occurrence in the first instance (primary prevention) is the ideal strategy. This requires care with drug prescribing, blood monitoring in the community, dietary intervention for patients at risk and patient education about the risks particularly during acute illness.

Recurrence after an initial episode should be anticipated and steps taken to avoid this (secondary prevention). The principles are similar to above, but the use of K^+-binders should be considered, particularly in the context of maintaining or optimising RAASi therapy.

Careful drug prescribing

Drug prescribing in the community and out-patient setting is a major factor for the development of hyperkalaemia. The elderly is very susceptible to hyperkalaemia and polypharmacy is a common problem. Increased awareness of drugs that can cause hyperkalaemia and monitoring

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patients at risk may reduce morbidity, hospital admissions and mortality. Drugs commonly implicated in hyperkalaemia are shown below in Table 9.

RAASi (ACE Inhibitors, Angiotensin II Receptor Blockers, Mineralocorticoid Receptor Antagonists) **Potassium supplements** **Potassium-sparing diuretics** **Trimethoprim/ Co-trimoxazole** **NSAIDs** **Non-selective beta-blockers**	**RISK OF HYPERKALMAEMIA INCREASED IN:** Renal Impairment Diabetes Mellitus Elderly Use of > 1 RAASi drug Combining any of these groups of drugs

Table 9: Drugs implicated in development of hyperkalaemia and exacerbating factors.

RAASi drugs are commonly used in patients with CKD, but there are a few considerations prior to initiation and during the course of treatment. The NICE Clinical Guideline on '*Chronic Kidney Disease: assessment and management*' (2021) states that:[1]

- Combination of RAASi drugs should be avoided in patients with CKD.[2]
- RAASi should not be routinely started in patients with a serum K^+ level ≥ 5.0 mmol/l.
- RAASi should be discontinued if serum K^+ is ≥ 6.0 mmol/l.
- RAASi therapy can be continued if the GFR decrease from pre-treatment baseline is < 25% or the serum creatinine rise from baseline is < 30%.

The NICE Clinical Guideline on '*Chronic Heart Failure in adults: assessment and management*' (2018) 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.[3]

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.[4] An increase in serum K^+ level of 0.36 – 1.21 mmol/l or higher can occur within 3-10 days of treatment.[5] Co-treatment with RAASi or NSAIDs exacerbates hyperkalaemia.[4, 6] The elderly

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and patients with poor renal function are predisposed to trimethoprim-associated hyperkalaemia.[6]

Trimethoprim

- Use trimethoprim with caution in patients with severe renal impairment (eGFR < 30 ml/min)
- Avoid trimethoprim in patients receiving RAASi drugs (high risk of AKI and hyperkalaemia)

Blood monitoring

Hyperkalaemia is an anticipated complication in patients with a history of CKD, heart failure or diabetes mellitus as many of these patients are receiving RAASi drugs.

Patients taking RAASi or MRA drugs for any clinical indications, e.g. spironolactone for decompensated liver disease, also require surveillance for hyperkalaemia.

Blood monitoring in the community is discussed in Guidelines 1.1-1.2.

Dietary intervention

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.[7] 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.

Constipation can cause hyperkalaemia in patients with advanced renal failure. 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.[7, 8]

Sick Day rules

The 'Sick day rules' provides information to patients taking drugs that can contribute to the development of AKI and hyperkalaemia (e.g. RAASi, NSAIDs, diuretics, metformin) during acute

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illness. Temporary discontinuation of these medications during acute illness, particularly in the context of volume depletion (e.g. diarrhoea and/or vomiting, fevers/ rigors) may help to avoid AKI, but this strategy is controversial.

'*Think Kidneys*' urge 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.[9] 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.

The NICE '*Clinical Guideline on Acute Kidney Injury*' (2019) advises that temporary cessation of RAASi drugs should be considered during acute illness (diarrhoea, vomiting or sepsis) until clinical condition has improve.[10]

Watson et al (2022) undertook a scoping review and advice that patients with diabetes, kidney or cardiovascular disease should receive guidance to temporarily stop some medications (RAASi, diuretics, metformin, SGLT2i) during acute dehydrating illness (e.g. diarrhoea and vomiting).[11]

The KDIGO CKD Guideline (2023) acknowledge the sick day rules and advise that if medications are discontinued during an acute illness, a clear plan for re-initiation must be communicated.[12]

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 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.

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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. (1B)

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 persistent mild hyperkalaemia (K^+ 5.5 – 5.9 mmol/l) warrant a review of medication (e.g. RAASi) and dietary K^+ intake. Treatment of metabolic acidosis (serum bicarbonate < 22 mmol/l) and initiation of diuretics may be helpful in chronic hyperkalaemia.

Patients with persistent moderate hyperkalaemia (K^+ 6.0 – 6.4 mmol/l) who are not acutely unwell require similar considerations, however some may be candidates for a potassium binder.

Patients with moderate hyperkalaemia who are acutely unwell and those with severe hyperkalaemia (K^+ ≥ 6.5 mmol/l) warrant referral to hospital for urgent assessment.

Blood monitoring is essential after a hyperkalaemic event and the urgency is guided by the severity. Recurrence of hyperkalaemia is common, particularly in patients with CKD, therefore it is important to consider preventative measures.

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SECTION II

MANAGEMENT OF HYPERKALAEMIA

IN

HOSPITAL

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II. Hyperkalaemia in Hospital

Introduction

Hyperkalaemia is a potentially life-threatening medical emergency. The incidence in hospitalised patients ranges from 1 – 10%.[1-5] It is associated with increased hospitalisation and mortality, [6-9] and the risk of death increases with worsening severity of hyperkalaemia.[10] Patients with a diagnosis of heart failure, CKD/ ESRD, AKI or type 2 diabetes have a 28.9% relative increase of prevalence of hyperkalaemia and a 4% higher inpatient mortality.[11] The higher prevalence of hyperkalaemia in this patient population is largely attributable to the widespread use of RAASi drugs for cardiorenal protection.

Despite the clinical importance and increasing frequency of hyperkalaemia, 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.[12] 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.[12] The longer a patient has a high K^+ level, the greater the risk of sudden deterioration.[13] Urgent treatment can avoid life-threatening complications.[14, 15]

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.[14, 16, 17] 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.[18]

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.[16] Intravenous calcium salts (gluconate and chloride) are life-saving, but there are no clinical trials to prove efficacy.[16] Insulin-glucose infusion is the most effective treatment to lower serum K^+, but the optimal dose of Insulin to reduce the risk of hypoglycaemia without compromising efficacy is unknown. Beta-agonists appear to be effective in lowering serum K^+, but some patients are

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unresponsive. Sodium bicarbonate was frequently used in clinical practice, but there is little favourable evidence of its efficacy in treating acute hyperkalaemia.[16, 19]

Over the past 5 years, there has been some progress in the treatment of hyperkalaemia relating to management in hospitalised patients, but addressing iatrogenic hypoglycaemia remains a major goal. A low pre-treatment blood glucose may be the most appropriate starting point to identify patients at risk. Clinical experience with the use of the novel potassium binders is growing but their efficacy in the acute setting has not yet been definitively proven.

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.

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II. Hyperkalaemia in Hospitalised Patient (Guidelines 13.1)

Guideline 13.1 – 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 13.2 – Hyperkalaemia: Clinical Assessment; NEWS

We recommend that all patients with known or suspected hyperkalaemia undergo urgent clinical assessment using an early warning scoring system to assess level of acuity. (1C)

Audit measures:

1. Length of hospital stay and in-hospital mortality of patients admitted with hyperkalaemia.

Rationale (Guideline 13.1-13.2)

A careful medical history may identify risk factors for hyperkalaemia as shown in Table 10. 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). Apply a high index of suspicion of hyperkalaemia in patients groups at risk, e.g. patients with end-stage renal failure, diabetes, heart failure or liver failure. 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.[1, 2] Muscle weakness and/ or paraesthesiae may occur in severe

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cases and may progress to flaccid paralysis.[3-6] Drugs are commonly implicated in the aetiology of hyperkalaemia, therefore a careful record of all medications is essential.[2, 6] Ask about current medication, recent changes and use of over the counter medications.

Risk factors for Hyperkalaemia
Acute Kidney Injury
Dialysis dependency (haemodialysis or peritoneal dialysis)
Chronic Kidney Disease Stages 4 & 5 (CKD, eGFR < 30 ml/min/1.73m^2)
Drugs (renin-angiotensin-aldosterone inhibitors, NSAIDs, trimethoprim)
Cardiac failure
Diabetes mellitus (renin-angiotensin drugs, diabetic keto-acidosis)
Liver disease (spironolactone, hepato-renal failure)
Addison's Disease (primary adrenal insufficiency)
Hyporeninaemic hypoaldosteronism (Type IV renal tubular acidosis)

Table 10: Factors associated with an increased risk of hyperkalaemia.

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 is an established method for rapid systematic assessment of the acutely ill patient and allows problems, including hyperkalaemia, to be identified and treated promptly.[7] The National Early Warning Score (NEWS) was developed by the Royal College of Physicians,[8] and is used to identify acute ill patients.[9] Baseline assessment and serial monitoring is essential in identifying patients who are deteriorating and may require escalation of care.

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

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II. Hyperkalaemia in Hospitalised Patient (Guidelines 14.1 – 14.2)

Guideline 14.1 – Hyperkalaemia: ECG

We recommend that all hospitalised 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)

Audit measures:

1. Proportion of patients with a serum K^+ level ≥ 6.0 mmol/L who had a 12-lead ECG recorded before and after treatment for hyperkalaemia.

Rationale (Guideline 14.1 – 14.2)

The ECG is a readily accessible, inexpensive and non-invasive method of assessing for cardiac toxicity in patients with known or suspected hyperkalaemia. In terms of clinical significance, the

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type of ECG changes present is an important factor in predicting the outcome of patients with severe hyperkalaemia.[1] ECG abnormalities may reflect the severity and rate of rise of serum K^+.[1, 2]

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.[3] 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.

The ECG changes may be progressive with worsening severity as shown in Figure 1, but these changes do not always occur sequentially and multiple changes may occur concurrently.

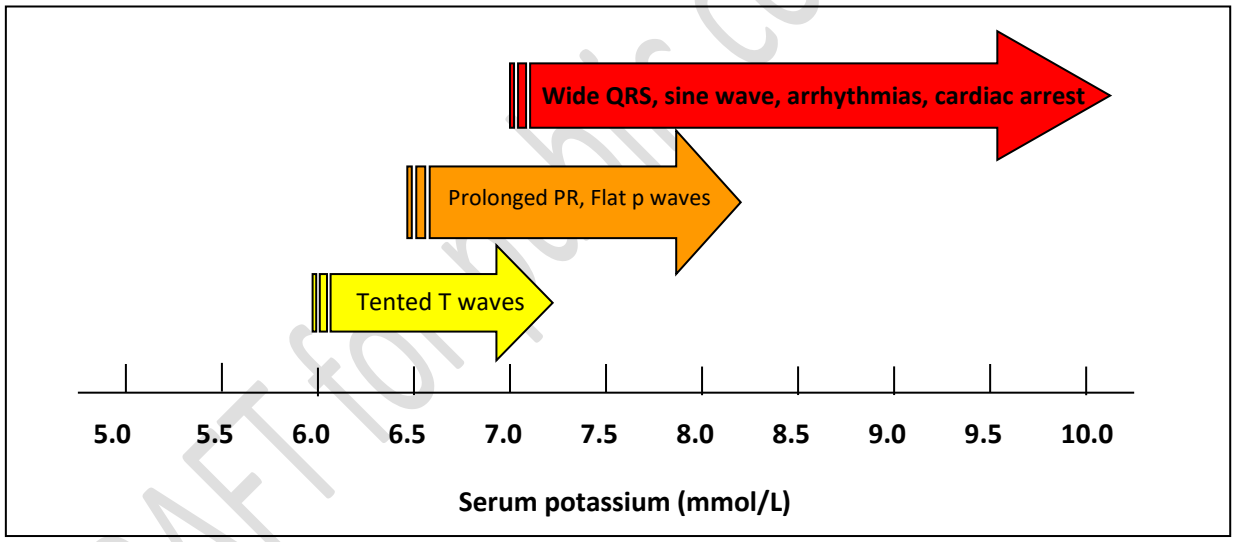


Figure 1: Progressive changes in ECG with increasing severity of hyperkalaemia.

The most commonly recognised ECG sign is peaked T waves, but on its own is rarely a sign of life-threatening hyperkalaemia.[2] A normal T wave usually has an amplitude of < 5mm in the precordial leads and < 10mm in the limb leads. The normal shape is asymmetric with a slow upstroke and a rapid down stroke. Peaked T waves have a high amplitude, narrow base, sharp pointy apex and are generally symmetrical.[4] Early studies reported the frequency of peaked T waves was 36% in hospitalised patients with hyperkalaemia.[5] Similarly, Freeman et al reported peaked T waves at presentation in 35% of patients with a serum K^+ > 6.0 mmol/l.[6] Durfey et al

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reported peaked T waves in 30% of patients with a serum $K^+ \geq 6.5$ mmol/l.[1] Given that peaked T waves occur in approximately one third of patients with moderate to severe hyperkalaemia, early recognition can prompt early intervention and prevent deterioration.

The typical ECG features of hyperkalaemia are shown below in Figure 2.

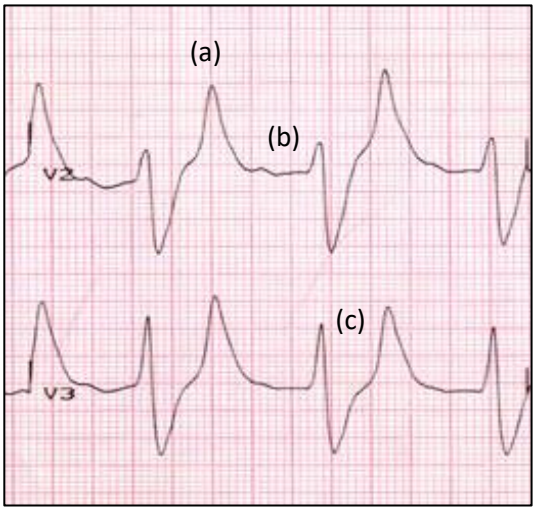


Figure 2: ECG in a patient with severe hyperkalaemia (serum K+ 9.1 mmol/l) illustrating peaked T waves (a), diminished P waves (b) and wide QRS complexes (c).

The reported utility of the ECG is variable. Some reports suggest that at least half of patients with a serum $K^+ \geq 6.5$ mmol/L show no ECG changes consistent with hyperkalaemia.[5-7] In contrast, Durfey 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 becomes more reliable with increasing severity.

When the diagnosis of hyperkalaemia can be established based on the ECG, treatment can be initiated even before serum biochemistry is available and this strategy was applied in 16% of patients in one series.[6] Durfey et al reported that the presence of a historical ECG for comparison did not affect the frequency of detection of ECG abnormalities suggestive of hyperkalaemia.[1]

The ECG can be used to risk stratify patients with severe hyperkalaemia. Durfey et al examined the ECG performed within 1 hour of K^+ measurement in patients with severe hyperkalaemia (serum $K^+ \geq 6.5$ mmol/l).[1] 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

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before any K^+-lowering treatment was initiated. All patients with an adverse event had a preceding ECG demonstrating at least one hyperkalaemic abnormality. Similarly, An et al demonstrated a higher in-hospital mortality in patients with serum $K^+ \geq 6.5$ mmol/l with typical ECG findings of hyperkalaemia compared with those with no ECG changes.

ECG features are present in approximately 66% of patients with severe hyperkalaemia ($K^+ \geq 6.5$ mmol/l).

The ECG may be normal even in severe hyperkalaemia.

Consider the clinical picture alongside ECG – severity of hyperkalaemia, rate of rise and level of acuity of patient.

Seek senior help if in doubt.

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 which is variable.[8, 9] Rafique et al reported a mean sensitivity of 0.19 (± 0.16) and specificity 0.97 (± 0.04).[8] This suggests that the ECG can be used to rule *in* a diagnosis of hyperkalaemia, but not to rule it *out*. Point-of-care Artificial Intelligence (AI) assisted ECG interpretation is being studied to reduce human error.[10] Secondly, the ECG may be normal even in the presence of severe hyperkalaemia.[11-16] Thirdly, the ECG appearance may be atypical with a pseudo-STEMI pattern or Brugada phenocopy.[2, 17-19] Finally, the first presentation with severe hyperkalaemia may be ventricular fibrillation or asystole.[20]

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.[21, 22] 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.

Continuous ECG monitoring allow for early recognition and prompt treatment of life-threatening arrhythmias in patients with hyperkalaemia. Hyperkalaemia causes arrhythmias by causing

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hyperpolarisation of cells, making them less able to depolarise when necessary.[23] Arrhythmias can occur at any time in the patient's presentation without prior toxic ECG changes.[24] All arrhythmias have been reported in patients with hyperkalaemia, including atrial fibrillation,[25] bradycardia,[26-33] and ventricular tachycardia.[34, 35] Some typical arrhythmias are shown in Figure 3.

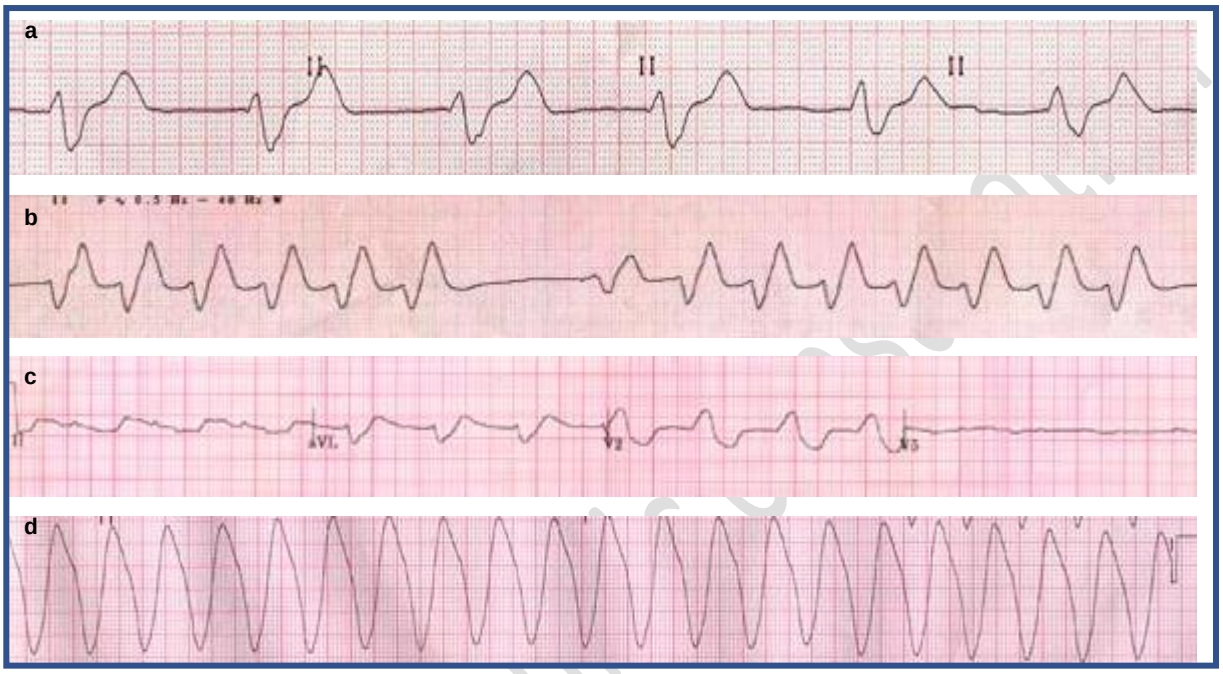


Figure 3: Arrhythmias in patients with severe hyperkalaemia illustrating bradycardia with wide QRS [K^+ 9.6 mmol/L] (a), sine wave with pause [K^+ 9.3 mmol/L] (b), sine wave without pause [K^+ 8.4 mmol/L] (c), and ventricular tachycardia [K^+ 9.1 mmol/L] (d).

ECG signs most closely correlated with adverse events are QRS prolongation, bradycardia (HR < 50), and/or junctional rhythms.[1] 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.[24, 29] Negatively chronotropic drugs (e.g. beta blockers) exacerbate bradycardia in hyperkalaemic patients.[30-33, 36] 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.[28, 37, 38]

The BRASH (Bradycardia, Renal failure, Atrioventricular node blockers, Shock and Hyperkalaemia) syndrome describes refractory bradycardia and haemodynamic instability in the context of

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hyperkalaemia in patients receiving rate controlling drugs.[39, 40] A systematic review found that more than half of all cases presented with non-severe hyperkalaemia (K^+ < 6.5 mmol/l).[40] In this report, most patients responded to medical therapy, but 20% required renal replacement therapy and 33% required temporary pacing.[40]

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II. Hyperkalaemia in Hospitalised Patient (Guidelines Hyperkalaemia 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)

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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]

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.

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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, 8-10]
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.[11-16] Point of care testing in the ED can also reduce length of stay and improve patient flow.[15] However, there

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are conflicting reports on the limits of agreement between BGA and laboratory K^+ measurement in this setting.[17]

4. In the Renal Unit setting, a prospective study has shown agreement between the BGA and laboratory K^+ levels (-0.04 mmol/l).[18] Importantly, this represents one of the few studies conducted with patients with K^+ level within the hyperkalaemic range. A wider difference between BGA and laboratory K^+ level of 0.62 mmol/l was noted in a study of patients with moderate and severe hyperkalaemia.[12] These findings suggest that the difference between the two methods increases at a higher range of potassium concentration.

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 the 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).[19] 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.

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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 is a laboratory artifact rather than a biological abnormality.[1] It

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was first reported in 1955 and describes the finding of a raised *serum* (clotted blood) K^+ value concurrently with a normal *plasma* (non-clotted blood) K^+ value.[2] Pseudo-hyperkalaemia is detected when the serum K^+ level exceeds that of the plasma by more than 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.[3] Consider pseudo-hyperkalaemia in the context of normal renal function, normal ECG and in patients with haematological disorders.[4]

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:

[Serum K^+] – [Plasma K^+] > 0.4 mmol/l

The most common cause of pseudo-hyperkalaemia is a prolonged transit time to the laboratory or poor storage conditions.[5] Other causes of pseudo-hyperkalaemia include difficult venepuncture, a high platelet count, haemolysis, erythrocytosis, prolonged storage time of clotted samples, or cold storage conditions.[5] 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).[4, 6] Another common cause of contamination is sampling from the arm into which K^+-containing fluids are being infused. An inverse relationship between ambient temperature and K^+ concentration has been reported with higher K^+ values in the winter months and has been termed 'seasonal' pseudo-hyperkalaemia.[5, 7] The KDIGO CKD Guideline (2023) provides a summary of the factors and mechanisms that impact on K^+ measurements.[8]

Laboratories have developed standard protocols to reduce the risks of pseudo-hyperkalaemia and pseudo-*normo*kalaemia. 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.

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The importance of recognition of pseudo-hyperkalaemia is the avoidance of unnecessary treatment which could cause harm.[9]

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II. Hyperkalaemia in Hospitalised Patient (Guidelines Hyperkalaemia 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 has varied considerably in clinical practice. A systematic approach, as shown in Figure 4, takes into account clinical priorities, may reduce variability, enhance patient outcome and reduce adverse events related to hyperkalaemia and its treatment.[1]

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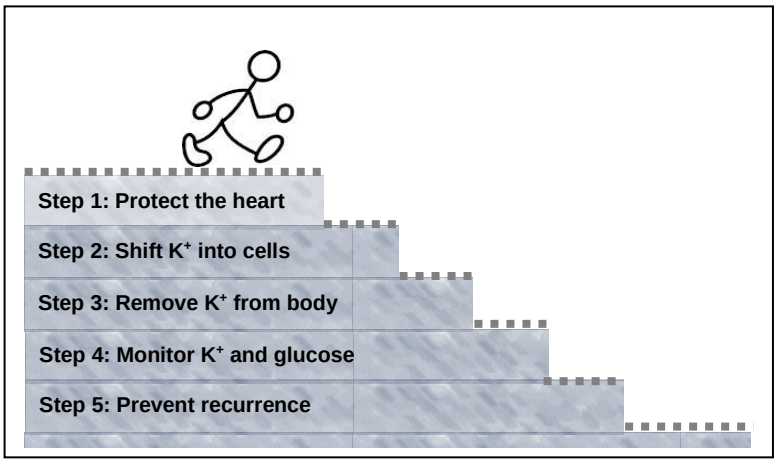


Figure 4: There are five key steps in the treatment of hyperkalaemia (*never walk away without completing all of these steps*).

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 22.1]. Drug therapies with mechanism of action and interventions for treating hyperkalaemia are shown in Table 11.

STEP 1	**Protect the heart**	Calcium Gluconate Calcium Chloride
STEP 2	**Shift potassium into cells**	Insulin-Glucose Salbutamol
STEP 3	**Remove potassium from the body**	Sodium Zirconium Cyclosilicate Patiromer

Table 11: Mechanism of action of drugs used in treatment of acute hyperkalaemia.

References

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Guideline 16.2a – Hyperkalaemia: STEP 1 – Protect the heart; intravenous calcium salts; dose and rate of administration

We recommend that an equivalent dose (6.8 mmol) of IV calcium is given to patients with hyperkalaemia in the presence of ECG changes at a dose and rate of 30ml 10% Calcium Gluconate over 10 minutes OR 10ml 10% Calcium Chloride over 5 minutes guided by the clinical setting. (1C)

Guideline 16.2b – Hyperkalaemia: STEP 1 – Protect the heart; intravenous calcium salts; choice guided by clinical setting

We recommend that IV Calcium Chloride is the preferred calcium salt in resuscitation (cardiac arrest or peri-arrest) and IV Calcium Gluconate should be used for all other patients in the presence of ECG signs of hyperkalaemia. (1C)

Audit Measures

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

Rationale (Guideline 16.2a and 16.2b)

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[1] and later confirmed in 1939.[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.[3-5]

The electrophysiological effect of K^+ on the heart is dependent on its extracellular concentration, direction of change (hypokalaemia or hyperkalaemia) and rate of change. The effect of K^+ 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^+ level.[6]

IV calcium antagonises the cardiac membrane excitability provoked by excess potassium, thereby protecting the heart against arrhythmias. Given that this is the first step in the emergency response to treating hyperkalaemia, it is crucial to optimise its efficacy from the outset. IV calcium is effective within 3 minutes at improving adverse ECG appearances (e.g.

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narrowing of the QRS complex) as shown below in Figure 5.[4, 7-9] 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^+, other interventions are urgently required.

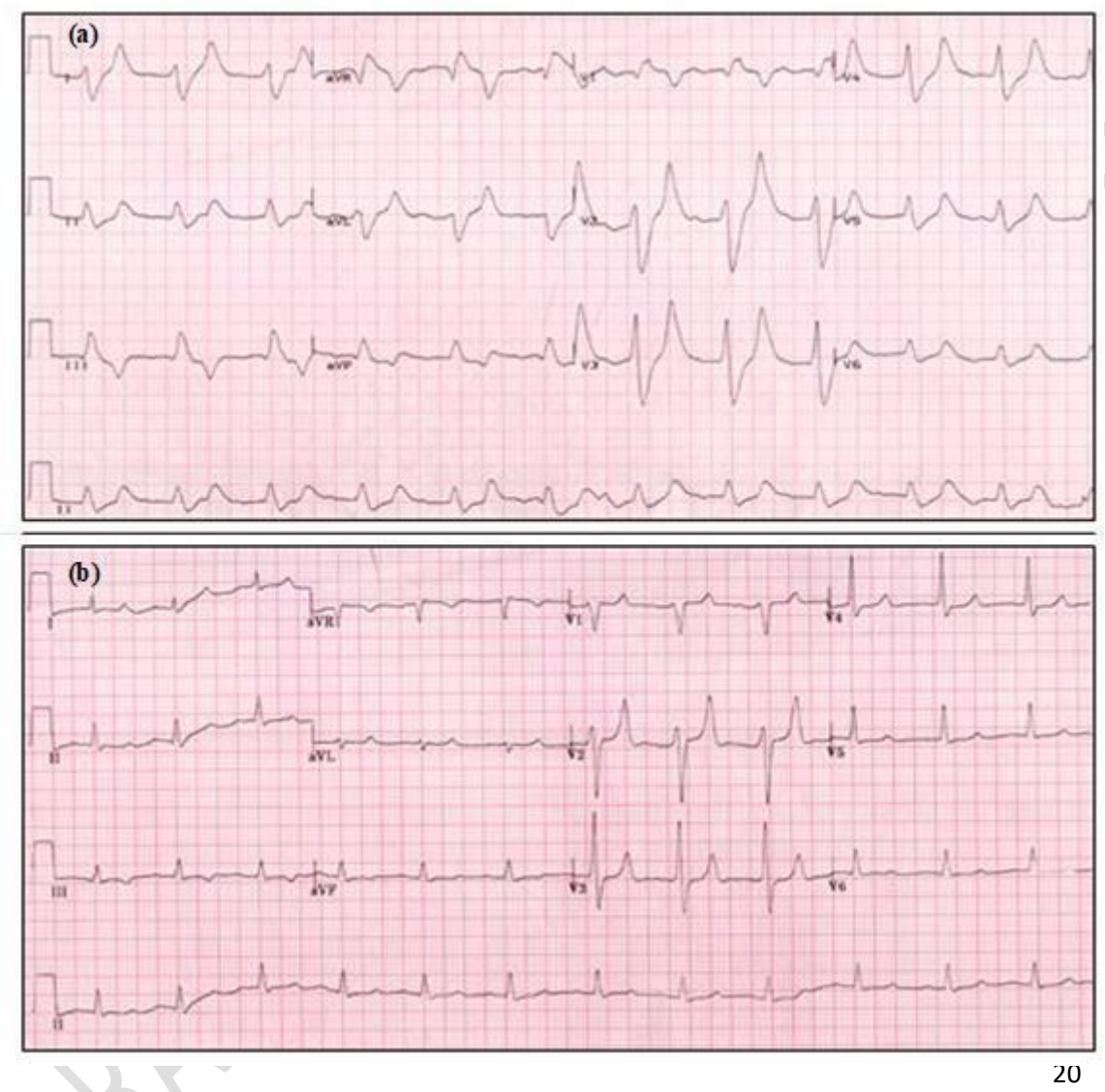


Figure 5: ECG on admission (a) and following 20ml 10% calcium gluconate IV (b) in a patient with serum K^+ 9.3 mmol/L who presented with generalised weakness.

Give IV calcium in patients with severe hyperkalaemia and ECG changes even when emergency dialysis is planned.

Patient Safety

Patient safety has been at the forefront of our approach in developing this Guideline. Following a recent enquiry from a clinician related to the rate of administration of calcium gluconate, we have identified that the Hyperkalaemia treatment algorithm (2020)[10] suggests that both IV calcium preparations can be administered over 5 minutes, whereas the original algorithm (2014)[11] stated over 5-10 min to account for the greater volume when using Calcium Gluconate. We have now amended in line with the original guideline as shown in Table 12.

IV Calcium salt	Dose	Rate of administration	Clinical setting
Calcium Chloride	10ml (6.8 mmol/l)	Over 5 minutes	Peri-arrest, cardiac arrest
Calcium Gluconate	30ml (6.8 mmol/l)	Over 10 minutes	All other patients

Table 12: Dose, rate of administration and choice of calcium salt guided by clinical setting.

There are some important differences between the two solutions. Both preparations, calcium chloride[12] and calcium gluconate[13], are available in the form of 10ml of 10% solution, but calcium chloride contains 3 times more calcium than calcium gluconate.

Calcium chloride is the preferred salt in critical circumstances such as peri-arrest or cardiac arrest and the gluconate salt is the preferred salt for the all other patients.

Adverse effects reported from the use of IV calcium salts include: [8,9]

- tissue necrosis if extravasation occurs (more common with the chloride salt)
- 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 IV calcium may potentiate digoxin toxicity, but this is limited to case reports [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[17], but some methodological concerns in this paper has

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been highlighted.[18] In instances where digoxin toxicity was unrecognised at presentation, no adverse event after IV calcium administration was reported.[19, 20]

MHRA Guidance

The MHRA have recently undertaken a review following several adverse events (5 fatal, 1 unknown) in the context of severe hyperkalaemia in which the dose of Calcium Gluconate was deemed to be inadequate.[21] NHS England also issued a Patient Safety alert in 2018 following 35 reports of cardiac arrest in patients known to be hyperkalaemic.[22] This alert highlighted the need for a structured time-critical response.

The use of calcium gluconate for treatment of hyperkalaemia has been 'off-label' for decades. This has resulted in variable clinical practice and inconsistent treatment guidelines. However, the MHRA has now formally authorised the use of calcium gluconate for treatment of severe hyperkalaemia in the UK and have provided clarity on the dose and rate of administration.[23] The licensed indications include all patients with severe hyperkalaemia ($K^+ \geq 6.5$ mmol/l) or in the presence of ECG changes, in keeping with the pre-existing EU guidance.[13] This is broader than the UKKA Renal Association Guideline recommendation.

This update of the UKKA guideline has carefully considered the rationale for clinical indications and for guiding the dose and rate of administration for calcium gluconate as discussed below.

Indication for IV Calcium in hyperkalaemia

There are two key considerations when deciding on the need to administer IV calcium – the severity of hyperkalaemia and the presence of toxic ECG signs. Several studies have reported on the frequency of ECG changes in patients with severe hyperkalaemia as shown in Table 13.[25-31] This data suggests that approximately two out of three patients with severe hyperkalaemia have ECG signs in keeping with hyperkalaemia. The literature is less clear to guide if all ECG signs warrant IV calcium.

There is general consensus that IV calcium is indicated for patients with life-threatening ECG changes (absent P waves, wide QRS, sine-wave pattern),[32, 33] arrhythmias [34] and in hyperkalaemic cardiac arrest.[35] There is also consensus that patients with moderate hyperkalaemia *without* ECG changes should not be treated with IV calcium.[34] However, there

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remains no consensus for the use of IV calcium for the remaining patients, particularly those *without* ECG changes.

Study	N=	Setting	Mean K^+ (mmol/l)	Incidence of ECG Changes
Acker (1998) [25]	220	Hospital inpatient	6.5 ± 0.6 (notification phase)	K^+ 6.0-6.8 mmol/l: 43% $K^+ \geq 6.8$ mmol/l: 55%
Freeman (2008) [26]	168	Emergency Department	6.5 (IQR 6.3 – 7.1)	Overall: 83% (*24% showed non-specific ST abnormalities*)
Montague (2008) [27]	90	Hospital inpatient	*6.6 (range 6.0-9.4)	$K^+ \geq 6.0$ mmol/l: 52% $K^+ \geq 7.2$ mmol/l: 39% (analysis stratified by strict criteria)
Fordjour (2014) [28]	154	Hospital inpatient	5.9	$K^+ \geq 6.5$ mmol/l: 50% (*Only 21% patients had $K^+ \geq 6.5$ mmol/l; ECG performed in only 44% of patients*)
Durfey (2017) [29]	188	Emergency Department	7.1 (range 6.5 – 9.3)	K^+ 6.5 – 6.9 mmol/l: 66% K^+ 7.0 – 7.4 mmol/l: 70% K^+ 7.5 – 7.9 mmol/l: 74% $K^+ \geq 8.0$ mmol/l: 100%
Peacock (2018) [30]	203	Emergency Department	6.3 (IQR 5.7 – 6.8)	Overall: 23% $K^+ \geq 7.0$ mmol/l: 45% (Includes only peaked T waves or wide QRS)
Pollack (2022) [31]	392	Emergency Department	6.3 (range 6.0-9.8)	Overall: 79.7% (*31% had $K^+ \geq 6.5$ mmol/l*)
Raffee (2022) [24]	67	Emergency Department	6.5 ± 0.7	Overall: 74.6% (*49.3% patients had $K^+ \geq 6.5$ mmol/l*)

Table 13: Incidence of ECG changes in patients with hyperkalaemia.

*Median; IQR – interquartile range

Risk of adverse events – when to give IV calcium

The next consideration is which ECG signs warrant treatment with IV calcium. Durfey et al found that the presence of ECG changes predicted adverse outcomes and the mean serum K^+ in this sub-group was 7.5 mmol/l. In this study, QRS prolongation and bradycardia were the most common abnormalities, but the majority of patients (86%) with an adverse event had > 1 hyperkalaemic ECG abnormality. Adverse events (symptomatic bradycardia, ventricular tachycardia, ventricular fibrillation, cardiac arrest and/ or death) occurred in 15% of patients before IV calcium was administered.[29] The median time from ECG to adverse event was only 47 minutes. There is no doubt that patients with QRS prolongation or an arrhythmia warrant IV calcium, but other ECG changes, in particular peaked T waves, is controversial.

Peaked T waves are the most easily recognizable ECG change, occur in about 30% of cases,[5, 25-27, 29] and are generally considered to be the earliest sign of hyperkalaemia. Raffee et al found that peaked T waves was the most common ECG sign followed by widened QRS in patients with severe hyperkalaemia,[24] however they noted a delay in initiation of treatment for a mean duration of 1 hour. The relatively high prevalence of peaked T waves and the observation that most patients who developed an adverse event had more than one ECG abnormality[29] is highly suggestive of a progressive pattern. Although Durfey found no adverse events in patients with isolated T waves, the rate of deterioration is unpredictable and is likely to vary from patient to patient. Delay in treatment is also common. On this basis, failure to rescue given these early signs of cardiac toxicity could have serious consequences.

Patients with severe hyperkalaemia without typical ECG signs pose a further challenge. Durfey et al found that no adverse events occurred in patients without ECG changes.[29] Although this guideline does not recommend IV calcium in the context of a normal ECG, the scope of the licensed indications for IV calcium currently includes all patients with severe hyperkalaemia.[13]

In clinical practice, the ECG is often available prior to laboratory confirmation of hyperkalaemia. Durfey et al found that all adverse events occurred either prior to laboratory result notification or immediately after.[29] This provides some evidence to support empirical treatment pending laboratory results when hyperkalaemia is clinically suspected.

Based on current evidence and expert opinion, we recommend IV calcium for patients with ECG changes, including isolated peaked T waves. IV calcium is not recommended for patients with a normal ECG given that the available evidence suggests a lower risk of adverse events and the administration of IV calcium itself is not without risk.

IV Calcium: Dose in Hyperkalaemia

Historically, 10ml 10% calcium gluconate has been administered in sequential doses with a pause between doses to re-assess response prior to giving a repeat dose. This strategy has been used in clinical studies, reviews and in hyperkalaemia guidelines.[36-38] In 2014, the joint guideline produced by the UKKA and Resuscitation Council amended this protocol and recommended an equivalent dose (6.8 mmol) of IV calcium to be administered as a single dose in patients with severe hyperkalaemia in the presence of ECG changes.[11] Over the past 9 years, no adverse events have been reported to either the UKKA or to the MHRA[21] via the Yellow Card system with regard to this protocol.

Rationale for a single dose of 30ml calcium gluconate rather than sequential dosing:

- The purpose of administration of IV calcium is to reduce the risk of arrhythmias by blocking the hyperkalaemic effect on the heart. Under-estimating this risk or inadequate dosage can lead to arrhythmias.
- Less experienced medical staff are often the first responders. If the clinician is doubtful about the interpretation of the initial ECG at diagnosis of hyperkalaemia, then it is very likely that they will also be doubtful about interpreting the repeat ECG if using a sequential dosing strategy (*operator-dependent*).
- The risk that junior doctors may 'over-call' ECG changes and use IV calcium when not indicated, needs to be balanced against the risk that they may 'under-call' ECG changes or omit sequential doses even when ECG changes persist.
- Coupled with IV calcium administration is the prompt initiation of potassium-lowering treatment. Failure to control the hyperkalaemia itself will compound the impact of a sub-optimal dose of IV calcium.
- Assuming secure venous access and cardiac monitoring for both approaches, the potential harm with a higher initial dose is predominantly hypercalcaemia (usually transient), whilst the potential harm with sub-optimal dosing is arrhythmias.
- Ultimately, the decision on dosing comes down to which is a greater risk - giving all patients a higher initial dose to provide greater cardiac protection or potentially giving some patients a sub-optimal dose as sequential dosing relies on clinical judgement.
- New evidence: A recent prospective observational study, 111 patients were treated with IV Calcium Gluconate for hyperkalaemia (mean K^+ 7.1 ± 0.6 mmol/l).[36] The protocol included sequential doses of 10ml 10% Calcium gluconate administered over 3-5 minutes and repeated up to 3 times by experienced Emergency care clinicians. Overall, 108/111 (97%) patients required 3 doses and the remaining 3 patients (3%) required 2 doses of IV calcium. A single dose was not adequate for any patient. This is one of the largest cohort studies available and provides some evidence that a single dose of 10ml 10% Calcium Gluconate may not be sufficient for the majority of patients with severe hyperkalaemia.

- Historical evidence: Chamberlain et al reported the outcome of a small series where doses of up to 30-60ml 10% Calcium Gluconate IV or 90ml 10% Calcium Chloride IV was administered over 5 minutes with 'immediate' improvement in ECG.[7] Transient hypercalcaemia occurred in one patient (Patient 5). Clinical outcome was largely affected by the lack of prompt dialysis in this era.
- Other indications for calcium gluconate in medical emergencies require a dose in excess of 10ml 10% calcium gluconate:
  - Hypocalcaemia: 10-20ml 10% calcium gluconate, followed by an infusion[13, 39]
  - Hypermagnaesemia: 15-30ml 10% calcium gluconate[39, 40]
  - Calcium channel blocker overdose: 30-60ml 10% calcium gluconate[39, 41, 42]
- Hyperkalaemia is the most immediately life-threatening electrolyte disorder, therefore the dosing strategy should reflect this.

IV Calcium: Rate of administration for Hyperkalaemia

Until recent the recent MHRA Update, the rate of administration of IV calcium gluconate has been guided by the regimen for treatment of hypocalcaemia in the product data sheet. Clinicians have extrapolated this guidance (2ml/min) and applied it to the treatment of hyperkalaemia.[13] This would mean that it would take 5 minutes to administer 10ml calcium gluconate and 15 minutes to administer 30ml calcium gluconate if given as a bolus. There are several reasons why this may not be appropriate in hyperkalaemia.

Rationale for administration of 30ml calcium gluconate over 10 minutes:

- A sequential dosing strategy requires a pause of 3-5 minutes between doses to allow time for the drug to take effect and to decide on administration of a further dose. Inexperienced clinicians could take even longer for decision-making. Therefore, this approach could take up to 25 minutes to administer 30ml calcium gluconate.
- Intravenous access is often difficult in acutely ill patients. A longer duration of administration of IV calcium could delay initiation of K^+-lowering treatment (Insulin-Glucose) particularly if IV access is limited.
- The mechanism of effect of IV calcium is different when used in various clinical settings. IV calcium is used for '*replacement*' in hypocalcaemia, but it is used for '*antagonism*' in

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the context of hyperkalaemia and other disorders. This is an important consideration for both the dose and rate of administration of IV calcium as shown below in Table 14.

Study/ Guideline		Indication	10% Calcium Gluconate IV		
			DOSE	ADMINISTRATION	RATE
Product Ref Guide		Hypocalcaemia	10-20ml bolus	10-20ml over 5-10 min	2 ml/min
UKKA Guideline (2014 [11]		**Hyperkalaemia**	30ml	30ml over 10 min	3 ml/min
UKKA Guideline (2020)[10]		**Hyperkalaemia**	30ml	30ml over 5 min	6 ml/min
UKKA Guideline (2023)		**Hyperkalaemia**	30ml	30ml over 10 min	3 ml/min
GAIN (2014) [45]		**Hyperkalaemia**	10-50ml	10ml over 2 min	5 ml/min
GAIN (2021)[38]		**Hyperkalaemia**	10-50ml	10ml over 5 min	2 ml/min
ALS Guideline (2021)[43]		**Hyperkalaemia**	30ml	30ml over 15 min	2 ml/min
AHA Guideline (2010)[44]		**Hyperkalaemia**	15-30ml	15-30ml over 2-5 min	6 ml/min
Medscape[39]		**Hyperkalaemia**	15-30ml	15-30ml over 2-5 min	6 ml/min
Medscape[39]		Hypermagnesaemia	15-30ml	15-30ml over 2-5 min	6 ml/min
Farkas et al (2019)[40]		Hypermagnesaemia	20ml	20ml over 5-10 min	3 ml/min
St-Onge et al (2017)[42] Consensus Paper		Calcium channel blocker overdose	30-60ml	30-60ml over 10-20 min	3 ml/min
Toxbase[41]		Calcium channel blocker overdose	30ml	30ml over 5 min	6 ml/min

Table 14: Calcium Gluconate dosing regimen for management of hyperkalaemia and other medical emergencies.

Mechanism of action for IV calcium: **Replacement** **Antagonism**

Ref – reference; GAIN – Guidelines & Audit Implementation Network; ALS – Advanced Life Support; ERC – European Resuscitation Council; AHA – American Heart Association

*UKKA Guideline - rate amended in July 2023

- The main adverse effects from administration of IV calcium include arrhythmias, circulatory collapse, feeling hot, hyperhidrosis, hypotension, vasodilation and vomiting. The frequency of these effects is 'unknown'. In real-world practice, if a patient reports any symptoms during drug administration, the clinician is likely to pause or reduce rate of drug delivery.
- In the International resuscitation literature, the rate of administration in the non-arrested patient with signs of cardiac toxicity reflects the urgency:
  - **UK**: The ALS Guideline (2021) recommends IV calcium for patients with toxic ECG changes: 6.8 mmol Calcium via 10 ml 10% Calcium Chloride IV over 2-5 minutes or 30ml 10% Calcium Gluconate over 15 minutes. [43]

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- **Europe**: The ERC Guideline (2021) recommends IV calcium for patients with toxic ECG changes: 10 ml calcium chloride 10% IV over 2-5 min (onset 1-3 min, repeat ECG, further dose if toxic ECG changes persist). [35]
- **USA**: The American Heart Association (2010) recommends IV calcium in patients with severe cardiotoxicity (or cardiac arrest): 5-10 ml 10% Calcium Chloride IV over 2-5 minutes or 15-30ml 10% Calcium Gluconate over 2-5 minutes.[44] This dose and rate of administration for Calcium Gluconate is also quoted in another healthcare resource. [39]

The UKKA Guidance on the administration of IV calcium salts has been in place since 2014 without any reported adverse events to our knowledge. This recommendation and current update was carefully considered in collaboration with senior nephrologists, Critical Care, Resuscitation experts and the MHRA.

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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 ($K^+ \geq 6.5$ 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 recommend initiation of an infusion of 10% glucose at a rate of 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. (2B)

Audit measure:

1. The proportion of patients with severe hyperkalaemia ($K^+ \geq 6.5$ mmol/L) treated with insulin-glucose infusion.

Rationale (Guidelines 16.3.1 – 16.3.3)

Insulin is the most reliable drug for shifting K^+ into cells in patients with hyperkalaemia.[1] Insulin shifts K^+ into cells by activating Na^+-K^+ ATPase and recruiting intracellular pump components into

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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 [2, 3], with the peak reduction (ranging from 0.65-1.0 mmol/l) occurring between 30-60 minutes.[2-6] 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.[7] Co-administration of salbutamol also appears to reduce the risk of insulin-induced hypoglycaemia. [8]

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.[9]

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

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

Dose of insulin for optimal efficacy

The evidence-base for efficacy of insulin-glucose in the treatment of acute hyperkalaemia is heterogenous consisting of variable study designs, insulin doses, glucose doses, method of administration (bolus or infusion), and study populations as summarised in Appendix 1.

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Early prospective studies [2, 3, 5, 6, 10, 11] and one more recent study [12], were performed predominantly in stable HD patients and included small patient cohorts. Few prospective studies included patients with acute kidney injury.[4, 8, 13]

Retrospective studies reported over the past decade have attempted to address the optimal regimen to reduce the risk of hypoglycaemia without compromising efficacy.[14-20] Some studies have considered reduced insulin dose (5 units) [14, 16, 18], higher glucose dose (50g) [15-17, 19, 21], body weight [15, 20], glycaemic status [22] and level of renal function [14, 22] to tailor treatment regimens. Importantly, assessment of efficacy is dependent on the timing of blood monitoring after treatment. Given the retrospective design of these studies, the timing of blood monitoring was variable with K^+ measurements ranging between 1 to 4 hours after administration of insulin-glucose.

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 as shown in Table 15.[2, 4, 5, 8, 10, 12, 13, 18, 19, 23-27] The most commonly used dose of glucose was 25g.[2, 5, 8, 18, 19, 24-27] The mean baseline serum K^+ ranged from 5.48 – 6.9 mmol/l. The efficacy demonstrated in these studies showed a reduction in serum K^+ ranging from 0.65 – 1.4 mmol/l.

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STUDY	Insulin dose (units)	Glucose Dose (g)	Baseline K^+ (mmol/l)	K^+ lowering (mmol/l)	DM (%)	Baseline blood glucose (mmol/l)	Hypo (BM ≤ 3.9) (%)
Allon 1990 (n=12) [2]	10	25	5.48	0.65	0	4.8	75
Ljutic 1993 (n=9) [5]	10	25	6.33	0.77	NA	NA	11
Ngugi 1997 (n=50) [8]	10	25	6.9	1.14	NA	NA	20
Mushtaq 2006 (n=15) [13]	10	25	6.5	0.8	NA	7.5	0
Pierce 2015 (n=99) [14]	10	25	6.3	1.08	55	NA	16.7
Garcia 2018 (n=309) [18]	10	25	6.15	0.9	36.2	8.7	10.7
Farnia 2018 (n=120) [19]	10	25	6.5	1.0	26.7	7.0	15.8
Boughton 2019 (n=662) [23]	10	20*	6.4	0.6	31.1	7.2	17.5
Lim 2021 (n=410) [24]	10	25	6.6	1.4	60	NA	NA
Humphrey 2022** (n= 1284) [25]	10	25	6.34	0.86	35	7.5	19.4
Verdier 2022 (n= 87) [27]	10	25	6.2	0.7	32.2	7.7	19.5
Finder 2022 (n= 191) [26]	10	25	6.09	0.9	40.8	10.0	8.4

Table 15: Efficacy and risk of hypoglycaemia with conventional regimen - 10 units Insulin with 25g glucose (*studies without efficacy or hypoglycaemia data excluded*)

Study size includes only patient arm treated with 10 units Insulin/ 25g Glucose (with or without co-treatments).
DM – Diabetes Mellitus. BM – Blood glucose. NA – not available.
* 100ml 20% Glucose (20g) used in this study
**94% of study population treated with 10 units Insulin/ 25g Glucose

Insulin dose – 5 versus 10 units

Several retrospective studies have compared the efficacy and hypoglycaemic risk of regimens using conventional dose (10 units) versus low dose (5 or <10 units) soluble insulin as shown in Table 16.[14, 16, 18, 26-30] The K^+-lowering achieved using conventional dose insulin was 0.7 – 1.13 mmol/l compared with 0.63 – 1.17 mmol/l using low-dose insulin.

Interpretation of the data in these studies is confounded by a lower proportion of patients (20-30%) receiving a low-dose insulin regimen in some studies [16, 18, 28, 29], the use of variable

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glucose regimens which may have influenced the incidence of hypoglycaemia, and the variable use of concomitant K^+-lowering drugs which may have influenced efficacy.

STUDY	Insulin dose (units)	Albuterol Use (%)	Baseline K^+ (mmol/l)	K^+ lowering (mmol/l)	DM (%)	Baseline blood glucose (mmol/l)	Hypo (BM ≤ 3.9) (%)	*Severe Hypo (%)
Pierce 2015 [14] (n =149)	10	NA	6.3	1.08	55	NA	16.7	8.9
	5	NA	6.3	1.1	46	NA	19.7	7.0
La Rue 2017 [16] (n=675)	10	30.3	6.4	1.0	49.1	7.6	28.6	6.8
	5	36.8	6.4	1.0	42.9	6.9	19.5	3.0
Garcia 2018 [18] (n=401)	10	15.2	6.15	0.9	36.2	8.8	10.7	NA
	5	#25	6.24	0.81	29.4	7.6	8.7	NA
Keeney 2020 [28] (n=442)	10	48	6.6	1.13	51	6.9	15.6	7.1
	5	48	6.5	1.17	54	6.6	6.1	2.7
Verdier 2022 [27] (n=174)	10	5.7	6.2	0.7	32.2	7.7	19.5	4.6
	5	5.7	6.0	0.8	27.6	7.7	9.2	1.1
Finder 2022 [26] **(n=377)**	10	12	6.09	0.9	40.8	10.0	8.4	1.0
	5	19.4	6.02	0.63	43.5	8.9	6.5	1.1
Moussavi 2020 [29] **(n=700)**	10	48.8	6.1	1.11	58.3	7.7	17.6	2.5
	<10	49.8	6.0	0.94	57.4	6.3	11.2	1.8
Pearson 2022 [30] **(n=386)**	10	2.5	6.2	0.8	49	8.3	19.2	NA
	<10	3.3	6.2	0.6	45.6	7.5	13.5	NA

Table 16: 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% [14]; La Rue: 20% [16]; Garcia: 23% [18]; Moussavi: 32% [29]; Keeney: 33% [28]; Verdier: 50% [27]; Finder: 49% [26].

Dose of glucose: Pierce: 25g [14]; La Rue: 25g + 25g at 1hr ± 25g at 3hrs if blood glucose < 3.9 mmol/l (poor adherence to this protocol) [16]; 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) [18]

*Definition of Severe hypoglycaemia: Pierce: glucose < 2.8 mmol/l [14]; La Rue: glucose < 2.2 mmol/l [16]

p = 0.03 NA – not available; DM- Diabetes mellitus; Hypo – hypoglycaemia; BM – blood glucose.

Potential dose-dependent effect of Insulin on K^+-lowering

There is some evidence of a dose-dependent effect of insulin on lowering K^+ level.

Garcia et al (2018) reported a post-hoc analysis of patients with a serum $K^+ \geq 6.0$ 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).[18]

Moussavi et al (2020) conducted a large study (n=700) and reported significantly greater K^+-lowering in patients treated with 10 units insulin (1.11 ± 0.8 mmol/l, p=0.008) compared with < 10 units insulin (0.94 ± 0.71 mmol/l).[29]

Finder et al (2022) found that the K^+-lowering effect of 10 units Insulin was significantly greater than with 5 units insulin (0.9 mmol/l vs 0.63; p=0.001) in patients with moderate renal dysfunction.[26] Low-dose insulin did not reduce hypoglycaemia.

Pearson et al (2022) assessed the impact of reducing the insulin dose from 10 to <10 units and found significantly lower efficacy in the low-dose group (0.9 vs 0.6 mmol/l; p=0.0095) without reducing the prevalence of hypoglycaemia.[30]

Moussavi et al (2021) conducted a meta-analysis including 10 retrospective studies (n=3437) to assess the K^+-lowering efficacy and risk of hypoglycaemia with standard dose (10 units) compared with low dose insulin (5 units, 0.1 units/kg or < 10 units).[31] They found a lower pooled odds of hypoglycaemia (OR 0.55) and no difference in K^+ reduction (mean difference -0.02 mmol/l), but acknowledged that prospective studies are necessary to confirm these findings. The two studies [26, 30] reported since this meta-analysis suggest caution is warranted before adopting a low-dose insulin protocol.

Impact of severity of hyperkalaemia on efficacy

It is unclear if the severity of hyperkalaemia affects the degree of K^+-lowering with insulin. The efficacy reported in studies using 10 units of insulin (Table 15) was compared between patients with a mean $K^+ \geq 6.5$ mmol/l (n=8) vs a mean $K^+ < 6.5$ mmol/l (n=8). Interestingly, this showed a trend towards higher K^+-lowering in studies with more severe hyperkalaemia (mean reduction 1.08 mmol/l vs 0.87 mmol/l; difference -0.21 mmol/l). The degree of correlation may be affected by the narrow range in K^+ level in these studies (mean $K^+ < 7.0$ mmol/l). However, there is now some evidence to support this observation.

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Lim et al (2021) demonstrated a significant positive correlation with the pre-treatment K^+ level (r=0.52, p< 0.001) in the cohort of patients treated with Insulin-glucose alone.[24] They found that for every 1.0 mmol increase in pre-treatment K^+ > 6.0 mmol/l, there was an associated 0.7 mmol/l increase in K^+ reduction with insulin-glucose. This study also demonstrated that there was no difference in K^+-lowering in patients without CKD (1.4 mmol/), with CKD (1.3 mmol/) and in dialysis patients (1.4 mmol/).

INSAKA is an ongoing multi-centre randomised controlled study to investigate the efficacy and safety of Insulin-glucose (10 units in 50g) and Salbutamol (10mg), alone and in combination, in patients with moderate and severe hyperkalaemia.[32] This prospective study conducted in an Emergency Department setting may help to confirm if there is a correlation between severity of hyperkalaemia and efficacy of Insulin.

Dose of insulin to reduce the risk of hypoglycaemia

Many studies have assessed the impact of reducing the dose of Insulin on the incidence of hypoglycaemia compared with the conventional regimen. Some studies have used a low-dose protocol for all patients whilst other studies have made this dose adjustment guided by low body weight or renal impairment.

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[13] 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 8 - 28%.[14, 18, 19, 21-27, 33]

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 – 50%) and the variable glucose dosing (Table 16).[14, 16, 18, 26-28] Reducing the dose of insulin does not appear to consistently reduce the risk of hypoglycaemia, but does appear to reduce the risk of severe hypoglycaemia.[31]

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Insulin dose – Weight-based regimen

Tailoring insulin dose to body weight is another potential strategy as shown in Table 17. [3, 6, 15, 20] Two small early studies in HD patients reported no hypoglycaemic events.[3, 6] More recently, Wheeler et al demonstrated a significant reduction in hypoglycaemic events with a weight based regimen.[15] However this study only reported the lowest serum K^+ level achieved in the 12 hours following treatment, making it difficult to assess efficacy. Brown et al found a marginally significant difference in hypoglycaemic rates (6.67% vs 5.8%, p=0.05) in favour of the weight-based cohort.[20] In clinical practice, a weight-based regimen would be difficult to safely and reliably implement in a medical emergency.

STUDY	Insulin dose (units)	Glucose Dose (g)	Baseline K^+ (mmol/l)	K^+ lowering (mmol/l)	DM (%)	Baseline blood glucose (mmol/l)	Hypo (BM ≤ 3.9) (%)	*Severe Hypo (%)
Allon 1996 [3] (n=8)	5 mU/kg/min	60	4.28	0.85	0	4.8	0	0
Kim 1996 [6] (n=8)	5 mU/kg/min	40	6.3	0.7	NA	NA	0	0
Wheeler 2016 [15] (n=132)	0.1U/kg	50	6.1	#NI	NA	8.2	12.1	NA
	10	50		#NI	NA	9.2	27.3	NA
Brown 2018 [20] (n=264)	0.1U/kg (8.3)	24	6.1	0.6	52	9.0	6.7	2.6
	8.7	26	6.2	0.6	45	8.5	**5.8	10.1

Table 17: 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.

Dose of Glucose to reduce the risk of hypoglycaemia

Studies assessing the effect of glucose dose (25g vs 50g) on hypoglycaemic risk are shown in Table 18. Farnia et al reported a trend towards a lower incidence of hypoglycaemia at 60 minutes in patients treated with 50g glucose.[19] Sub-group analysis of patients with a baseline blood glucose < 6.1 mmol/l and those without diabetes showed a significant reduction in hypoglycaemic

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events when treated with 50g glucose. Coca et al delivered an infusion of 50g glucose with 10 units insulin over 4 hours and showed a low hypoglycaemic rate at 6.1% with this strategy.[17]

STUDY	Glucose dose (units)	Insulin Dose (units)	Baseline K^+ (mmol/l)	K^+ lowering (mmol/l)	DM (%)	Baseline blood glucose (mmol/l)	Hypo (BM ≤ 3.9) (%)	*Severe Hypo (%)
Chothia 2014 [12] (n =10)	50	0	6.23	0.50	NA	5.1	0	NA
	50	10	6.01	0.83	NA	5.6	20	NA
Wheeler 2016 [15] (n=132)	50	0.1 U/kg	6.1	#NI	NA	8.2	12.1	NA
	50	10		#NI	NA	9.2	*27.3	NA
Coca 2017 [17] (n=164)	-	-	-	-	-	-	-	-
	50	10	6.85	1.18		8.3	6.1	1.2
Garcia 2018 [18] (n=401)	0	5 (2%)	6.24	0.81	29	7.6	8.7	
	25	5 (16%)						
	50	5 (5%)						
Garcia 2018 [18] (n=401)	0	10 (4%)	6.15	0.9	36	8.8	10.7	
	25	10 (63%)						
	50	10 (9%)						
Farnia 2018 [19] (n=240)	25	10 (50%)	6.5	1.0	27	7.0	**15.8	
	50	10 (50%)	6.3	1.1	27	5.9	8.3	

Table 18: 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.[12, 34] 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).[12] Tee et al also postulate that the normal physiological response to a glucose load may be adequate in non-diabetic patients with hyperkalaemia to avoid iatrogenic hypoglycaemia.[35]

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.[1, 36] This approach also risks a

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paradoxical worsening of hyperkalaemia by causing a shift of K^+ out of cells.[37-39] Based on current evidence, this strategy is not recommended.

Risk threshold for Iatrogenic Hypoglycaemia

Hypoglycaemia is the most serious, and potentially avoidable, complication of treatment with insulin-glucose for acute hyperkalaemia. Hypoglycaemia after insulin administration is associated with a significantly higher inpatient mortality and longer length of hospital stay. Reducing harm, whilst maintaining efficacy, is the main objective in designing this treatment protocol.

In the 2020 UKKA Hyperkalaemia Guideline, we demonstrated that a pre-treatment blood glucose < 7 mmol/l appeared to be the threshold for identifying patients at high risk of iatrogenic hypoglycaemia based on available evidence at that time. Since then, several studies have supported this threshold as shown in Table 19.

Study	N=	Incidence of Hypoglycaemia	Baseline glucose (mmol/l)	
			Hypo	No Hypo
Schafers et al (2012) [21]	219	8.7%	6.7	8.6
Apel et al (2014) [33]	221	13%	5.8	9.0
Coca et al (2017) [17]	164	6.1%	6.2	8.5
Boughton et al (2019) [23]	662	17.5%	5.8	8.7
Jacob et al (2019) [40]	172	19.8%	5.5	8.6
Crnobrnja et al (2020) [41]	421	21%	6.5	8.8
Tee et al (2021) [35]	132	11.8%	5.9	7.6
Humphrey et al (2022) [25]	1284	19.4%	7.1	9.1
Kijprasert et al (2022) [42]	385	25.2%	6.3	7.1
Pearson et al (2022) [30]	204	17.6%	6.8	9.8

Table 19: Incidence of hypoglycaemia and correlation with pre-treatment blood glucose following treatment with Insulin-Glucose for hyperkalaemia.

New evidence available since 2020 UKKA Guideline.[25, 30, 35, 41, 42]

Crnobrnja et al (2020) performed a retrospective multicentre study and included patients with a serum $K^+ \geq 6.0$ mmol/l treated with 10 units soluble insulin with 25g glucose.[41] They found

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that hypoglycaemia occurred in 21% of patients and pre-treatment blood glucose was an important risk factor. In this study, every 1 mmol/l increase in pre-treatment blood glucose was associated with a 12% lower odds of hypoglycaemia after allowing for diabetic status and other covariates.

Tee et al (2021) conducted a retrospective audit and found the incidence of hypoglycaemia was 11.8% following treatment with 10 units soluble insulin and 25g glucose.[35] The pre-treatment glucose was significantly lower in patients who developed hypoglycaemia compared with those who did not (5.9 mmol/l vs 7.6 mmol/l; p=0.000) and this factor was associated with an odds ratio of 4.146 for hypoglycaemic events. More specifically, this UK study demonstrated a pre-treatment blood glucose threshold of < 7 mmol/l as illustrated in Figure 6. The authors have proposed further study using an insulin-free protocol (75-100g glucose only) for clinically stable patients with moderate hyperkalaemia.

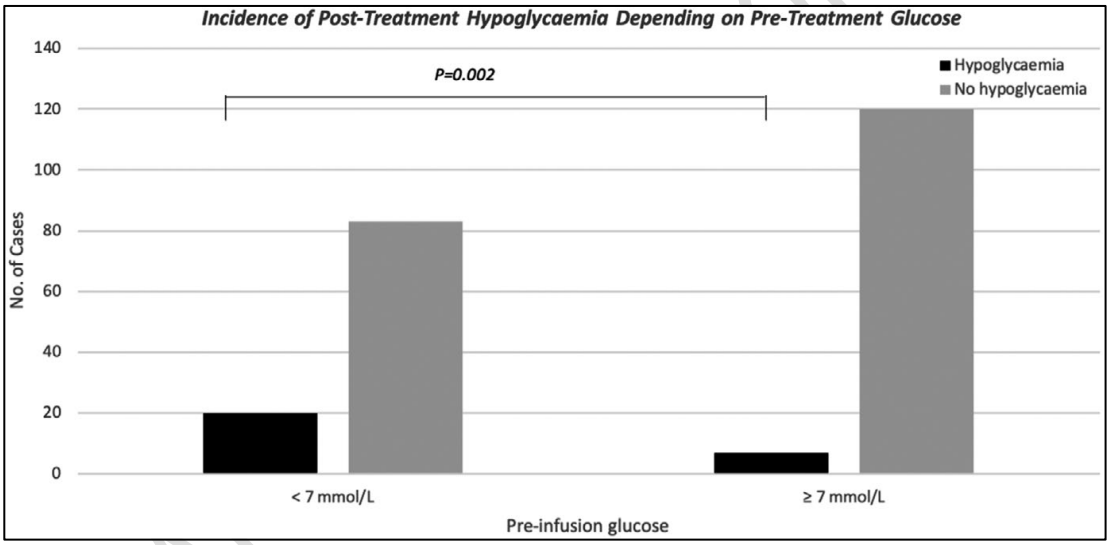


Figure 6: Incidence of post-treatment hypogylcaemia with glucose above and below 7 mmol/l. Reproduced with permission from *Tee et al, Clin Endocrinol (Oxf) 2021; 94: 176-182*.[35]

Similarly, Humphrey et al (2022) investigated clinical outcomes in over 1200 patients treated with Insulin-Glucose for hyperkalaemia.[25] The majority of patients (94%) were treated with 10 units soluble insulin with 25g glucose. Hypoglycaemia occurred in 19.4% of patients within 6 hours of treatment. Importantly, they also found that the odds ratio (OR) for developing hypoglycaemia after Insulin-glucose in patients with CKD was 1.5, in patients who received

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multiple doses of Insulin-glucose was 3.0 and in patients with a baseline glucose < 7.0 mmol/l was even greater at 3.4.

Kijprasert et al (2022) recently reported a retrospective study in which 25.2% developed hypoglycaemia after administration of 10 units soluble insulin with 25g glucose.[42] A low pre-treatment blood glucose (≤ 5.6 mmol/l) correlated with a significantly increased risk of hypoglycaemia.

Pearson et al (2022) compared efficacy and hypoglycaemia risk before and after implementing a low-dose insulin (5 units) regimen.[30] There was no significant difference in incidence of hypoglycaemia (17.7% vs 18.7%; p=0.7924). This study also showed that a pre-treatment blood glucose level < 7 mmol/l was associated with a higher incidence of hypoglycaemia after treatment with 10 units insulin in the pre-implementation sub-group.

Study	N=	Odds Ratio (95% CI)	p
Coca et al (2017) [17]	164	4.44 (0.91 – 21.57)	0.055
Crnobrnja et al (2020) [41]	421	0.88 (0.81 - 0.95)	0.002
Tee et al (2021) [35]	132	4.146 (1.676 – 10.255)	0.002
Humphrey et al (2022) [25]	1284	3.4 (2.5 - 4.6)	ns
Kijprasert et al (2022) [42]	385	0.84 (0.78 - 0.91)	0.002

Table 20: Risk of iatrogenic hypoglycaemia after treatment for hyperkalaemia based on the pre-treatment blood glucose level.

ns – not stated.

Chothia et al (2022) undertook a scoping review of 62 studies (n= 15,363) to assess the incidence and risk factors for hypoglycaemia after insulin-glucose therapy.[43] Overall, the prevalence of hypoglycaemia was 17.2% and the most common predictor of hypoglycaemia was the pre-treatment blood glucose level which ranged from < 5.6 – 7.8 mmol/l. There was no difference in the prevalence of hypoglycaemia when comparing insulin dose (≥ 10 units vs < 10 units), rate of insulin administration, type of insulin or timing of insulin administration relative to dextrose. However, lower insulin doses were associated with fewer episodes of severe hypoglycaemia. An important observation in this study is that the incidence of hypoglycaemia was lower when glucose was administered as a continuous infusion compared with bolus administration. This study provides some rationale for the current UKKA protocol.

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Long et al (2023) also undertook a systematic review of 22 studies to investigation risk factors and preventative strategies for iatrogenic hypoglycaemia and found that a pre-treatment blood glucose < 7 mmol/l was a key factor.[44]

On the basis of the current evidence as summarised above and in Tables 19 and 20, we have amended the GRADE recommendation for this guideline statement. We anticipate that future studies conducted using this 2-step approach will show a reduced incidence of iatrogenic hypoglycaemia as the 5-hr Glucose infusion is delivered over the period with the highest risk of developing hypoglycaemia.

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 21. Insulin has a longer half-life in patients with renal failure making them more at risk of hypoglycaemia.[45-47] The reported incidence of hypoglycaemia in patients with ESRD is up to 33%.[14, 15, 21] Treatment-related factors include the dose of insulin and dose of glucose used.

Potential risk Factors for Iatrogenic Hypoglycaemia
Patient-related: **Low pre-treatment blood glucose** Renal impairment (AKI, CKD 4-5, ESRD) Low body weight Older age Non-diabetic status (no prior history and no diabetic medication)
Treatment-related: High Insulin dose regimen (≥ 10 units soluble insulin) Low Glucose dose regimen (≤ 25g glucose)

Table 21: 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. There is growing evidence that a pre-treatment blood glucose < 7 mmol/l is a reliable threshold for identifying patients at risk of hypoglycaemia.[12, 15-21, 23, 25, 30, 33, 35, 40-42, 48] Both treatment-related factors are modifiable.

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Tailoring the treatment protocol to address one or more of these additional risk factors will increase complexity and likely affect adherence as seen in two reports.[16, 22] However, a single protocol to fit all will continue to risk hypoglycaemia.

Summary

Historical evidence has guided clinical practice with the conventional regimen of 10 units soluble insulin with 25g glucose being standard practice for decades. However, the incidence of hypoglycaemia with this protocol is unacceptably high. A comprehensive review of the literature has been undertaken to determine if a change in practice is warranted. Unfortunately, the evidence is limited by the lack of robust prospective studies, the use of multiple insulin-glucose treatment regimens and variable blood glucose monitoring.

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.[19] Reducing the dose of insulin alone is insufficient to reduce hypoglycaemic events which remains at 6.1-19.7%, although it does appear to reduce the incidence of severe hypoglycaemia. 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%.[17, 19]

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).[16] Coca et al administered 50g glucose with insulin over a 4-hour infusion and reported a low rate of hypoglycaemia (6.1%), but this strategy delays assessment of efficacy.[17] Another approach is the initiation of a continuous infusion of 10% glucose at 50ml/hr following initial treatment with 25g glucose.[37][49] 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 hypoglycaemia, rate adjustment guided by blood glucose level and avoids the transient hyperglycaemia after a 50g glucose bolus.

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, four reports have highlighted a dose-dependent effect with 10 units insulin

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showing greater efficacy than 5 units insulin.[18, 26, 29, 30] There also appears to be a correlation between the degree of K^+ reduction and severity of hyperkalaemia in patients treated with 10 units insulin.[24] Therefore the higher the K^+ level, there may be a greater magnitude of K^+ reduction.

These observations raise potential concern for the treatment of patients with potentially life-threatening hyperkalaemia. The standard multi-modal approach to treating hyperkalaemia may not be feasible in critical illness and in cardiac arrest, leaving insulin-glucose as the main therapeutic option. On balance, the risk of sub-optimal K^+-lowering treatment out-weighs the risk of hypoglycaemia in the setting of life-threatening hyperkalaemia as hypoglycaemia can be pre-empted. Further study is required before a reduction in insulin dosage to 5 units can be recommended.

The UKKA guideline recommends the use of 10 units soluble insulin with 25g glucose, followed by an infusion of 10% glucose at 50ml/hour for 5 hours (25g) in patients with a pre-treatment blood glucose < 7 mmol/l as shown in Table 22. This approach is also likely to benefit patients without diabetes and those with low body weight. Blood glucose monitoring is discussed in Guideline 17.2 and the treatment of hypoglycaemia should follow existing guidelines.[50]

Administration will depend on the concentration of glucose solution chosen (Appendix 4B). The use of 50% glucose has reduced in recent years in view of the potential risk of extravasation injury. Although 20% glucose is readily available in most hospitals, the administration of 25g requires 125ml of solution. This poses a challenge for administration as 20% glucose is generally available in 100ml bottles (i.e. 20g). As the concentration of glucose solution reduces, the volume required to achieve 25g increases (i.e. 50% = 50ml, 20% = 125ml, 10% = 250ml). Volume overload is a potential concern in patients with renal failure. The choice of solution may be influenced by local availability, ease of administration and the volume status of the patient.

UKKA Insulin-glucose protocol for treatment of acute hyperkalaemia
▪ Check blood glucose prior to insulin administration.
▪ Give 10 units soluble Insulin with 25 g glucose.

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▪ **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
▪ Monitor serum K^+ and blood glucose (see treatment algorithm).
▪ Anticipate and treat hypoglycaemia promptly.

Table 22: 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. Potassium binders are becoming embedded in clinical practice and may indirectly reduce the incidence of iatrogenic hypoglycaemia by reducing the need for repeated insulin-glucose infusions.

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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 ($K^+ \geq 6.5$ 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)

Rationale (Guideline 16.4.1 – 16.4.3)

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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.

Dose	Efficacy
10mg	decreases serum K^+ by 0.53 - 0.88 mmol/l
20mg	decreases serum K^+ by 0.66 - 0.98 mmol/l

Table 23: Efficacy of Nebulised Salbutamol.

The effect of salbutamol is dose-dependent as shown above in Table 23. The onset of action is within 30 minutes and duration of action is for at least 2 hours as shown below in Table 24.[2, 3, 6-11] A Cochrane review (2015) found that Salbutamol significantly reduced serum K^+ compared with placebo.[4] The peak effect of 10mg nebulised salbutamol was 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 therapy[13] and 1.2 mmol/L with nebulised beta-agonist therapy[9]. Lim et al found a modest additive benefit of salbutamol of 0.3 mmol/l.[14]

STUDY	N	Dose of Salbutamol	Mean initial K^+ (mmol/L)	Peak reduction in K^+ (mmol/L)	Time of max action	Duration of Effect (min)
Allon [6] 1989	10	10 mg	5.93	0.62	90	>120
Allon [7] 1996	8	10 mg	4.29	0.53	60	>60
Liou [2]	17	10 mg	5.8	0.88	90	>60

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1994						
Montoliu [11] 1990	10	15 mg	6.5	0.9	30	>360
Kim [8] 1997	9	15 mg	5.99	0.57	60	> 60
Allon [6] 1989	10	20 mg	5.81	0.98	90	>120
Allon [9] 1990	12	20 mg	5.56	0.66	60	>60
McClure [3] 1994	11	2.5/ 5 mg*	5.9	0.61	30	>300
Mandelberg [10] 1999	17	1200□g (via MDS-I)	5.5	0.4	60	ns

Table 24: 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.[15] 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 is currently not recommended to be used as monotherapy for treatment of hyperkalaemia.[4]

INSAKA is a prospective, multi-centre, open-label RCT which will assess the efficacy of Salbutamol (10mg) compared with Insulin-glucose (10 units in 50g) alone and in combination with Salbutamol.[16] This study within an acute setting is due to be completed in 2025 and may provide definitive evidence of efficacy.

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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[4, 6] and salbutamol[5], 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.[6]

There are few studies of the efficacy of sodium bicarbonate in the acute setting. Geng et al showed that there was no significant additive K^+-lowering with sodium bicarbonate

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compared with the control group (1 mmol/l vs 0.9 mmol/l, p=0.976).[7] Lim et al undertook a study including patients with AKI and reported that the effect of sodium bicarbonate as a co-treatment for hyperkalaemia was weak and may not be clinically significant.[8]

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).[9] 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 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.[10]

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.[3, 11] There is also no evidence to suggest that sodium bicarbonate is more effective in patients as the severity of hyperkalaemia increases.[3]

Some studies advocate use of sodium bicarbonate in the critical care setting. Jaber et al performed at RCT using hypertonic sodium bicarbonate in critically ill patients with severe metabolic acidosis and noted a significantly lower K^+ level in the bicarbonate group and a lower requirement for RRT.[9] Depret et al advocate 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).[12]

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.

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

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

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

We suggest that Sodium Zirconium Cyclosilicate is considered in the acute management of moderate hyperkalaemia (serum K^+ 6.0 – 6.4 mmol/l). (1B)

Audit Measures:

1. The proportion of patients with acute severe hyperkalaemia (serum $K^+ \geq 6.5$ mmol/l) treated with Sodium Zirconium Cyclosilicate.

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2. The proportion of hospitalised patients with moderate hyperkalaemia (serum K^+ 6.0-6.4 mmol/l) treated with Sodium Zirconium Cyclosilicate.

Rationale (Guideline 16.6.1)

Until recently, there have 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]

Regulatory bodies across the UK, National Institute for Health and Care Excellence (NICE)[3] and the Scottish Medicines Consortium (SMC),[4] have now both approved the use of Sodium zirconium cyclosilicate (SZC) in the management of potentially life-threatening acute hyperkalaemia. Robust evidence in the acute setting is still lacking, but clinical experience is growing and further clinical trials are underway.

Evidence for SZC in the acute setting

The SZC clinical trials have been discussed in detail in Guidelines 10.1-10.3 and include three RCTs [5-7] and one open-label clinical trial.[8] 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.

Acute Phase	ZS-003 [6]	ZS-004 [7]	ZS-005 [8]
24 hours		66%	66%
48 hours	86.4%	88%	75%
72 hours			78%

Table 25: Proportion of patients taking SZC 10g three times daily achieving restoration of normokalaemia (K^+ 3.5-5.0 mmol/l) during acute phase.

SZC provides a potential option for treating severe acute hyperkalaemia for several reasons:

- It has a rapid onset of action within 1 hour. [1]

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- The ZS-003 and ZS-004 trials demonstrated a greater K^+-lowering effect with increasing severity of hyperkalaemia.[6, 7]
- The efficacy of SZC over the first 24-72 hours (Table 25), demonstrates that 66% of patients achieved normokalaemia within 24 hours.
- SZC lowers serum K^+ by 1.1 mmol/l within 48 hours.[7]
- In patients with a serum K^+ > 6.0 mmol/l, SZC lowers serum K^+ by 1.5 mmol/l within 48 hours.[7]

Severity of hyperkalaemia in SZC studies

The number of patients with a serum K^+ of 5.5-5.9 mmol/l was 38.8% in ZS-004[7] and 45% in ZS-005[8]. The number of patients with $K^+ \geq 6.0$mmol/l was 15.1% in ZS-004 and 16.8% in ZS-005. A post-hoc analysis of the sub-group of patients with $K^+ \geq 6.0$ 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.

SZC studies in the acute setting

The ENERGIZE study was a pilot study to investigate the efficacy of SZC alongside standard management of hyperkalaemia in the acute setting.[9] It was a double-blind, placebo controlled RCT, but did not reach its recruitment target (n=132) to achieve statistical power. It included a total of 70 patients with a serum $K^+ \geq 5.8$ mmol/l. The mean serum K^+ was 6.4 mmol/l in the SZC group (n=33) and 6.5 mmol/l in the placebo group (n=37). Patients in the SZC arm received 10g up to three times over a 10 hour period (i.e. 1, 4 and 10 hours). All patients required more than a single dose (10g) of SZC, 86.2% required ≥ 2 doses and 65.5% required ≥ 3 doses. There were several limitations in this small study including early treatment withdrawals and missing data at a critical time-point (4 hours). However, a notable observation is that the fall in serum K^+ in the first hour appears to be predominantly attributable to Insulin-glucose and an additive effect was apparent for SZC at 2 hours.

The KBindER study is the first head-to-head clinical trial to evaluate the efficacy of oral potassium binders in the acute setting.[10] It will include patients presenting to the Emergency Department or hospitalised with a serum $K^+ \geq 5.5$ mmol/l. The primary endpoint is serum K^+ at 2 and 4 hours. It will also evaluate length of stay and adverse effects.

It will consist of 4 arms (recruitment target is 20 patients per group):

1. SPS – one dose of 30g

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2. Patiromer – single dose of 25.2g
3. Sodium zirconium cyclosilicate [SZC] – single dose of 15g
4. Polyethylene glycol 3350 [MiraLax] – single dose of 17g (laxative)

Compared with the ENERGIZE study, this study will include patients with less severe hyperkalaemia, smaller sub-groups and a lower treatment dose of SZC. There is also no placebo arm. The use of temporizing drugs (e.g. Insulin-glucose) is at the discretion of the clinician. It is anticipated that SZC will be the most effective therapy based on existing evidence. This study may provide some evidence to guide the most appropriate choice of potassium binder in the acute setting and justify the cost of the novel binders.

Threshold for using SZC in acute hyperkalaemia

A specific threshold was not stated by either NICE or SMC, therefore this leaves some scope for interpretation of a 'life-threatening' level of serum potassium. In the original Renal Association Guideline (2020), this threshold was considered to be a serum $K^+ \geq 6.5$ mmol/l as this level defines 'severe' hyperkalaemia and the group of patients most at risk of arrhythmias. At the time publication, there was also little clinical experience of SZC in the UK and no completed clinical trials in the acute setting.

The management of patients with moderate hyperkalaemia is important as this could prevent a further rise in serum K^+ and reduce the risk of adverse events. In the acute setting, the strategy is generally guided by the acuity of the patient, likely aetiology, and the degree and chronicity of renal impairment. The approach to a clinically well patient with an incidental finding will be different to an acutely unwell oliguric patient.

To our knowledge, there are no studies comparing the efficacy of SZC in patients with moderate versus severe hyperkalaemia in the acute setting. However, some studies have shown that the efficacy of SZC increases with worsening hyperkalaemia. On this basis, it is possible that the degree of K^+ reduction will be lower in patients with moderate compared with severe hyperkalaemia. This would only be clinically relevant if the rate of rise in serum K^+ exceeds the efficacy of K^+-lowering therapies in patients with moderate hyperkalaemia.

Despite the lack of evidence in the acute setting, patients with severe hyperkalaemia warrant treatment with SZC alongside standard care. The approach to patients with moderate hyperkalaemia requires some clinical judgement to consider the risk of further rise in serum K^+

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and the likelihood of reversibility of the underlying aetiology (e.g. drugs, urinary retention, volume depletion).

Administration of SZC in the acute setting

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.[1] 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. Further research in the acute setting is required to demonstrate the need for maintenance therapy.

Further study

Insulin-glucose is the most effective medical therapy for lowering serum K+ in the acute setting, but is associated with significant risk of hypoglycaemia. Studies to assess the efficacy of SZC alongside standard treatment in patients with moderate and severe hyperkalaemia is needed. SZC may indirectly reduce the risk of hypoglycaemia by reducing the need for repeated Insulin-glucose infusions but this remains to be shown.

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Guideline 16.6.2 – Hyperkalaemia: STEP 3 – Remove K^+ from body; Potassium binders

We suggest that Patiromer is an option for the emergency management of acute hyperkalaemia (serum $K^+ \geq 6.0$ mmol/l). (1C)

Audit Measures:

1. The proportion of hospitalised patients with acute hyperkalaemia (serum $K^+ > 6.0$ mmol/l) treated with Patiromer.

Rationale (Guideline 16.6.2)

Patiromer is a novel potassium binder that has been discussed in detail in Guidelines 9.1-9.3. It is a non-absorbed, sodium free, K^+-binding polymer.[1] Calcium is used, rather than sodium, as the counter ion for K^+ exchange. This avoids the potential for excessive sodium absorption and volume overload. The onset of action is slow (4-7 hours)[1] therefore its contribution to rapid control of serum potassium (within the first 4 hours) may be limited in the acute setting.

Patiromer is approved by NICE for treating patients with life-threatening hyperkalaemia alongside standard medical therapy[2], but has not been approved by the SMC. Therefore, this guidance does not apply to Scotland.

Evidence for Patiromer in the acute setting

Most clinical trials of patiromer have been performed in stable out-patients with mild hyperkalaemia.[3-8] 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).[3]

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The first study to assess the efficacy of patiromer in the acute setting was a pilot study within an Emergency Department.[9] This was a single-centre randomised open-label study of patients with ESRD with a serum $K^+ \geq 6.0$ mmol/l. Patients were randomised to receive standard care (n=15) or standard care plus a single dose of patiromer 25.2g (n=15). The mean baseline K^+ was 6.7 mmol/l vs 6.4 mmol/l. Patients treated with patiromer showed a significantly lower serum K^+ at 2 hours (6.51 mmol/l vs 5.9 mmol/l, p=0.009), but there was no difference at 1, 4 or 6 hours. PLATINUM is an ongoing Phase 4, multicentre, randomised, double-blind, placebo-controlled study which included 300 patients presenting to the Emergency Department with hyperkalaemia.[10] Patients with a serum $K^+ \geq 5.8$ mmol/l were included and have been randomised to receive standard care (Glucose 25g/ Insulin 5 units and albuterol) in combination with either a single dose of Patiromer 25.2g or placebo. A second dose of Patiromer 8.4g or placebo was given at 24 hours. The primary end-point is the net clinical benefit defined as the mean change in the number of additional interventions less the mean change in serum K^+ at 6 hours. The outcome of this study is awaited.

Patiromer has also been assessed as monotherapy for non-life-threatening hyperkalaemia. This retrospective study included 881 patients with a serum $K^+ > 5.0$ mmol/l (mean 5.6 mmol/l) across the hospital site including ED and intensive care.[11] Approximately 47% of patients had moderate hyperkalaemia (K^+ 6.0 – 6.4 mmol/l) and only 2.2% of patients had severe hyperkalaemia ($K^+ > 6.5$ mmol/l). Patients requiring dialysis and those treated with Insulin-glucose within 3 hours before or after Patiromer dose were excluded to remove the influence of other K^+-lowering treatments. The majority of patients (82%) received a low dose of Patiromer, 8.4g. The mean reduction in serum K^+ was 0.5 mmol/l at 0-6 hours, 0.46 mmol/l at 6-12 hours and 0.52 mmol/l at 12-24 hours. The authors note that this may suggest that the onset of action of Patiromer may be more rapid than previously reported.

Threshold for using Patiromer in acute hyperkalaemia

Similar to SZC, a specific threshold was not stated by NICE,[2] therefore this leaves some scope for interpretation of a 'life-threatening' level of serum potassium. In the original Renal Association Guideline (2020), this threshold was considered to be a serum $K^+ \geq 6.5$ mmol/l as this level defines 'severe' hyperkalaemia and the group of patients most at risk of arrhythmias. However, patients with moderate hyperkalaemia are at risk of deterioration and binders pose an option to gain earlier control.

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Pending the outcome of the PLATINUM Trial, Patiromer can be considered for the treatment of moderate or severe hyperkalaemia in the acute setting.

Administration of Patiromer in the acute setting

The recommended starting dose is 8.4g once daily and the maximum dose is 25.2g daily. It should not be used to replace standard emergency treatment for hyperkalaemia. Patiromer has the potential to bind to some co-administered drugs, therefore it cannot be taken within 3 hours of other medications.[1]

Although the dosing regimens in clinical trials were twice daily, the FDA and NICE have approved patiromer for single daily dosing only in view of the potential risk of drug interactions.

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Guideline 16.2 – Hyperkalaemia: STEP 3 – Remove K^+ from body; Cation-exchange resin

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We recommend that calcium resonium should no longer be routinely used in the management of acute hyperkalaemia. (2B)

Rationale (Guideline 16.6.3)

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 Ca^{2+}.[1] The onset of action is slow (> 4 hours) and efficacy is unpredictable excluding its use in emergencies. These drugs are poorly tolerated due to taste and constipation and there are substantial reports of harm due to adverse events including intestinal necrosis.[2, 3]

Although these resins have been used in clinical practice for decades, there have been only 4 RCTs evaluating SPS to reduce potassium levels and only one of these studies showed a statistically significant reduction after seven days.[4-7] Several observational studies have also been conducted and have shown a small reduction (< 1 mmol/l) in serum potassium after 24 hours.[8] Evidence in the acute setting remains sparse. Cochrane reviews conducted in 2005[9] and 2015[10] evaluating SPS in acute hyperkalaemia and in 2020[11] evaluating SPS in chronic hyperkalaemia have all concluded there is insufficient high-quality evidence to recommend their use.

Joyce et al (2023) conducted a recent retrospective review comparing the efficacy and safety of Sodium Zirconium Cyclosilicate (SZC) versus SPS in the acute setting alongside standard care.[12] A total of 246 patients were included with a baseline K^+ of 5.98 mmol/l in the SZC group and 6.03 mmol/l in the SPS group. A similar proportion of patients received Insulin-glucose (43.3% vs 49.2%; n=0.4) and other treatments for hyperkalaemia. There was no significant difference in efficacy at 1-4 hours (0.88 mmol/l vs 0.77 mmol/l; p=0.48) or at 24 hours (0.78 mmol/l vs 0.91 mmol/l; p=0.22). This finding is comparable with the efficacy demonstrated in a large RCT which showed SZC reduced K^+ by 0.7 mmol/l at 24 hours.[13] The efficacy of a single dose of SZC and SPS increased with higher dosage as shown in Table 26 below. Five adverse events were reported in the SPS group, but none in the SZC group.[12]

	SZC N=128			**SPS (n=118)**	
Dose	**5g**	**10g**	**15g**	**15g**	**30g**

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K^+ reduction at 24 hrs	0.58	0.80	0.96	0.80	1.10
% patients achieving normalisation of K^+ at 24 hrs	33.3%	37.4%	50%	44.7%	42.9%

Table 26: Potassium lowering effect after a single dose of oral binder. Adapted from Joyce et al, *J Pharm Prac* 2023.[12] SZC – Sodium Zirconium Cyclosilicate; SPS – Sodium Polystyrene Sulfonate

The KBindER trial is an ongoing clinical trial to evaluate the most effective oral potassium binder in the acute setting.[14] It will compare the safety and efficacy of single doses of SPS (30g), SZC (15g), Patiromer (25.2g) and Polyethylene glycol [MiraLax] (17g). This study may provide some evidence of the most effective oral potassium binder in the acute setting.

Given the evolution in clinical practice, lack of evidence and the availability of more tolerable oral therapies to treatment hyperkalaemia, calcium resonium is no longer recommended as a first line drug in the acute setting. Similar conclusions have been drawn by Cochrane reviews,[9, 10] other authors,[15] the American Heart Association resuscitation guidelines (2020)[16] and at the KDIGO conference (2020)[17] who do not support the use of SPS in the acute setting.

Calcium resonium may still have a role in some circumstances including intolerance of other oral potassium binders and potentially in the chronic setting in patients who do not meet NICE[18] or SMC[19] criteria.

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II. Hyperkalaemia in Hospitalised Patient (Guidelines Hyperkalaemia 17.1 – 17.2)

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 to monitor for rebound hyperkalaemia after the initial response to treatment wanes. (1B)

Guideline 17.1.2 – Hyperkalaemia: STEP 4 - Blood monitoring; serum K^+

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 the first 2 hours of treatment for severe hyperkalaemia [Audit Standard: 100%].

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Rationale (Guidelines 17.1.1 – 17.1.2)

The timing for assessing response to treatment is guided by the onset of action and duration of action of K^+-lowering drugs. Insulin-glucose 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 minutes [1-5] and for nebulised salbutamol from 30-90 minutes.[1, 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.[10] The onset of action of the potassium binders vary. Sodium zirconium cyclosilicate (SZC) works within 1 hour [11] and Patiromer works within 4-7 hours.[12]

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 three of the K^+-lowering drugs can be assess 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 insulin-glucose and salbutamol wears off.[13-17] The use of potassium binders may lower this rebound phenomenon and may provide better control of hyperkalaemia beyond initial acute treatment. Measure the serum K^+ at 24 hours to ensure that control of hyperkalaemia has been maintained. Schedule for monitoring is shown in Table 27.

Pre-treatment	**BASELINE**	Send bloods before initiating treatment
1-HR post treatment	**EFFICACY**	Check if treatment has worked
2-HR post treatment	**EFFICACY**	Check again if uncontrolled at 1-hr
4-HR post treatment	**RE-BOUND**	Watch for K^+ level rising again after effect of Insulin-Glucose and Salbutamol wears off
6-HR post treatment	**RE-BOUND**	
24-HR post treatment	**CONTROL**	Ensure K^+ controlled and action taken to avoid recurrence

Table 27: Timing of blood monitoring in patients with acute hyperkalaemia.

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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 and 360 minutes) after administration of insulin-glucose infusion in all patients with hyperkalaemia. (1C)

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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.[1-5] Hypoglycaemia is associated with an increased risk of ICU admission [6] prolonged length of stay [7] and hospital mortality.[3, 7, 8] Severe hypoglycaemia, is defined as a blood glucose of < 2.8 mmol/L.[2, 4]

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.[9] The impact of hypoglycaemia is independent of diabetic status and adverse outcomes have been shown in patients with diabetes mellitus or without diabetes.[9, 10]

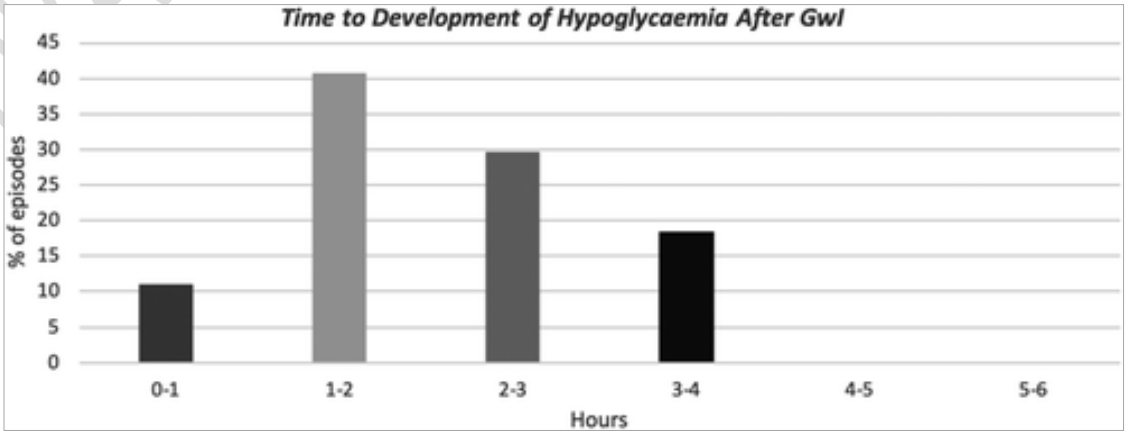
Iatrogenic hypoglycaemia is a significant patient safety concern, therefore should be anticipated. Risk factors for hypoglycaemia are discussed in Guideline 16.3. Variables related to treatment (dose of insulin, dose of glucose) and baseline clinical parameters (e.g. pre-treatment glucose) appear to have a greater influence on the rate of hypoglycaemia than non-modifiable baseline patient characteristics.[2, 5] In patients without diabetes, hypoglycaemia may occur within 1 hour after insulin-glucose.[11] The risk of hypoglycaemia persists for as late as 6 hours after administration of IV insulin.[1, 4, 5, 12, 13]

We previously recommended blood glucose monitoring for a period of 12 hours after insulin-glucose administration following consultation with the Joint British Diabetes Societies for inpatient care. However, in real-world clinical practice, blood glucose monitoring is generally poor making adherence to a protocol for this duration difficult to achieve.

A further review of the literature to guide the duration of blood glucose monitoring is now warranted and some key findings are documented below and summarised in Table 28.

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- Lim et al (2023) recently reported a retrospective review (n=135) and demonstrated hypoglycaemia in 20.7% of patients.[14] Of these events, the highest proportion (11.9%) occurred within the first hour. The rate declined subsequently to 7.4% in the 2nd hour, 2.2% in the 4th hour and 1.5% in the 6th hour.
- Chothia et al (2022) conducted a review of 62 studies including >15,000 patients and found the median time for development of hypoglycaemia after Insulin-glucose was 124 minutes.[15]
- Humphrey et al (2022) reported all hypoglycaemic episodes occurred within 6 hours of receiving insulin-glucose.[6]
- Crnobrnja et al (2020) reported most episodes occurred during the second hour after insulin administration with a peak at 90 minutes.[16] Furthermore, they noted that hypoglycaemia was rare before 30 minutes and beyond 5 hours unless repeated Insulin-glucose therapy was given.
- Tran et al (2020) compared two protocols for blood glucose monitoring following Insulin-Glucose treatment and demonstrated an incidence of hypoglycaemia of 21% when monitoring was performed at 1, 2, 4 and 6 hours post-treatment.[17] Most of these episodes (92%) occurred within 3 hours of treatment.
- Tee et al (2020) found that approximately 10% of hypoglycaemic events occurred within the first hour, 40% between 1-2 hours, 30% between 2-3 hours and 18% between 3-4 hours after Insulin-glucose treatment as shown above in Figure 7. [18] There were no episodes between 4-6 hours. This study was led by an endocrinology team in the UK and advocate blood glucose monitoring for 6 hours.



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Figure 7: Time to development of hypoglycaemia following Glucose-Insulin (GwI) infusion.
Reproduced with permission from *Tee et al, Clin Endocrinol (Oxf) 2021; 94: 176-182.*[18]

- Two studies have shown that only 8% of hypoglycaemic events occurred between 3-6 hours.[16, 17]
- Coca et al (2017) used a protocol of 10 units soluble insulin in 50g glucose delivered over 4 hours by infusion.[5] The higher glucose load and administration by infusion likely explains the lower incidence of hypoglycaemia with only one late episode.

Study	N=	Incidence of hypoglycaemia	Time to developing Hypoglycaemia (minutes)	Comments
Schafers et al (2012) [1]	219	8.7%	**180***	Poor documentation of hypoglycaemic event noted
Apel et al (2014) [4]	221	13%	**120 (IQR 60-180)**	75% of events occurred within first 3 hours
Estep et al (2015) [19]	86	17%	**87 (IQR 63 – 108)**	*'Aspart'* formulation of insulin used in this study
Coca et al (2017) [5]	164	6.1%	**210****	Insulin-glucose (50g) infusion given over 4 hours; only 1 event occurred after 6th hour
Crnobrnja et al (2020) [16]	421	21%	**142 (SD 74)**	Peak incidence between 60-150 minutes
Tee et al (2021) [18]	132	11.8%	**110 (range 35-221)**	Advocates either additional glucose infusions or glucose-only regimen***
Kijprasert et al (2022) [20]	385	25.2%	**253 (range 190 – 435)**	Patients with history of diabetes was excluded
Chothia et al (2022) [15]	15,363	17.2%	**124 (IQR 102-168)**	Analysis of 62 studies

Table 28: Time to development of hypoglycaemia after Insulin-glucose treatment.

IQR – interquartile range; *median; **mean; ***see text

- Pierce et al (2015) reported late hypoglycaemia as long as 7.5 hours after Insulin-glucose treatment, but this group still concluded that monitoring should be performed for up to 6 hours after insulin-glucose therapy.[12]

On the basis of current evidence, we now recommend blood glucose monitoring should be performed every 30 minutes during the first two hours (30, 60, 90, 120 minutes) and thereafter hourly for a minimum of 6 hours (180, 240, 300, 360 minutes) after Insulin-glucose

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administration. Patients deemed to be at high risk for late hypoglycaemia, e.g. repeat insulin-glucose infusions, should have extended monitoring beyond 6 hours.

Given the timing of hypoglycaemic episodes, the administration of a 10% glucose infusion over 5 hours to patients with a pre-treatment blood glucose < 7 mmol/l, could potentially avoid a significant number of episodes. Vigilance is still required for patients with a pre-treatment blood glucose ≥ 7mmol/l to avoid and treat hypoglycaemia.

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II. Hyperkalaemia in Hospitalised Patient (Guidelines Hyperkalaemia 18.1 – 18.4)

Guideline 18.1 - Hyperkalaemia: Treatment in haemodialysis patients

We recommend that haemodialysis patients with severe hyperkalaemia (serum $K^+ \geq 6.5$ mmol/L) receive dialysis treatment urgently. (1A)

Guideline 18.2 - Hyperkalaemia: Treatment in haemodialysis patients

We recommend that haemodialysis patients with severe hyperkalaemia (serum $K^+ \geq 6.5$ mmol/L) and toxic ECG changes be treated with intravenous calcium salt to reduce risk of arrhythmias even when dialysis is immediately available. (1C)

Guideline 18.3 - Hyperkalaemia: Treatment in haemodialysis patients

We recommend that haemodialysis patients with severe hyperkalaemia (serum $K^+ \geq 6.5$ mmol/L) be treated with standard medical therapies to lower serum potassium if dialysis is not immediately available. (1B)

Guideline 18.4 - Hyperkalaemia: Treatment in haemodialysis patients

We suggest that potassium binders may be considered to reduce the risk of hyperkalaemia during the inter-dialytic period. (1B)

Audit measures:

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

Rationale (Guidelines 18.1 – 18.4)

Haemodialysis (HD) patients have a high risk of hyperkalaemia. Hyperkalaemia has been found to be a significant factor contributing to mortality in dialysis patients [1-6] and was shown to be responsible for 3-5% of deaths. [1, 4] Factors contributing to hyperkalaemia in HD patients are

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summarised in Table 29. These include dietary K^+ intake, frequency and duration of dialysis, blood glucose level and constipation.[7-9]

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).[10, 11] The long inter-dialytic break also correlates with hospitalisation [12, 13] and mortality in HD patients.[10, 13-15] The PORTEND (Potassium and Cardiac Rhythm Trends in MainENance HemoDialysis) observational study showed an incidence of pre-dialysis hyperkalaemia ($K^+ > 5.0$ mmol/l) after the long inter-dialytic interval of 37% in patients dialysing on a dialysate K^+ concentration of ≤ 2mmol/l and 21% in patients dialysing on a dialysate $K^+ \geq 3$mmol/l.[16] The UK Renal Association Clinical Practice Guideline on Haemodialysis (2019) recommends an optimal pre-dialysis serum K^+ in the range of 4.0 – 6.0 mmol/l.[17]

Factors contributing to hyperkalaemia in Haemodialysis 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 K^+ intake ▪ Diabetic status – glycaemic control ▪ Constipation ▪ Compliance – poor attendance, shortened treatment time

Table 29: Factors associated with an increased risk of hyperkalaemia in HD patients.

Dialysis: Dialysis is the definitive treatment for hyperkalaemia in patients receiving longterm HD. In one report, hyperkalaemia was the reason for emergency dialysis 24% of the time in their maintenance HD program.[18] Although a degree of 'tolerance' to hyperkalaemia has been postulated in HD patients,[19] there remains a risk of arrhythmias, cardiac arrest or sudden death in HD patients with severe hyperkalaemia.

Each HD session removes approximately 70 – 100 mmol K^+.[20] The dialysate K^+ concentration determines the rate of K^+ removal. Serum K^+ concentration typically falls by 1 mmol/l during the first hour of dialysis when the gradient between the serum and dialysate K^+ is highest, then by 1

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mmol/l over the next 2 hours.[20] The serum K^+ reaches a steady state during the last hour of the treatment. The choice of dialysate fluid is guided by the severity of hyperkalaemia as shown below in Table 30. The use of a 1 mmol/l K^+ dialysate fluid is potentially associated with an increased risk of arrhythmias,[21] therefore telemetry and close monitoring of K^+ level is essential. An alternative approach is the use of sequential dialysis sessions.[22]

Pre-dialysis serum K^+ (mmol/l)	DIALYSATE POTASSIUM (mmol/l)
	CHRONIC HAEMODIALYSIS
4.5 – 5.5	2 or 3 (based on individual trend)
5.6 – 8.0	2
>8.0	1 (telemetry + 30min K^+ checks and switch to K^+ 2 when serum K^+ < 7)

Table 30: Dialysate K^+ prescription in chronic HD patients.[22]

Bridging to dialysis initiation: Intravenous calcium reduces the risk of arrhythmias (Guideline 16.2), therefore is warranted in patients with severe hyperkalaemia and toxic ECG changes even if dialysis can be established quickly. More frequently, dialysis may not be immediately available and temporising measures will also be necessary. Drugs used in lowering the serum K^+ may have a variable effective in HD patients. Fortunately, the K^+-lowering effect of insulin is preserved in patients with renal failure,[23] but these patients are more prone to hypoglycaemia. Although some studies have suggested a lower dose of insulin in treating patients with poor renal function,[24, 25] a pre-treatment blood glucose < 7 mmol/l was the most consistent risk factor for hypoglycaemia (Guideline 16.3). The effectiveness of salbutamol may be reduced, with studies demonstrating up to 40% of patients with ESRD appear to be resistant to the hypokalaemic effect of salbutamol, even those who are not receiving beta-blockers.[26, 27] Medical therapies provide a bridge to dialysis initiation, but a gradual rebound in hyperkalaemia should be anticipated.

Inform the Renal Team immediately if a dialysis patient presents with hyperkalaemia as medical treatments will only temporarily control K^+ level.

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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 HD. Driver et al conducted a retrospective study (n=479) in patients presenting to the Emergency Department with hyperkalaemia who subsequently underwent HD.[28] 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 HD 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 K^+ shifting before emergent dialysis is not associated with recurrent hyperkalaemia or need for multiple HD 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.

Prevention: Until recently, the options for preventing hyperkalaemia in HD patients has been limited to dietary K^+ restriction and low K^+ dialysis solutions. Novel potassium binders may provide an additional strategy.[29] Patiromer and SZC may help to control serum K^+ levels in patients treated with less frequent HD. Selection of patients for this strategy is important as poor adherence to medication and diet could have potentially serious consequences.

Patiromer: Three studies have investigated the use of patiromer in HD patients.[30-32] Kovesky et al demonstrated that patiromer reduced serum K^+ by an average of 0.5 mmol/l and in HD patients with severe hyperkalaemia ($K^+ \geq 6.5$ mmol/l), the reduction was in the order of 1.0 mmol/l.[31] The relative proportion of patients with severe hyperkalaemia in this study was reduced by approximately 50%. Similarly, Chatoth et al showed a reduction in the number of hyperkalaemic events and hospitalisation in HD patients treated with patiromer.[32] Bushingsky et al performed an inpatient study of only 6 HD patients showing a significant decrease in serum K^+.[30] 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.

The TWOPLUS-HD pilot trial studied twice versus thrice weekly HD in patients with incident ESRD to investigate whether patiromer can have a dialysis-sparing effect.[33] Patiromer was included in the protocol for the Incremental HD group. One episode of hyperkalaemia occurred in the Incremental group and none in the conventional group.

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SZC: The DIALIZE trial was a Phase IIIb RCT designed to evaluate SZC in controlling hyperkalaemia in haemodialysis (HD) patients.[34] This was the first randomised, double-blind, placebo controlled trial to assess a potassium binder in HD patients. 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 study demonstrated a significant reduction in pre-dialysis hyperkalaemia at the highest risk period (41.2% vs 1.0% in the placebo arm) and a reduction in need for emergency treatment for hyperkalaemia (2.1% vs 5.1% in placebo arm).

The DIALIZE-Outcome study (NCT03303521) is an ongoing multi-centre RCT in chronic HD patients to evaluate the efficacy of SZC in reducing occurrence of sudden cardiac death, stroke, emergency department attendances, arrhythmia-related hospital admission.[35]

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II. Hyperkalaemia in Hospitalised Patient (Guidelines Hyperkalaemia 19.1 – 19.6)

Guideline 19.1 - Hyperkalaemia: Specialist Referral

We suggest that patients with severe hyperkalaemia (serum $K^+ \geq 6.5$ 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 19.2 - 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 19.3 - 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 19.4 - 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 19.5 – Hyperkalaemia: Treatment facilities – Ward, Enhanced Care or Critical Care 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, enhanced care area, or critical care unit (HDU or ICU) depending on local facilities or practice. (1C)

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Guideline 19.6 – Hyperkalaemia: RRT in treatment of hyperkalaemia in acutely unwell patients.

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)

Rationale (Guidelines 19.1 – 19.6)

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, level of acuity, response to initial medical treatment and availability of services locally.[1] Further considerations to guide escalation of care are the likelihood of survival (e.g. reversible illness), extent of comorbidity, accurate assessment of pre-morbid functional status, and the patient's wishes. The management plan, ceiling of care (i.e. ward, HDU or ICU) and resuscitation status should be documented early.

Placement is guided by the level of care required. The need for basic or advanced organ support, including dialysis, defines the appropriate clinical area. Patients with severe hyperkalaemia require continuous cardiac monitoring and need to be triaged to an area with these facilities.[2] Enhanced care areas have been developed in some regions to provide a level of care between high dependency and ward level.[3] Patients requiring acute RRT (e.g. haemodialysis or haemofiltration) meet the criteria for Level 2 care which can be delivered in a renal 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.[4]

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Severe hyperkalaemia can cause abrupt cardiac arrest, sometimes without warning ECG changes. It is a key indication for emergency RRT.[5] Where a decision has been taken to treat with RRT, it should be performed with due regard for potential deterioration.[1][3][6] 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.[7] Conventional intermittent haemodialysis (IHD) is thought to be the most effective method for K^+ removal, but continuous venovenous haemofiltration (CVVH) and continuous veno-venous haemodiafiltration (CVVHDF) are more frequently available in ICUs in the UK.[8] Nearly 90% of UK ICUs have facilities for RRT.[9]

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.[10] Potassium removal with IHD decreases after 2 hours and rebound occurs after dialysis is stopped.[10]

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.[3]

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II. Hyperkalaemia in Hospitalised Patient (Guidelines Hyperkalaemia 20.1 – 20.2)

Guideline 20.1 - 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 20.2 - 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 20.1 – 20.2)

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 a 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.

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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. Critical care review is essential for patients with any concern regarding oxygenation, ventilation or haemodynamic instability. The decision to accept a transferred patient should be made by a consultant in the receiving unit.

Pre-transfer stabilisation is important,[1][3] but should not cause undue delay if transfer is required to facilitate urgent dialysis. Inter-hospital transfer of a patient with severe hyperkalaemia carries increased risk, therefore this decision should be taken by a consultant who will carefully weigh this risk guided by the location of intensive care and dialysis facilities.

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

Table 31: Minimum standards for safe patient transfer.

Adapted from Dunn (2007)[3], FICM guidelines (2019)[1], ICS guidelines (2011)[4], NICE(2017) [5]

The organisation of the patient transfer itself requires a coordinated approach and liaison with the receiving team.[2] The use of a transfer checklist, protocols and skilled staff

reduce mortality.[4] 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.[4] Hospitals should form transfer networks to co-ordinate and manage clinically indicated transfers.[2] Record keeping is a legal requirement for all patient transfers.[1] 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 31.

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 17.1). The potential for hypoglycaemia after administration of insulin-glucose should be considered and blood glucose checked on arrival. Kitchlu et al found that inter-hospital transfer to facilitate RRT did not confer higher mortality or worse renal outcomes.[6]

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II. Hyperkalaemia in Hospitalised Patient (Guidelines Hyperkalaemia 21.1 – 21.4)

Guideline 21.1 – Hyperkalaemia: Prevention of hyperkalaemia in hospitalised patients

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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 21.2 – Hyperkalaemia: Prevention of hyperkalaemia in hospitalised patients

We recommend a low potassium diet for hospitalised patients with moderate or severe hyperkalaemia. (1C)

Guideline 21.3 – 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 21.4 – 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 21.1 – 21.4)

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 AKI with hyperkalaemia which may be present at the time of hospital admission. 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.

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Drugs that affect aldosterone secretion • ACE inhibitors (*inhibit conversion of Angiotensin I to Angiotensin II*) • Angiotensin Receptor Blockers (*inhibit activation of Angiotensin IR by Angiotensin II*) • Non-steroidal anti-inflammatory drugs (*inhibit renin release*) • Calcineurin inhibitors (*inhibits Na^++-K^++-ATPase necessary for K^+ secretion*) • Heparins (*reduced production of aldosterone*) • Antifungals (e.: ketoconazole, fluconazole and itraconazole)
Drugs that block aldosterone binding to mineralocorticoid receptor (MRA) • Spironolactone, Eplerenone • Finerenone (*non-steroidal MRA*)
Drugs that inhibit activity of epithelial sodium channel • Potassium sparing diuretics (e.g. amiloride and triamterene) • Trimethoprim; Co-trimoxazole • Pentamidine
Drugs that alter transmembrane potassium movement • β-blockers (atenolol, metoprolol, propranolol) • Digoxin (*inhibits Na^++-K^++-ATPase necessary for K^+ secretion*) • 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

Table 32: Drugs commonly associate with hyperkalaemia and mechanisms.

Hyperkalaemia often occurs after hospital admission. A study of in-patients with hyperkalaemia showed that 33.3% of cases developed after hospital admission.[2] 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 half of these. 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.[2] The severity of hyperkalaemia was also found to correlate ($p< 0.01$) with the number of potentially hyperkalaemia-inducing drugs used concurrently. Medications frequently implicated in hyperkalaemia are summarised in Table 32.

Robert et al found that hyperkalaemia developed 3 or more days after hospital admission in 4.5% of elderly hospitalised patients.[3] AKI was present in 51% of cases and hyperkalaemia-inducing drugs were implicated in 80.5% of cases.[3] Overall, 79.9% of hyperkalaemic events were potentially avoidable.

Hyperkalaemia is particularly common in patients with CKD. Furuland et al reported hyperkalaemia in 48.4% of patients. Multiple episodes occurred in 28.8% of patients with CKD Stage 3-5 .[4] Patients with hyperkalaemia were shown to have a longer duration of hospital stay and higher mortality risk than those without hyperkalaemia.[4]

Steps can be taken to avoid hyperkalaemia occurring from the outset (Primary Prevention) and should be taken to avoid recurrence after an episode (Secondary Prevention).

Primary Prevention *These are steps taken to avoid an initial episode of hyperkalaemia.*
Non-dialysis Patients: ▪ Regular blood monitoring for patients at risk (e.g. CKD, heart failure, diabetes, any patient taking RAASi or MRA) ▪ Avoid drug combinations that potentiate hyperkalaemia (e.g. ACE-I and Trimethoprim) ▪ Dietary advice in patients with CKD 4 & 5 ▪ Sick day rules – withhold drugs that may contribute to hyperkalaemia during acute illness ▪ Consider who is at risk at time of hospital admission ▪ Consider need to withhold drugs that potentiate hyperkalaemia during acute illness
***Dialysis* Patients:** ▪ Low K^+ diet (guided by specialist dietician) ▪ Regular blood monitoring ▪ Maintain good dialysis access, optimise adequacy, and minimise re-circulation ▪ Avoid prolonged fasting – give 5% Glucose infusion ▪ K^+-binders – potential role to bridge if dialysis delayed (e.g. access problems)

Table 33: Primary prevention of hyperkalaemia in non-dialysis and dialysis patients.

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.[5] 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^+ level.[5] Patient education and community monitoring should be in place before hospital discharge.

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Secondary Prevention *These are steps taken to avoid recurrence of hyperkalaemia after an episode.*
Non-dialysis Patients: ▪ As above + ▪ Consider K^+-binder (SZC or Patiromer) if patient meets NICE criteria (K^+ 6.0 mmol/l, heart failure or CKD 3-5/non-dialysis, on RAASi) ▪ Consider diuretic in patients with heart failure or CKD, particularly if volume overloaded ▪ Sick day rules – ensure patient aware of guidance
***Dialysis* Patients:** ▪ As above + ▪ Increase frequency of blood monitoring (vigilance if high likelihood of recurrence) ▪ K^+-binders – potential role for chronic hyperkalaemia if other strategies fail

Table 34: Secondary prevention of hyperkalaemia in non-dialysis and dialysis patients.

Re-instating RAASi or other medication following an acute illness associated with hyperkalaemia is another important consideration. This decision requires balancing the risk-benefit ratio and considering the original indication of the drug (e.g. heart failure).[6] Wetmore et al found that within 1 year of initiating a RAASi, approximately 33% of patients experienced interruption or cessation of treatment.[7] The risk of RAASi interruption and cessation increased as CKD stage progressed.[7, 8] Trevisan et al found that stopping MRA after an episode of hyperkalaemia was associated with reduced risk of recurrence, but there was a higher risk of death and cardiovascular events.[9]

It is reasonable to consider re-introduction and re-titration of an essential drug, in patients who previously had stable renal function and K^+ levels prior to the acute illness.[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.

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II Hyperkalaemia in Resuscitation (Guidelines 22.1)

Guideline 22.1 – 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. (1B)

Rationale

Treatment algorithms are widely used in clinical practice and are particularly useful in the context of medical emergencies. This Algorithm has been designed to be used at the bedside to assist medical and nursing staff with management and monitoring. A structured approach may also help to avoid delays in initiation of treatment and reduce variability in clinical practice.

The UKKA hyperkalaemia algorithm has been updated to include several key changes:

- Amended rate of administration of 10% Calcium Gluconate (30ml over 10 minutes IV) which is in line with the original UKKA Hyperkalaemia guideline (2014), recent MHRA guidance and updated product information.
- Emphasis of the 2-step approach for administration of Insulin-glucose to ensure that patients at high risk of hypoglycaemia (pre-treatment blood glucose < 7mmol/l) receive a continuous infusion of 10% glucose (50ml/hr for 5 hours) following the Insulin-glucose infusion to prevent hypoglycaemia.

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- Amended scope for the use of the novel oral potassium binders (Sodium Zirconium Cyclosilicate and Patiromer) to include patients with moderate hyperkalaemia pending further evidence in the acute setting.
- Removal of Calcium Resonium in the treatment protocol for acute hyperkalaemia.
- Amended blood glucose monitoring schedule which has been reduced from 12 hours to 6 hours (30, 60, 90, 120, 180, 240, 300, 360 minutes) post Insulin-Glucose treatment. This change has been based on current evidence and may improve adherence to glucose monitoring.

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SECTION III

MANAGEMENT OF HYPERKALAEMIA

IN

RESUSCITATION

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III: Hyperkalaemia in Resuscitation (Guidelines 23 – 27)

Introduction

Hyperkalaemia is an uncommon, but potentially reversible cause of cardiac arrest.[1, 2] It most often occurs in patients with pre-existing renal disease or in the context of an AKI. Patients with ESRD 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 (OHCA), occurring 20 times more frequently than in the general population.[3] Hsiesh et al (2022) reported that patients with ESRD had a higher risk of OHCA (adjusted-HR = 2.11, p<0.001) but had a higher odds of attaining ROSC (adjusted-OR -= 2.47, p<0.001) and better 30-day hospital survival than non-ESRD patients.[4] Therefore, futility should not be assumed in patients with ESRD.

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%).[5] In contrast, Wang et al[6] reported an incidence of 12% (n=1114) and Saarinen et al[7] 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^2 compared with the general population without CKD. [8] Cardiovascular disease is highly prevalent in the dialysis population and the added insult of hyperkalaemia may contribute to sudden death, presumably from cardiac arrest.

Pre-dialysis hyperkalaemia and hypokalaemia have both been shown to be associated with higher all-cause mortality.[9] 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.[10] 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

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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.[11] In this study, hyperkalaemia ($K^+ \geq 6.0$ 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 long-term HD patients with a pre-dialysis serum K^+ of 4.6 – 5.3 mmol/l.[9] 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.[12]

This section of the guideline will cover:
1) special considerations in the resuscitation of patients receiving haemodialysis including aetiology, out-patient dialysis setting, dialysis access, and defibrillation practice,
2) medical management of hyperkalaemic cardiac arrest, and
3) approach to treatment of refractory hyperkalaemic cardiac arrest including dialysis initiation during CPR and the use of ECMO.

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III Hyperkalaemia in Resuscitation (Guideline 23.1)

Guideline 23.1 – 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 23.1)

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. There may be a window of opportunity to intervene before cardiac arrest, although, An et al reported that approximately 20% of patients presented with cardiac arrest at the time of diagnosis of hyperkalaemia.[1] This window is more clearly demonstrated by Durfey et al who found that there was a short time interval (median = 47 minutes) between performing an ECG and onset of an adverse event (symptomatic bradycardia, ventricular tachycardia, cardiac arrest and death).[2] All of these events occurred prior to the administration of IV calcium.

There is a perception that longterm HD patients have a degree of tolerance to hyperkalaemia. Some studies have reported that ECG abnormalities and adverse events typically occur at a higher serum K^+ level in HD patients compared with patients with preserved renal function.[3, 4] In contrast, Durfey et al showed no significant difference between frequency of ECG abnormalities and adverse events in HD compared with non-HD patients.[2]

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Early identification of patients at risk and prompt initiation of K^+-lowering treatment in patients with severe hyperkalaemia reduces the risk of cardiac arrest. Wang et al (2016) conducted the largest study (n=109) of hyperkalaemic IHCA.[5] Chronic dialysis patients (n=25) represented 22.9% of the group. Surprisingly, 20% (5/25) of dialysis patients who suffered a hyperkalaemic cardiac arrest did not receive either intravenous calcium or sodium bicarbonate. 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.

NHS England issued a National Patient Safety Alert (2018) highlighting 35 cases of cardiac arrest in patients with hyperkalaemia which were reported due to concerns related to treatment and/ or monitoring.[6] The MHRA have also recently issued a National Patient Safety Alert (2023) following 6 incidents in which an incorrect dosing of calcium gluconate and inadequate monitoring of patients with severe hyperkalaemia resulted in cardiac arrest.[7] This emphases the importance of early recognition and treatment of hyperkalaemia.

The probability of cardiac arrest is likely to correlate with the severity of hyperkalaemia, but the threshold for arrhythmias in hyperkalaemia appears to vary from patient to patient. For these reasons, arrhythmias should be anticipated and may be avoided with prompt treatment.

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III Hyperkalaemia in Resuscitation (Guidelines 24.1 – 24.2)

Guideline 24.1 – Hyperkalaemia; Cardiac Arrest – Resuscitation strategy in haemodialysis patients

We recommend that standard ALS practice in cardiac arrest be applied to patients requiring dialysis. (1A)

Guideline 24.2 – 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)

Rationale (Guidelines 24.1 – 24.2)

The risk of sudden cardiac death (SCD) is higher in patients receiving dialysis compared with the general population, non-dialysis CKD 5 patients, and even patients with heart failure.[1] Data from the USRDS database showed that compared with peritoneal dialysis, the rate of SCD is approximately 50% higher in HD patients 3 months after dialysis initiation.[2] The initial approach to resuscitation in dialysis patients is similar to non-dialysis patients, but there are some important considerations during CPR. It is also important to consider the incidence, potential aetiology of cardiac arrest, location and outcome in dialysis patients compared with the general population.

In-hospital cardiac arrest (IHCA)

Annual data from the UK National Cardiac Arrest Audit (NCAA) between 2011-2021 found the incidence of IHCA ranged between 1 and 1.6/ 1000 hospital admissions.[3, 4] In comparison, the incidence of IHCA in the USA is 9.7/ 1000 hospital admissions.[5] Survival at 30-days has been found to be higher after IHCA at 24% compared with OHCA at 17%.[6]

Little data is available on the incidence of IHCA in patients on long-term HD, but survival does not appear to be consistently poor. Moss et al (1992) assessed the outcome of in-

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hospital CPR in patients with ESRD showed a survival to hospital discharge of only 8%.[7] In contrast, Wong et al (2015) reported a rate of 1.4 events per 1000 in-hospital days with a survival to hospital discharge of 22%.[8] Similarly, Saeed et al (2015) reported a 26% survival to hospital discharge after IHCA in longterm dialysis patients.[9]

Starks et al (2020) investigated the outcome of IHCA in longterm HD patients using the Get With The Guidelines-Resuscitation registry.[10] Although longterm HD patients were less likely to have a shockable rhythm and less likely to have defibrillation within 2 minutes, they had similar adjusted odds of survival to discharge, better acute survival and were more likely to have a favourable neurological status compared with non-dialysis patients.

Allencherril et al (2022) conducted a systematic review and meta-analysis to assess the aetiology of IHCA and found that electrolyte disturbances was responsible for 3.01% of events.[11] Interestingly, other causes with a similar frequency included cardiac tamponade (3.0%) and pulmonary embolism (2.66%). Therefore, the true incidence of electrolyte disorders may have been under-estimated. Similarly, Penketh et al (2022) found that electrolyte disturbances accounted for 2% of IHCA and a similar rate for cardiac tamponade (2%) and pulmonary embolism (2%).[12] Arrhythmias accounted for 12-14.95% of events in these studies, but there may have been some overlap with the cohorts with electrolyte disorders.[11, 12]

Intra-dialysis sudden cardiac arrest

The European Dialysis Working Group of ERA-EDTA has reviewed the causes of 'extra-dialysis' sudden cardiac death (SCD) and 'intra-dialysis' sudden cardiac arrest (SCA) in patients with ESRD and potential strategies to reduce the incidence of these events.[13] The reported incidence is difficult to quantify as many studies have combined these events despite differences in the clinical circumstance.

Intra-dialysis SCA is defined as events occurring during a dialysis session, or in the period immediately before or after a session. Most publications have only considered events in an out-patient dialysis setting and have not included SCA occurring during dialysis for in-patients. The incidence of cardiac arrest in the out-patient dialysis setting ranges from 3.4 – 7.8 / 100,000 HD sessions as shown in Table 35.

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Study	Number of HD sessions	Number of cardiac arrests	Incidence of CPR /100,000 dialysis sessions	Survival to Hospital Discharge
Karnik 2001 [14]	5, 744,708	400	7	NA
La France 2006 [15]	307,553	24	7.8	75%
Davis 2008 [16]	2, 611,119	110	3.4	24%
Pun 2011 [17]	17,564,181	784	4.5	NA

Table 35: 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 36. Karnik et al reported that the mean time into dialysis at cardiac arrest was 123 ± 77 minutes.[14] 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. The incidence of SCA is highest after the longest inter-dialytic gap. Obremska et al (2021) reported that 42% of SCA occurred in dialysis patients on Mondays and Tuesdays compared with 29% in non-dialysis patients.[18] This trend was also noted in an earlier report.[19]

Study	N=	Before HD	During HD	After HD
Karnik 2001 [14]	400	7%	81%	12%
La France 2006 [15]	38	8%	78%	14%
Davis 2008 [16]	152	10%	70%	20%

Table 36: Timing of cardiac arrest during dialysis in out-patient centres.

HD – haemodialysis

Effect of rhythm on outcome

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/VT

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in 42%, VT in 20% and asystole in 15%.[14] 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).[15]

		PEA/Asystole			VF/VT		
Study	**N=**	**Events %**	**ROSC Achieved (%)**	**Survival to D/C (%)**	**Events %**	**ROSC Achieved (%)**	**Survival to D/C (%)**
Davis 2008 [16] HD patients Out-pt HD unit	152	35	37	11	65	51	31
La France 2006 [15] HD patients Out-pt HD unit	24	*50	NA	NA	*50	NA	NA
Meaney 2010 [20] US gen pop IHCA	51,919	76	42	11	24	64	37
Nolan 2014 [3] UK gen pop IHCA	23,554	72	26	11	17	76	49
Thompson 2018 [21] US gen pop	45,567	80	NA	12	20	NA	34

Table 37: Outcome of cardiac arrest in patients receiving haemodialysis (HD) in an outpatient dialysis facility versus all in-hospital cardiac arrests.

PEA – pulseless electrical activity; VF – ventricular fibrillation; VT – ventricular tachycardia; ROSC – return of spontaneous circulation; IHCA – In hospital cardiac arrest
NA – not available; D/C – discharge; Out-pt – out-patient; gen pop – general population
* Data available for primary cardiac arrest rhythm in only 12/24 patients

Shockable 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 37. 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.[3, 20] 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.[22]

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

Survival after cardiac arrest is better with shockable rhythms.

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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 38. 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.[23] The ERC Guidelines (2021) recommends disconnection from dialysis equipment prior to defibrillation, unless defibrillator-proof, in keeping with the International Electrotechnical Committee (IEC) standards 60601-2-4.[24] Most haemodialysis equipment is not defibrillator-proof.

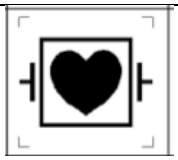
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Special considerations during resuscitation of haemodialysis patients

Reversible causes – 4 Hs & 4 Ts – electrolyte disorder (hyperkalaemia, hypokalaemia, calcium disorder), pulmonary oedema

Dialysis access – arteriovenous fistulas and dialysis lines can be used in life-threatening emergencies.

Defibrillation practice – disconnect prior to defibrillation unless dialysis machine is 'defibrillator proof' (check for these symbols on machine)

	IEC 60417-5841	DEFIBRILLATION-PROOF TYPE B APPLIED PART
	IEC 60417-5334	DEFIBRILLATION-PROOF TYPE BF APPLIED PART
	IEC 60417-5336	DEFIBRILLATION-PROOF TYPE CF APPLIED PART

Post-resus care – repeat serum K^+, blood glucose and ECG; preserve dialysis access; move to an area with dialysis facilities (ICU or Renal HDU); consider timing and need for dialysis after ROSC

29

Table 38: Special considerations during resuscitation in haemodialysis patients.

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) mandated that all dialysis facilities should have on-site capability of defibrillation and the use of AEDs is the simplest and most cost effective device.[25] 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.

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%.[26] 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 within a dialysis centre is a witnessed event.

CPR should be initiated by nursing staff.

First responders require regular training in use of an AED.

Ensure safety: Disconnect patient from haemodialysis machine prior to defibrillation (most machines are not 'defib-proof').

Within out-patient dialysis centres, cardiac arrest occurs most often during dialysis thereby are witnessed events. Shockable rhythms are 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.

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III Hyperkalaemia in Resuscitation (Guidelines 25.1 – 25.4)

Guideline 25.1 – 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. (1C)

Audit measures:

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

Rationale (Guidelines 25.1)

There is a sparsity of evidence for the use of specific medical interventions in hyperkalaemic cardiac arrest, therefore the approach is largely an extrapolation from management in the non-arrested patient.

Calcium has been used in cardiac arrest dating back to the 1950's.[1] The routine use of calcium in cardiac arrest was recommended by the American Heart Association in 1970,[2] but following the publication of studies showing no benefit and potential harm,[3-5] further guidelines were amended removing empirical use. Although the use of IV calcium for IHCA appeared to reduce in the 1980's to 1990's,[6] a more recent report found that the odds of patients with IHCA receiving IV calcium doubled from 2001 to 2016 with almost 30% of patients received this medication.[7]

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.[1] 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.

Current international resuscitation guidelines recommend IV calcium administration for cardiac arrest where hyperkalaemia, hypocalcaemia, hypermagnesaemia or calcium

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channel-blocker intoxication is proven or strongly suspected.[8, 9] In the absence of these specific indications, IV calcium is not recommended in cardiac arrest as it can have deleterious effects due to cellular calcium overload and cardiac hypercontraction.[10, 11]

The Calcium for Out-of-Hospital Cardiac Arrest (COCA) trial was a RCT (n=397) designed to investigate the effect of calcium vs saline on ROSC and found that calcium (IV or intraosseous) did not significantly improve ROSC and this study was stopped early due to safety concerns.[12] A further study assessing the sub-group with PEA (n=104) in the COCA trial showed that a lower rate of ROSC was achieved in the calcium vs placebo group (20% vs 39%).[13] Analysis of first available K^+ level showed that no patients had severe hyperkalaemia.

The evidence for the use of IV calcium in hyperkalaemic cardiac arrest is not extensive. Wang et al (2016) reported the outcome of IV calcium in hyperkalaemic IHCA.[14] 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%). Interestingly, ROSC was achieved in 75% patients when neither drug was administered, although the majority of these patients were in the lowest severity sub-group.

A systematic review (2022) of calcium use during cardiac arrest concluded that there was no benefit and potential harm to the administration of calcium in cardiac arrest.[15] However, one study (Wang et al) which included only patients with hyperkalaemic cardiac arrest [14] was excluded from the quantitative analysis as this group have a formal indication for IV calcium during cardiac arrest.

A recent retrospective study (2023) was conducted over 9 years (n=781) to assess the efficacy of IV calcium for cardiac arrest in the Emergency Department.[16] Despite national guidelines, 39.4% of patients received IV calcium in this study. IV calcium was found to be associated with a significant decrease in patient survival to hospital admission, but no data to assess for the direct clinical indication for calcium administration (e.g. hyperkalaemia, hypocalcaemia) was available.

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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 or during prolonged resuscitation attempts.

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Guideline 25.2.1 – Cardiac Arrest: Treatment – Insulin-glucose

We recommend that 10 units soluble insulin and 25g glucose is administered if hyperkalaemia is known or suspected to be the cause of cardiac arrest. (1B)

Guideline 25.2.2 – Cardiac Arrest: Treatment – Insulin-glucose

We suggest 10% glucose infusion be initiated if the blood glucose is < 7.0 mmol/l at the time of cardiac arrest. (2C)

Rationale (Guidelines 25.2.1 – Guideline 25.2.2)

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 [1, 2] with a peak reduction in serum K^+ ranging from 0.65 – 1.0 mmol/l by 60 minutes.[1-5]

Although several studies have shown equivalent efficacy with conventional (10 units) vs low dose (5 units) insulin, Garcia et al (2018) have found a trend towards greater efficacy with 10 units compared with 5 units insulin in patients with a serum K^+ > 6.0 mmol/l.[6] Moussavi et al (2020) also demonstrated significantly greater K^+-lowering with 10 units insulin compared with low-dose insulin.[7] Two further studies reported in 2022 have also found that conventional dose insulin has greater efficacy than low dose Insulin.[8, 9] These observations are important in patients with life-threatening hyperkalaemia. The main adverse effect is hypoglycaemia, therefore blood glucose monitoring is essential.

International resuscitation guidelines recommend the use of insulin-glucose for hyperkalaemic cardiac arrest based on treatment in the non-arrested patient.[10, 11] The efficacy of insulin-glucose is augmented with the use of salbutamol and novel potassium binders 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. For consistency, the treatment protocol in hyperkalaemic cardiac arrest is the same as in the non-arrested patient.

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.[12, 13] Subsequent ERC guidelines (2010, 2015, 2021) altered the dose of glucose to 25g based on the available

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evidence and the Cochrane review on the emergency interventions for hyperkalaemia published in 2005.[11, 14-16]

Given the sparsity of evidence for medical treatments in hyperkalaemic cardiac arrest, it is interesting to consider an analogous circumstance. 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.[17] Therefore, hyperkalaemia frequently occurs after cardioplegia.[17, 18] 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 (dose unspecified) if the serum K^+ exceeds 6.5 – 7.0 mmol/l.[17]

The optimal dose of insulin and glucose during cardioplegia is unclear. Morgan et al suggested 30-50g per 10 units of insulin.[19] 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.[20] Kocoglu et al suggested 2g of glucose for 1 unit of insulin, but hypoglycaemia was common and required treatment with 10% glucose.[18] This data demonstrates that 25g glucose was insufficient to prevent hypoglycaemia when administered with 10 units insulin [10, 15, 16] and in one study 10% glucose infusion was required.[18]

The UKKA Hyperkalaemia guideline recommends 10 units insulin with 25g glucose for treating acute hyperkalaemia (Guideline 16.3.1). An infusion of 10% glucose (50ml/hr for 5 hours) is suggested if the pre-treatment blood glucose < 7.0 mmol/l to avoid iatrogenic hypoglycaemia (Guideline 16.3.3). Although it is important to prevent hypoglycaemia in cardiac arrest, there is some evidence that the administration of glucose during resuscitation results in lower rates of survival and worse neurological outcome.[21] In this observational study, it was not possible to determine the reason, timing or dosage for glucose administration and the effect was more prominent in patients without diabetes mellitus.

Hyperkalaemic cardiac arrest usually requires prolonged resuscitation and often occurs in patients with other risk factors for iatrogenic hypoglycaemia including renal failure. The first available blood glucose post arrest and subsequent monitoring, should guide the need for initiation and rate of a 10% glucose infusion during the resuscitation attempt. In practical terms, a blood glucose range of 6 – 10 mmol/l is accepted for critically ill patients.[22]

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Guideline 25.3 – 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)

Audit measure:

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

Rationale (Guidelines 25.3)

The use of sodium bicarbonate in cardiac arrest has evolved since it was first introduced into resuscitation practice in the 1970s. 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 SB in cardiac arrest are an increase in intracellular acidosis, reduced cardiac output and worsening tissue acidosis.[1]

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 SB 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.[2]

The last formal evidence review by the American Heart Association on the management of electrolyte abnormalites in cardiac arrest was conducted in 2010 and recommended restricted use of sodium bicarbonate in special circumstances (i.e. hyperkalaemia and tricyclic antidepressant overdose).[3] Despite this, the use of sodium bicarbonate has remained common in Emergency Departments. Chan et al (2020) reported that SB was the third most common during used in OHCA.[4]

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Several studies have shown no benefit to SB in resuscitation. Weng et al (2013) showed no benefit of SB during prolonged CPR.[5] Velissaris et al (2016) conducted a comprehensive review of the literature and found that there was little evidence to support the routine use of SB during CPR.[1] Wu et al (2020) conducted a meta-analysis to assess the effectiveness of SB and found no benefit for ROSC or patient survival.[6] Wang et al (2021) performed a retrospective study to assess the therapeutic effect of SB in IHCA.[7] SB use was associated with better neurological recover in patients with CPR duration ≥ 20 min. Non-SB use was associated with better survival in patients with blood pH > 7.18.

In contrast, other studies have shown improved outcome with the use of SB during resuscitation.[8-11] Most recently, Niederberger et al (2023) also found that pre-hospital administration of SB was associated with improved survival in asystolic and PEA OHCA.[12] The authors suggest that the benefit seen in patients with non-shockable rhythms may reflect the acid-base status and longer duration of arrest, but several limitations were noted in this study.[13]

Although there is little evidence that sodium bicarbonate lowers serum K^+, the rationale for its use in hyperkalaemic 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%).[14] 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. Chronic dialysis patients (n=25) represented 22.9% of the study group. Of note, 20% (5/25) of dialysis patients who suffered a hyperkalaemic cardiac arrest did not receive either intravenous calcium or sodium bicarbonate.

Benz et al (2020) performed a retrospective study of IHCA (n=181), which included patients with ESRD (24.8%).[15] Overall, SB was associated with a lower rate of ROSC (OR = 0.39). In this ESRD sub-group, 71% received SB and no medications were significantly associated with a change in ROSC or survival.

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The treatment of hyperkalaemic cardiac arrest is multi-modal and International resuscitation guidelines recommend the use of SB for limited indications (i.e. hyperkalaemia and tricyclic overdose with or without cardiac arrest).[16, 17]

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Guideline 25.4 – Hyperkalaemia; Cardiac Arrest – Initiation of dialysis during CPR

We suggest that renal replacement therapy with ongoing CPR may be considered for hyperkalaemic cardiac arrest, if hyperkalaemia is resistant to medical therapy and appropriate staff and facilities are available. (2C)

Audit measure:

1. The number and outcome of patients with refractory hyperkalaemic cardiac arrest treated with dialysis initiation during CPR.

Rationale (Guidelines 25.4)

The outcome of hyperkalaemic cardiac arrest is poor, therefore urgent action is required to prevent it from occurring. Prompt medical treatment and initiation of dialysis in patients with severe hyperkalaemia are crucial steps in avoiding cardiac arrest. If cardiac arrest occurs, survival is dependent on urgent control of the serum K^+ level. Intravenous calcium does not lower 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: 32/72 (44%) patients with a serum K^+ 6.5 – 7.9 mmol/l, 7/30 (23%) patients with a serum K^+ 7.9 – 9.4 mmol/l and in 1/7 (14%) patients with a serum K^+ > 9.4 mmol/l. 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 several case reports of successful resuscitation following hyperkalaemic cardiac arrest in adults and children as shown in Table 39.[2-15] Survival with good neurological outcome 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 recent years, extra-corporeal

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membrane oxygenation (ECMO) support has been used to augment systemic perfusion. [6, 11-14]

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 [16-18] and in cardiac arrest.[19, 20] 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.[19] This patient made a full neurological recovery, returned to work within 6 weeks and has become a parent.

It is important to acknowledge that this evidence is limited, but large scale studies to demonstrate efficacy of dialysis during CPR is not feasible. Despite advances in resuscitation practice in recent years, ROSC remains unlikely if hyperkalaemia is not controlled. Although these reports likely reflect publication bias illustrating good outcomes, they do show that dialysis with and without ECMO may be technically feasible in cardiac arrest. These reports also illustrate the evolution of the use of dialysis during CPR with ECMO providing a method to enhance resuscitation alongside conventional dialysis in recent years.

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 39 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 in patients who received a haemodialysis modality was 6.0 mmol/l (range 4.2-7.6 mmol/l). Therefore, the mean reduction in K^+ level required to achieve ROSC was 3.2 mmol/l and this would be difficult to achieve with drugs alone.

The term 'extreme hyperkalaemia' has been used in the literature.[21-23] It has been defined as a serum $K^+ \geq 9.0$ mmol/l.[24] Wang et al reported no survivors in patients with a serum $K^+ > 9.4$ mmol/l treated without dialysis during CPR.[1] In contrast, in the series of patients treated with dialysis during CPR (Table 39), 10/16 (62%) had a serum $K^+ \geq 9.0$ mmol/l and 9/10 (90%) survived with full neurological recovery. Although this evidence is limited and subject to publication bias, it would suggest that dialysis during CPR can potentially improve the outcome for patients with extreme hyperkalaemia.

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Study	Age (yrs)	Arrest Rhythm	[K] at arrest (mmol/L)	CPR pre-RRT (min)	Dialysis modality	Dialysis duration (min)	[K] at ROSC (mmol/L)	Outcome
Gomez-Arnau 1981 [2]	36	Asystole	**9.7**	70	HD	75	**6.6**	Full recovery
Torrecilla 1989 [3]	53	Asystole	**10.2**	15	HD	90	**6.5**	Full recovery
Lin 1994 [4]	27	VT	**9.6**	55	HD	25	**7.6**	Full recovery
	58	VF	**8.5**	35	HD	30	**7.2**	Full recovery
	77	VT	**8.5**	155	HD	25	**5.2**	Died
Costa 1994 [5]	57	Asystole	**9.6**	15	HD	95	**7.2**	Survived (3 days)
Lee 1994 [6]	11	Asystole	**10.2**	140	HF on CPB	ns	**ns**	Full recovery
Jackson 1996 [7]	16	Asystole	**9.8**	165	PD	60	**4.3**	Full recovery
Kao 2000 [8]	68	VT	**8.3**	150	HD	40	**5.1**	Full recovery
Schummer 2000 [9]	68	ns	**9.0**	ns	HDF	15	**ns**	Full recovery
Iwanczuk 2008 [10]	53	ns	**8.5**	ns	HD	40	**5.4**	Full recovery
Chiu 2014 [11]	66	VF	**8.6**	ns	CVVH on VA-ECMO	ns	**ns**	Full recovery
Tijssen 2017 [12]	17	Asystole	**8.3**	ns	CRRT on ECMO	ns	**ns**	Full recovery
Kim 2019 [13]	13	Sine wave	**9.6**	90	HF on VA-ECMO	ns	**ns**	Full recovery
Klingkowski 2019 [14]	5	VF	**9.2**	ns	CVVH and ECMO	25 (ECMO prolonged)	**4.2**	Full recovery
Kose 2021 [15]	39	VF	**9.95**	20	HD	40	**5.2**	Full recovery

Table 39: Outcome of hyperkalaemic cardiac arrest with RRT during CPR.

(ns = not specified)

The ERC Guidelines (2021) suggest considering dialysis initiation for hyperkalaemic cardiac arrest resistant to medical therapy.[25] 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.

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- Secondly, it seems logical to consider the most effective intervention for the most serious complication of hyperkalaemia, particularly when unresponsive to medical therapies.
- 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 for 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. Large scale studies are unlikely to be feasible to demonstrate the efficacy of dialysis during CPR.

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.[26] A summary of the procedure is outlined in Table 40.

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.

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. This intervention is unlikely to be available outwith a Renal Unit or Critical Care area.

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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 HD/CVVH was 74 minutes (range 15-150 minutes). The mean duration of dialysis to achieve ROSC was 45.4 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. Notably, prolonged refractory cardiac arrest is often associated with a poor outcome emphasising a role for ECMO if available.

Use existing dialysis access (i.e. fistula or tunnel dialysis catheter) to initiate dialysis if available. If dialysis access is not available, the most practical approach during cardiac arrest is the insertion of a femoral line using ultrasound guidance.

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. ECMO offers greater opportunities for prolonged cardiac arrest management and can be used simultaneously with dialysis where available.[6, 11-14] Studies reported over the last three decades suggests that chest compression can support adequate blood flow for RRT during CPR. Given that defibrillation is frequently unsuccessful until the serum K^+ is controlled, analogous to rewarming for hypothermic cardiac arrest, defibrillation can be paused until K^+ level is adequately controlled with dialysis. ROSC was achieved at a mean K^+ level of 6.0 mmol/l in available studies.

"*Like most things in life, you may not always succeed, but failure is usually guaranteed if you do not try*." [27]

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Initial Approach

- Follow ALS Algorithm
- Give medical treatment for hyperkalaemia during CPR as per Hyperkalaemic Cardiac Arrest Algorithm
- Refer for Expert Help
- Consider mechanical chest compression device

Preparation for Dialysis Initiation

- If ROSC not achieved within 15 minutes consider initiating dialysis if clinically appropriate.
- Choose RRT modality depending on local availability
- Consider ECMO if available
- Use renal trained nurse (preferably two) to deliver dialysis treatment
- Prepare dialysis machine with a low K^+ dialysate
- Use existing dialysis access (i.e. fistula or line) if available or alternatively insert dialysis line whilst machine is being prepared - use femoral vein with ultrasound guidance; easier site during CPR

Initiation of Dialysis during CPR

- Give fluid bolus (250ml) once connected to dialysis machine and record starting time
- Start with pump speed of 100ml/min and gradually increase aiming for 200ml/min
- Give anticoagulation unless contraindicated (e.g. history of trauma)
- Give further IV Calcium Chloride if resuscitation is prolonged
- Check K^+ level at least every 15 min using arterial blood gas analyser and monitor blood glucose
- Allow time for K^+-lowering on dialysis before attempting further defibrillation

Defibrillation

- Do not perform defibrillation during dialysis unless machine is defibrillation-proof 
- Disconnect patient from dialysis machine just before defibrillation, then immediately reconnect
- If ROSC achieved, resume dialysis until serum $K^+ < 6.5$ mmol/L to maintain ROSC
- If ROSC not achieved, resume dialysis until serum $K^+ < 6.5$ mmol/L and attempt defibrillation again if shockable rhythm

Post-resuscitation care

- Re-assess serum K^+, blood glucose and ECG when ROSC achieved
- Terminate dialysis when serum K^+ controlled ($K^+ < 6.5$ mmol/L) and cardiac rhythm stable
- Record time of termination of dialysis and serum K^+ at ROSC
- Transfer to ICU

Table 40: Summary of procedure for initiation of dialysis during CPR.

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III Hyperkalaemia in Resuscitation (Guidelines 26.1 – 26.2)

Guideline 26.1 – 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 26.2 – 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)

Rationale (Guidelines 26.1 – 26.2)

The outcome of hyperkalaemic cardiac arrest is generally poor, therefore efforts to avoid its occurrence in the first instance is the best approach.

Early recognition, a high index of suspicion in patients at risk and prompt intervention can reduce the risk of cardiac arrest in patients with hyperkalaemia. Initiation of treatment prior to confirmation of hyperkalaemia is warranted if the suspicion of hyperkalaemia is high. Look for toxic ECG changes which may precede cardiac arrest - wide QRS complex, bradycardia or sine wave (Guidelines 14.1-14.2; Figure 3). Limb weakness is an ominous sign. Cardiac monitoring is essential to detect arrhythmias.

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The ECG is a helpful tool in risk stratification. Durfey et al found that adverse events including symptomatic bradycardia (n=22), VT (n=2), CPR (n=2) and death (n=4) occurred prior to administration of IV calcium and all but one event occurred before administration of K^+-lowering medication.[1] This highlights the importance of timely treatment to prevent arrhythmias and cardiac arrest.

Treat severe hyperkalaemia as a medical emergency.

IV calcium is a crucial step in the prevention of arrhythmias and cardiac arrest in hyperkalaemia.[2] Ensure that the appropriate dose is administered (30ml Calcium Gluconate over 10 minutes IV) to stabilise the heart. Adverse events have been noted when an inappropriate dose of IV calcium is administered.[3] Vigilance is also required as toxic ECG changes may recur when the effect of IV calcium has worn off after approximately 30-60 minutes.

Unfortunately, delays in treatment are well recognised and has resulted in patient harm.[4][5] The potential for clinical deterioration may not be appreciated by medical or nursing staff prior to cardiac arrest. Refer early for specialist advice particularly for patients with ESRD and those who do not respond to medical treatment. Blood monitoring is essential to assess efficacy of treatment and for re-bound hyperkalaemia. Rebound may also occur after dialysis and may be exaggerated if temporising drugs have been used.[6]

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.[7, 8]
- 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.

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III Hyperkalaemia in Resuscitation (Guidelines 27.1)

Guideline 27.1 – 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 (Guidelines 27.1)

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 25.1 - 25.3) and the degree of K^+-lowering required to achieve ROSC may not be achievable with drugs alone (Guideline 25.4). The hyperkalaemic cardiac arrest algorithm outlines the modifications to ALS and the specific interventions to address hyperkalaemia as illustrated in Appendix 8.

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Conflict of Interest

The authors have no conflict of interest.

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APPENDICIES

Appendix 1: Efficacy of Insulin-Glucose in treatment of hyperkalaemia.

Appendix 2: Oral potassium lowering drugs.

Appendix 3: Summary of Clinical Trials of oral potassium lowering drugs.

Appendix 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

Appendix 5: ECG in Hyperkalaemia – sine wave.

Appendix 6: Algorithm – Management of Hyperkalaemia in the Community.

Appendix 7: Algorithm – Management of Hyperkalaemia in Hospital.

Appendix 8: Algorithm – Management of Hyperkalaemia in Resuscitation.

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APPENDIX 1: Efficacy of Insulin-Glucose in treatment of Hyperkalaemia.

		Insulin Dose		Glucose Dose (g)		Potassium Level		
						Mean Baseline K^+ (mmol/L)	Serum K^+ Reduction (mmol/L)	
Study	**n=**	**10 Units**	**Other Units**	**25g**	**Other Dose**		**10 Units**	**Other Units**
Lens 1989 [1]	10	10			40	6.7	**1.0**	
Allon 1990 [2]	12	10		25		5.48	**0.65**	
Ljutic 1993 [3]	9	10		25		6.33	**0.76**	
Allon 1996 [4]	8		0.5 U/ kg/min		60	4.28		0.85
Duranay 1996 [5]	20	10			30	6.71	**0.99**	
Kim 1996 [6]	8		0.5 U/ kg/min		40	6.3		0.7
Ngugi 1997 [7]	70	10		25		6.9	**1.14**	
Mahajan 2001 [8]	30		12	25		6.59		0.83
Mushtaq 2006 [9]	15	10		25		6.5	**0.8**	
Chothia 2014 [10]	10	10	0		50	6.01 [10 units] 6.23 [0 units]	**0.83**	0.50
Pierce 2015 [11]	149	10	5	25		6.3	**1.08**	1.1
Wheeler 2016 [12]	132	10	0.1 U/kg		50	6.1	**#NI**	#NI
La Rue 2017 [13]	675	10	5	25 + 25 ± 25		6.4	**1.0**	1.0
Coca 2017 [14]	164	10			50	6.85	**1.18**	
Garcia 2018 [15]	401	10	5	25	0, 12.5, 50	6.15 [10 units] 6.24 [5 units]	**0.90**	0.81
Farina 2018 [16]	240	10		25	50	6.5 [25g] 6.3 [50g]	**1.0 [25g] 1.1 [50g]**	
Boughton 2019 [17]	662	10			20	6.4	**0.6**	
Lim 2021 [18]	410	10		25		6.6	**1.4**	
Humphrey 2022 [19]	1284	10		25		6.4	**0.86**	

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APPENDIX 2: Oral potassium lowering drugs.

Characteristic	Calcium resonium	Patiromer	SZC
Mechanism of action	Entraps K^+ in exchange for Ca^{2+}	Non-specific binding of K^+ in exchange for Ca^{2+}	Selective K^+ binding in exchange for Na^+
Site of action	Distal Colon	Distal colon	Entire intestinal tract
Administration	Oral or rectal	Oral	Oral
Dosing	15-60g/ day	8.4-25.2 g/day	5-15 g/day
Onset of effect	>4 hours	4-7 hours	1 hour
Efficacy	Unpredictable and variable	-0.36 mmol/l at Day 3 [Meaney et al, 2018] −1.01 mmol/l in 4 weeks [OPAL-HK]	-0.17 mmol/l at 1hr [Meaney et al, 2018] - 1.1 mmol/l in 48 hours [ZS-003, ZS-004] Median time to normalisation of serum K^+ is 2.2 hours [ZS-004]
Common adverse effects	Gastrointestinal disorders Hypokalaemia	Gastrointestinal disorders Hypokalaemia Hypomagnesaemia	Gastrointestinal disorders Hypokalaemia Oedema
Serious adverse effects	Colonic necrosis	No episodes of colonic perforation or necrosis reported	No episodes of colonic perforation or necrosis reported
FDA Approval	June 1958	October 2015	May 2018
NICE Appraisal status	N/A	Approved	Approved

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APPENDIX 3: Summary of Clinical Trials using oral potassium lowering drugs.

STUDY	N=	INTERVENTION	CKD (eGFR <60)	DIABETES	HEART FAILURE	RAASi
Lepage 2015 RCT	33	SPS	100%	72%	9%	76%
Nasir 2014 RCT	97	CPS SPS	100%	65%	NA	0% (excluded)
Gruy-Kapral 1998 RCT	6	SPS	HD	NA	NA	NA
Ash 2015 Phase II RCT **ZS-002**	90	SZC	100%	56%	NA	62%
Packman 2015 Phase III RCT **ZS-003**	753	SZC	75%	60%	40%	67%
Kosiborod 2014 Phase III RCT HARMONIZE **ZS-004**	258	SZC	66%	66%	36%	70%
Fishbane 2017 **ZS-005**	751	SZC	73%	62%	38%	64%
Pitt 2011 PEARL-HF (RCT)	104	Patiromer	27%	32%	100%	NA
Bakris 2015 AMETHYST-DN (RCT)	222	Patiromer	87%	100%	35%	71%
Bushinsky 2015 Phase I Trial	25	Patiromer	100%	60%	28%	100%
Weir 2015 OPAL-HK (RCT)	243	Patiromer	100%	57%	42%	100%
Pergola 2017 TOURMALINE (RCT)	112	Patiromer	76%	82%	9%	59%
Pitt 2018 Open-label	63	Patiromer	100%	43%	100%	98%

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

NA – not available

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Appendix 4A: Drug administration and safety - IV CALCIUM PREPARATIONS

Calcium Chloride	
Available as	• Calcium chloride 10% pre-filled syringe 10mL (contains 6.8mmol of calcium in 10mL) [1]
Preparation	• Can be used undiluted
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 5 minutes in peri-arrest setting**. [1,2] • Give as a bolus injection during cardiopulmonary 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	
Available as	• Calcium gluconate 10% ampoules (contains 2.2mmoL of calcium in 10mL) [3,4]
Preparation	• Can be used undiluted.
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	• **Give 30ml 10% Calcium Gluconate IV over 10 minutes**.[2-6] • 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.

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Appendix 4B: Drug administration and safety – INSULIN-GLUCOSE INFUSION

10 units of Soluble Insulin in 50mL Glucose 50% (25g)	
Available as	Vials containing human soluble insulin 100 units per mL (Actrapid®)
	Vials containing 50mL glucose 50% (25g)
Preparation	• Withdraw 10 units of Actrapid® insulin. **This should be done only using an insulin syringe which is graduated in units**. Due to the potential for dosing errors, it is recommended that this is independently checked by another healthcare professional. • Inject the insulin into a 50mL glucose 50% vial and mix well. • Withdraw contents of vial into 50mL intravenous syringe.
Final concentration	10 units soluble insulin in 50mL
Dilution/flush solutions	Sodium chloride 0.9% - flush well to reduce vein irritation
Administration	IV Injection: Administered over 5-15 minutes intravenously into a large vein Monitor for phlebitis if 50% glucose is given peripherally.
Storage and handling	Do not use unless solution is clear and without visible particles.
Specialist technical information	Glucose 50% has a high osmolarity and administration into a peripheral vein may result in vein irritation, vein damage and thrombosis.
Cautions and side effects	• Hypoglycaemia – follow monitoring recommendations in guideline and treat according to local guidelines. • Infusion site reactions including phlebitis, erythema and thrombophlebitis. • Hypersensitivity/ anaphylactic reactions have been reported thought to be due to corn allergy. Should be used with caution, if at all in patients with a known allergy to corn products.

References

1. Electronic Medicines Compendium: Summary of Product Characteristics – Actrapid 100 international units/ml, Solution for Injection in a vial. Novo Nordisk Limited. Available at: https://www.medicines.org.uk/emc/product/3849/smpc#gref. Last updated 11 November 2022.

2. Electronic Medicines Compendium: Summary of Product Characteristics – Glucose 50% w/v Concentrate for solution for infusion. Baxter Healthcare Ltd. Available at https://www.medicines.org.uk/emc/product/1826/smpc. Last updated 28 July 2017.

3. Electronic Medicines Compendium: Summary of Product Characteristics – Glucose intravenous infusion BP 50% w/v. Hameln Pharmaceutical Ltd. Available at https://www.medicines.org.uk/emc/product/6266/smpc. Last updated 26 June 2020.

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Alternative Glucose preparations

20% Glucose	
Available as	100 ml bottle
Volume required for 25g glucose	125 ml (two bottles required)

10% Glucose	
Available as	500 ml bag
Volume required for 25g glucose	250 ml

References

1. Electronic Medicines Compendium: Summary of Product Characteristics – Glucose intravenous infusion BP 20% w/v. Baxter Healthcare Ltd. Available at https://www.medicines.org.uk/emc/product/3189/smpc#gref. Last updated 26 June 2020.
2. Electronic Medicines Compendium: Summary of Product Characteristics – Glucose intravenous infusion BP 10% w/v. Baxter Healthcare Ltd. Available at https://www.medicines.org.uk/emc/product/1823/smpc#gref. Last updated 9 October 2019.

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Appendix 4C: Drug administration and safety - SALBUTAMOL

Salbutamol Nebulised Solution	
Available as	• 2.5mg/2.5mL nebuliser solution • 5mg/2.5mL nebuliser solution
Administration	• 10mg DOSE = 10ml of 2.5mg/2.5mL nebuliser solution. = 5ml of 5mg/2.5mL nebuliser solution. • 20mg DOSE = 10ml of 5mg/2.5mL nebuliser solution. • Use a face mask or T-piece.
Cautions and side effects	• **Cautions:** – Consider only giving 10mg in patients with ischaemic heart disease. – Tachyarrhythmia – Open angle glaucoma • **Side-Effects:** – Tremor – Tachycardia – Headache

References

1. Electronic Medicines Compendium: Summary of Product Characteristics – Ventolin Nebules. GlaxoSmithKline UK. Available at https://www.medicines.org.uk/emc/product/851/smpc#gref. Last updated 24 September 2020.

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Appendix 4D: Drug administration and safety – PATIROMER

▼ Patiromer	
Available as	8.4g, 16.8g and 25.2g sachets
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. • Can be taken with food or without 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.*

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References

1. Electronic Medicines Compendium: Summary of Product Characteristics – Veltassa (Patiromer). Vifor Fresenius Medical Care Renal Pharma UK Ltd. Available at https://www.medicines.org.uk/emc/product/779. Last updated 21 July 2021.

Appendix 4E: Drug administration and safety – SODIUM ZIRCONIUM CYCLOSILICATE

▼ Sodium Zirconium Cyclosilicate	
Available as	5g, 10g sachets (powder oral suspension)
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.*

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References

1. Electronic Medicines Compendium: Summary of Product Characteristics – Lokelma 10g powder for oral suspension. AstraZeneca UK Limited. Available at https://www.medicines.org.uk/emc/product/10074/smpc. Last updated 18 May 2023.

Appendix 4F: Drug administration and safety – CALCIUM RESONIUM

Calcium Resonium	
Available as	Calcium Resonium Powder (99.934%)

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.

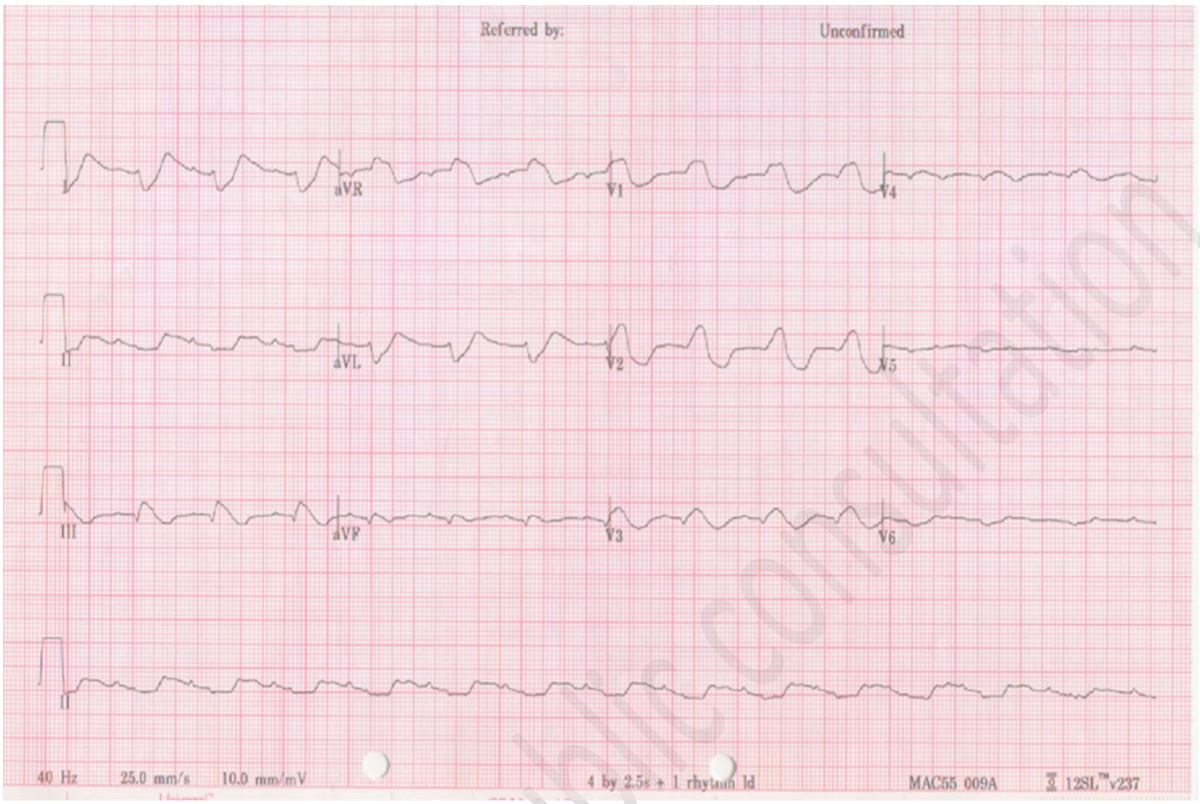
Administration	• For oral administration, administer at least 3 hours before, or 3 hours after other medication. In patients with gastroparesis consider a 6-hour separation. • For rectal administration, the enema should be retained for at least 9 hours then the colon should be irrigated to remove the resin.
Cautions and side effects	• Contra-indicated in hypercalcaemia or in obstructive bowel disease. • Concomitant use with sorbitol is not recommended due to gastro-intestinal stenosis and intestinal ischaemia.

References

1. Electronic Medicines Compendium: Summary of Product Characteristics – Calcium Resonium 99.934% w/w powder for oral/rectal suspension. Sanofi. Available at https://www.medicines.org.uk/emc/product/1439. Last updated 8 August 2022.

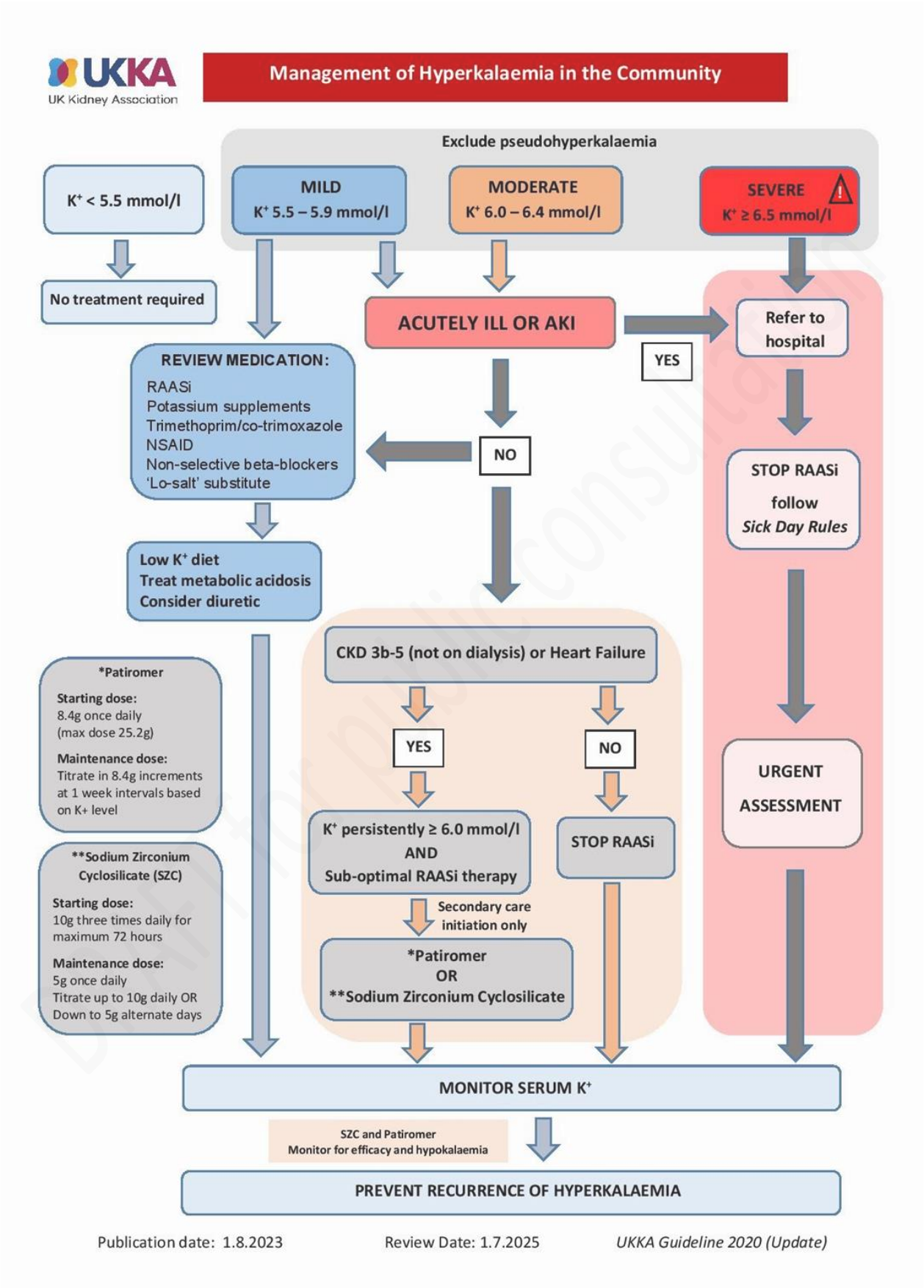
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Appendix 5 – Sine wave ECG

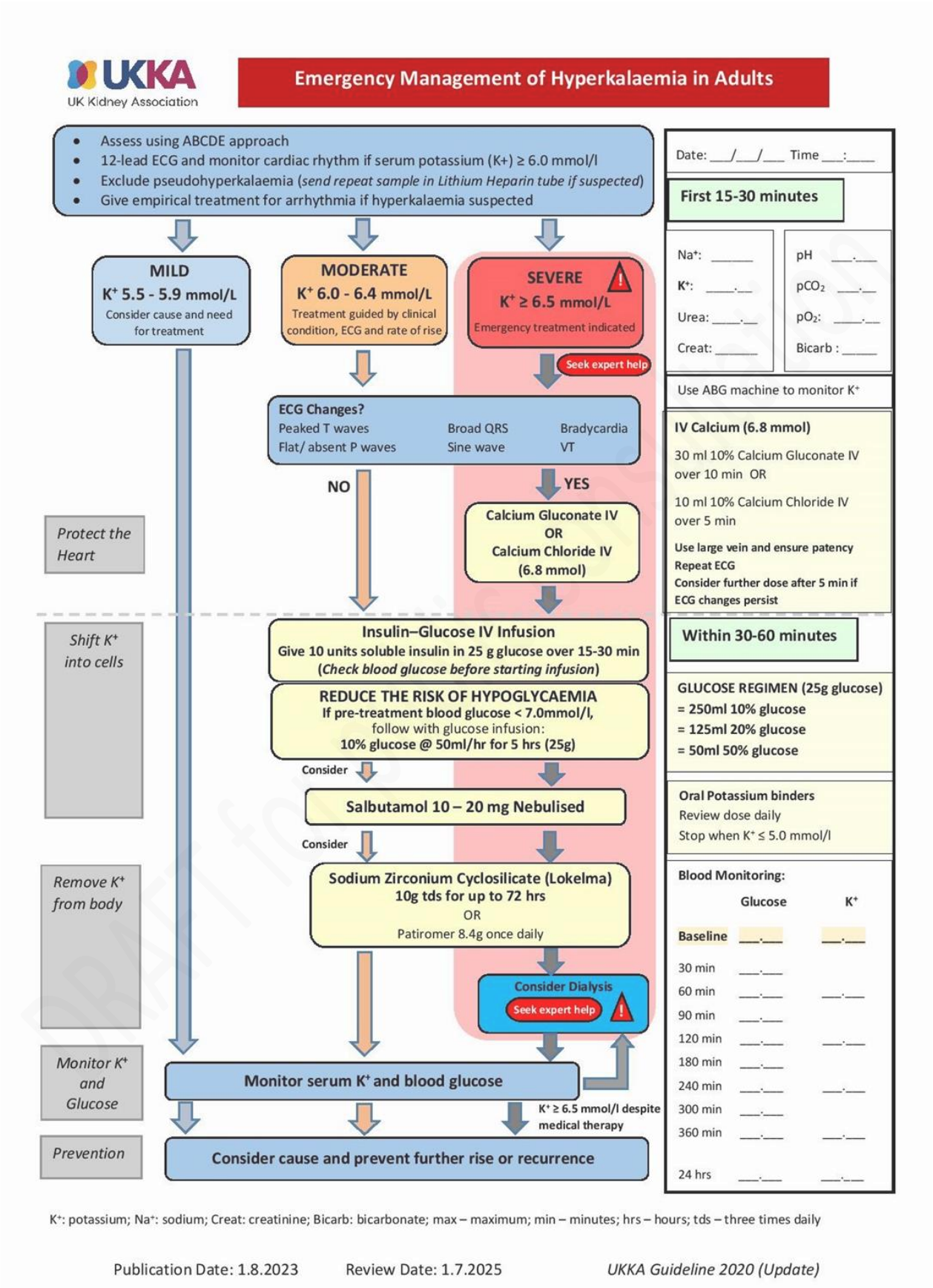


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Appendix 6 – ALGORITHM: Treatment of Hyperkalaemia in the Community



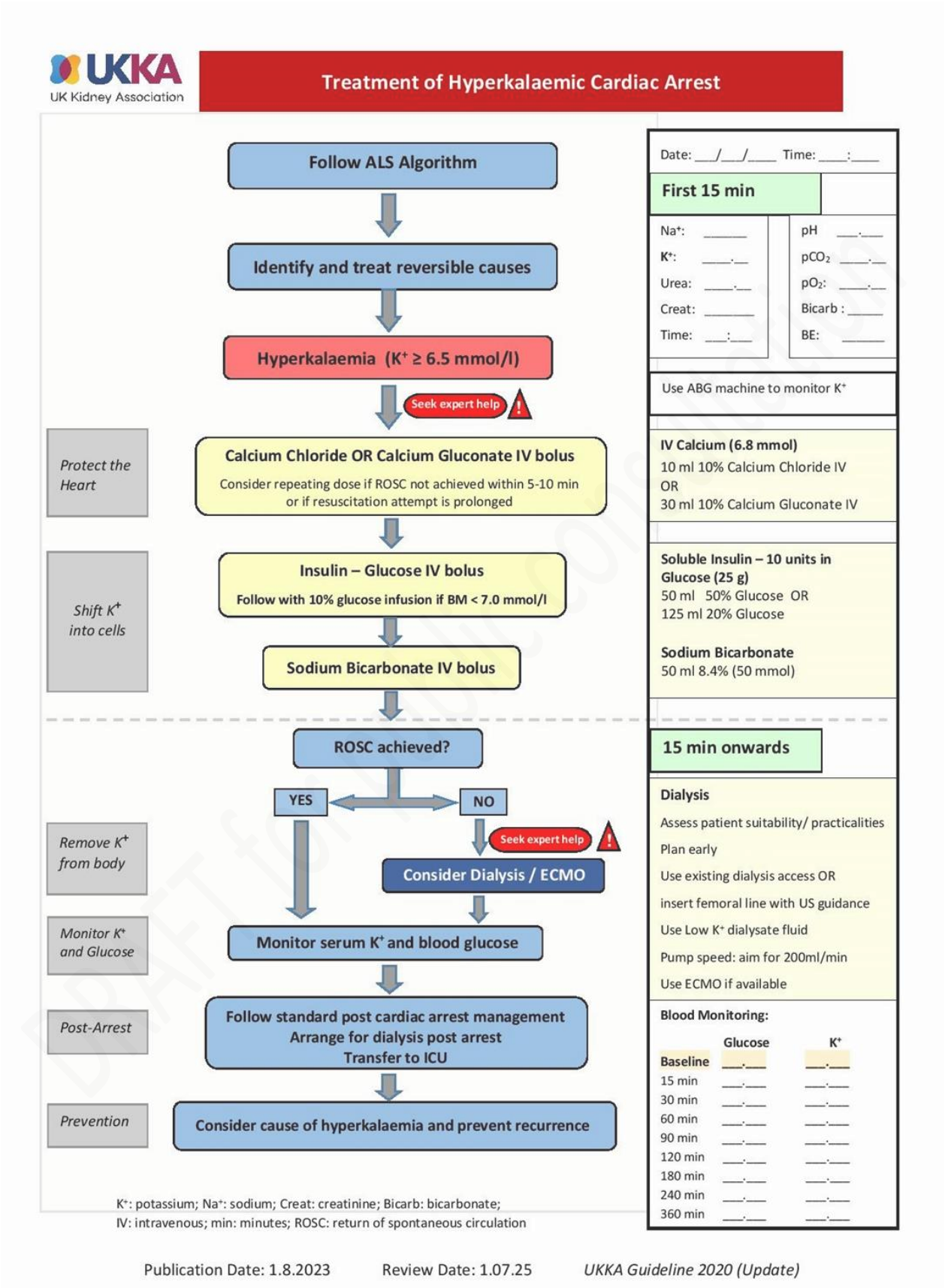
Appendix 7 – ALGORITHM: Treatment of Hyperkalaemia in Hospital



K+: potassium; Na+: sodium; Creat: creatinine; Bicarb: bicarbonate; max – maximum; min – minutes; hrs – hours; tds – three times daily

Publication Date: 1.8.2023 Review Date: 1.7.2025 *UKKA Guideline 2020 (Update)*

Appendix 8 – ALGORITHM: Treatment of Hyperkalaemia in Cardiac Arrest



Publication Date: 1.8.2023 Review Date: 1.07.25 *UKKA Guideline 2020 (Update)*

Abbreviations

AAGBIG	Association of Anaesthetists of Great Britain and Ireland Guideline
ABCDE	Airway – Breathing – Circulation – Disability – Exposure
ACC	American College of Cardiology
ACE-i	Angiotensin converting enzyme inhibitor
AED	Automated External Defibrillator
AHA	American Heart Association
AKI	Acute Kidney Injury
ALS	Advanced Life Support
ARB	Angiotensin II receptor blocker
ARDS	Adult respiratory distress syndrome
AUC	Area under the curve
AV	Arterio-venous
AVPU	Alert – Verbal – Pain - Unresponsive
BGA	Blood gas analyser
BM	Blood glucose
BP	Blood pressure
Ca^{2+}	Calcium ion
CKD	Chronic kidney disease
CPR	Cardiopulmonary resuscitation
CPS	Calcium polystyrene sulphonate
CV	Cardiovascular
CVVH	Continuous veno-venous haemofiltration
CVVHDF	Continuous veno-venous haemodiafiltration
DM	Diabetes Mellitus
DNACPR	Do Not Attempt Cardiopulmonary Resuscitation
DOPPS	Dialysis Outcomes and Practice Patterns Study
ECG	Electrocardiogram
ECMO	Extra-corporeal membrane oxygenation
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ERC	European Resuscitation Council
ESC	European Society of Cardiology
ESRD	End-stage renal disease
FDA	Food and Drug Administration

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1	FICM	Faculty of Intensive Care Medicine
2	GCS	Glasgow coma scale
3	GFR	Glomerular filtration rate
4	HBP	Hypertension
5	HD	Haemodialysis
6	HDF	Haemodiafiltration
7	HDU	High dependency unit
8	HF	Haemofiltration
9	HFrEF	Heart failure with reduced ejection fraction
10	HK	Hyperkalaemia
11	HR	Hazard ratio
12	Hypo	Hypoglycaemia
13	ICS	Intensive Care Society
14	ICU	Intensive Care Unit
15	IEC	International Electrotechnical Committee
16	IHCA	In-hospital cardiac arrest
17	IHD	Intermittent haemodialysis
18	ILCOR	International Liaison Committee on Resuscitation
19	IV	Intravenous
20	K^+	Potassium ion
21	KDOQI	Kidney Disease Outcomes Quality Initiative
22	MET	Medical emergency team
23	Mg^+	Magnesium ion
24	MHRA	Medicines and Healthcare products Regulatory Agency
25	MRA	Mineralocorticoid receptor antagonist
26	Na^+	Sodium ion
27	NA	Not available
28	NCEPOD	National Confidential Enquiry into Patient Outcome and Death.
29	NEWS	National Early Warning Score
30	NHS	National Health Service
31	NI	Not included
32	NICE	National Institute for Health and Care Excellence
33	NSAIDS	Non-steroidal anti-inflammatory drugs
34	OHCA	Out-of-hospital cardiac arrest
35	OR	Odds ratio
36	PEA	Pulseless electrical activity
37	POCT	Point of care testing

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RAASi	Renin-Angiotensin-Aldosterone-System inhibitor
RCT	Randomised controlled trial
ROSC	Return of spontaneous circulation
RRT	Renal replacement therapy
SB	Sodium bicarbonate
SBAR	Situation – Background – Assessment – Recommendation
SCD	Sudden cardiac death
SMC	Scottish Medicines Consortium
SPS	Sodium polystyrene sulphonate
SZC	Sodium Zirconium Cyclosilicate
UK	United Kingdom
UKKA	United Kingdom Kidney Association
USA	United States of America
USRDS	United States Renal Data System
VF	Ventricular fibrillation
VT	Ventricular tachycardia

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