
Clinical Practice Guidelines

Treatment of Acute Hyperkalaemia in Adults

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Endorsements



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

Method used to arrive at a recommendation

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

Conflicts of Interest Statement

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

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Executive Summary of changes since 2014 Hyperkalaemia Guideline

Format of the Guideline

The 2020 Hyperkalaemia guideline has been divided into 3 sections to allow easy navigation:

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

New therapies for treating hyperkalaemia

Sodium zirconium cyclosilicate (SXC)

SZC is an oral potassium binder approved by NICE in September 2019 for the following indications:

- life-threatening hyperkalaemia ($K^+ \geq 6.5 \text{ mmol/l}$) alongside standard treatment with insulin-glucose and salbutamol.
- confirmed serum $K^+ \geq 6.0 \text{ mmol/l}$ in out-patients with CKD Stage 3b-5 (not on dialysis) or heart failure receiving a sub-optimal dose of RAASi therapy.

Patiromer

Patiromer is an oral potassium binder approved by NICE in February 2020 for the following indications:

- life-threatening hyperkalaemia ($K^+ \geq 6.5 \text{ mmol/l}$) alongside standard treatment with insulin-glucose and salbutamol.
- confirmed serum $K^+ \geq 6.0 \text{ mmol/l}$ in out-patients with CKD Stage 3b-5 (not on dialysis) or heart failure receiving a sub-optimal dose of RAASi therapy or who are not taking RAASi because of hyperkalaemia.

NICE has recommended that therapy with either SZC or Patiromer is started in secondary care and discontinued if RAASi therapy is stopped.

New recommendations for therapies in treating hyperkalaemia

Insulin-glucose infusion

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

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

Preserving efficacy is essential in treating hyperkalaemia. There is some evidence to suggest that conventional dose insulin (10 units) has a greater K⁺-lowering effect than low dose insulin. Analysis of studies using 10 units insulin also show a trend towards greater efficacy with worsening hyperkalaemia. These observations require confirmation before a reduction in insulin dose can be recommended.

The 2020 Hyperkalaemia Guideline for moderate or severe hyperkalaemia recommends:

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

Hyperkalaemic Cardiac Arrest

This is the most serious consequence of hyperkalaemia and yet the most effective treatment, dialysis, is rarely used. The largest study of hyperkalaemic cardiac arrest demonstrated that survival in patients with extreme hyperkalaemia (K > 9.0 mmol/l) treated without dialysis was very poor. Over the past three decades, successful outcomes with all dialysis modalities have been reported during CPR. ECMO enhances neurological outcome. This approach will be guided by the suitability of the patient and availability of clinical expertise and equipment.

The 2020 Hyperkalaemia Guideline suggests that dialysis is considered for refractory hyperkalaemic cardiac arrest and provides a protocol for the initiation of dialysis during resuscitation.

Guideline development

Purpose

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

Scope

The original RA Hyperkalaemia Guideline (2014) focussed predominantly the management of hyperkalaemia in secondary care. The current RA Hyperkalaemia Guideline (2020) provides a comprehensive overview of the detection and treatment of hyperkalaemia in the community and hospital settings.

Review of Evidence

The literature was reviewed using a multiple database search - PubMed (1960-2020), Ovid MEDLINE (1946-2020), EMBASE (1974-2020), Science Direct (1995-2020), The Cochrane Library (1995-2020), Web of Knowledge (2001-2020) for all human studies published in English pertaining to the treatment of hyperkalaemia in adults. Websites searches included National Institute for Health and Care Excellence (NICE), Scottish Medicines Consortium (SMC), Healthcare Improvement Scotland, Medicines and Healthcare products Regulatory Agency (MHRA) and European Medicines Agency (EMA).

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

The 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).

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 2005¹ and maintained to current date.^{2,3} 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 hospital patients ranges from 1.1% and 10%.⁴⁻⁸ The incidence in the community varies dependent on the case mix of the population studied. Studies in the general population report an incidence of hyperkalaemia (K+ >5.5 mmol/l) ranging from 2.3 - 7.2% in patients with an eGFR > 60 ml/min^{9,10} and 2.9 - 40% in patients with an eGFR < 30 ml/min.¹¹⁻¹³

In-hospital mortality is significantly higher in patients with hyperkalaemia (18.1%) compared to those with hypokalaemia (5.0%) or normokalaemia (3.9%).⁸ A U-shaped association between serum potassium and mortality has been shown in patients with ischaemic heart disease,¹⁴ CKD^{11,15,16} and in patients receiving longterm haemodialysis (HD).¹⁷ Patients with severe hyperkalaemia (K+ > 6.5 mmol/l) are most at risk and in one report, the hospital mortality was 30.7%.¹⁸

The treatment of hyperkalaemia is likely to evolve in the coming years with the availability of novel drugs and the development of new strategies to improve 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 Guidelines 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⁺ ≥ 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)

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)

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

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

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

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

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

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

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

We recommend that Patiromer is 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 (S2C) 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 (S2C) is initiated in secondary care only. (1A)

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)

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 16.2 – Hyperkalaemia: STEP 1 - Protect the heart; intravenous calcium salts

We recommend that intravenous calcium chloride or calcium gluconate, at an equivalent dose (6.8mmol), is given to patients with hyperkalaemia in the presence of ECG evidence of hyperkalaemia. (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 ($K+ \geq 6.5 \text{ mmol/l}$). (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 ($K+ 6.0 - 6.4 \text{ mmol/l}$). (2C)

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

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

Guideline 16.4.1 – Hyperkalaemia: STEP 2 – Shift K+ into cells; Salbutamol

We recommend nebulised salbutamol 10-20 mg is used as adjuvant therapy for severe ($K+ \geq 6.5 \text{ mmol/L}$) 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 ($K+ 6.0-6.4 \text{ mmol/L}$) 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 16.6.1 – Hyperkalaemia: STEP 3 – Remove K+ from body; Potassium binders

We recommend that Sodium Zirconium Cyclosilicate is used as an option in the emergency management of acute life-threatening hyperkalaemia (serum $K+ \geq 6.5 \text{ mmol/l}$). (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 life-threatening hyperkalaemia (serum $K+ \geq 6.5 \text{ mmol/l}$). (1C)

Guideline 16.6.3 – Hyperkalaemia: STEP 3 – Remove K+ from body; Cation-exchange resin

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

Guideline 17.1.1 – Hyperkalaemia: STEP 4 - Blood monitoring; serum potassium

We recommend that the serum K+ is monitored closely in all patients with hyperkalaemia to assess efficacy of treatment and to monitor for rebound hyperkalaemia after the initial response to treatment wanes. (1B)

Guideline 17.1.2 – Hyperkalaemia: STEP 4 - Blood monitoring; serum potassium

We suggest that serum K+ is assessed at least 1, 2, 4, 6 and 24 hours after identification and treatment of moderate or severe hyperkalaemia. (2C)

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

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

Guideline 18.1 - Hyperkalaemia: Treatment in haemodialysis patients

We recommend that haemodialysis patients with severe hyperkalaemia (serum K+ ≥ 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+ ≥ 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+ ≥ 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+ ≥ 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)

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)

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

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 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).

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) and sine wave without pause [K+ 8.4 mmol/L] (c) and ventricular tachycardia [K+ 9.1 mmol/L] (d).

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

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.

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 of 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+ ≤ 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 S2C who achieved a serum K+ ≤ 5.0 mmol/l within 48 hours.
8. The proportion of out-patients who achieve maximal dose RAASi therapy whilst taking S2C.
9. Proportion of patients with severe hyperkalaemia (Serum K+ ≥ 6.5 mmol/l) on admission to hospital who had been provided with 'Sick Day Rules' advice.
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+ ≥ 6.5 mmol/L) treated with insulin-glucose infusion.
14. The proportion of patients with acute severe hyperkalaemia (serum K+ ≥ 6.5 mmol/l) treated with Sodium Zirconium Cyclosilicate.
15. The proportion of patients with acute severe hyperkalaemia (serum K+ ≥ 6.5 mmol/l) treated with Patiromer.
16. The proportion of patients in whom serum K+ was measured at least once within 2 hours of treatment for severe hyperkalaemia [Audit Standard: 100%].
17. 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%].
18. The frequency of hypoglycaemia occurring in patients receiving treatment with insulin-glucose for hyperkalaemia.
19. The incidence of patients requiring emergency dialysis for severe hyperkalaemia.
20. The frequency of hyperkalaemia developing beyond 24 hours of hospital admission.
21. The frequency of prescribed drugs potentially contributing to hyperkalaemia.
22. All cardiac arrests should be audited – hospital participation in the National Cardiac Arrest Audit is encouraged as part of quality improvement and benchmarking.
23. The proportion of patients treated with intravenous calcium for hyperkalaemic cardiac arrest.
24. The proportion of patients treated with sodium bicarbonate for hyperkalaemic cardiac arrest.

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

Future Research

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

1. The optimal dose of insulin and glucose to treat acute hyperkalaemia required to minimise iatrogenic hypoglycaemia without compromising efficacy.
2. The efficacy of 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 potassium binders (patiromer and sodium zirconium cyclosilicate) in the treatment of moderate hyperkalaemia without the administration of insulin-glucose in hospitalised patients.
4. The efficacy of sodium bicarbonate in the treatment of severe hyperkalaemia in patients with AKI.

Future Developments

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

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

Section I

Management of Hyperkalaemia in the Community and Out-patient Clinic

Hyperkalaemia in the Community (Guidelines 1.1 – 12.1)

Introduction

Hyperkalaemia is commonly detected in the community and the patient groups most at risk are those with CKD, diabetes mellitus and heart failure. Hyperkalaemia may also occur in the context of an AKI triggered by acute illness, initiation or titration of RAASi medications, or worsening of heart failure.¹ 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.²

The management of patients with heart failure is challenging given the high prevalence of renal impairment and increased risk of hyperkalaemia. In clinical trials of RAASi monotherapy, the incidence of hyperkalaemia ranges from 3 – 7%.³ The overall incidence of hyperkalaemia was generally higher in clinical trials involving aldosterone antagonists.³ Combination therapy of RAASi and aldosterone antagonist increases the risk of hyperkalaemia and hospitalisation.⁴ Mortality in patients with heart failure is significantly increased with worsening severity of hyperkalaemia: serum K+ levels between 4.8 – 5.0 mmol/l (HR 1.34), 5.1 – 5.5 mmol/l (HR 1.60) and 5.6 – 7.4 mmol/l (HR 3.31).⁵

Risk Factor for Hyperkalaemia	Odds Ratio [Turgutalp] [6]	Odds Ratio [Sarafidis] [7]	Odds Ratio [Nakhoul] [8]	Odds Ratio [Horne] [9]
Renal Failure	5.55	2.06 (eGFR < 15)	1.25 (per 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	

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

Several risk factors contribute to community-acquired hyperkalaemia as shown in Table 1. The presence of multiple co-morbidities or other risk factors further increase the risk of hyperkalaemia.⁶⁻⁹ RAASi drugs are frequently implicated in AKI and hyperkalaemia, but there are conflicting reports in the literature.^{10, 11} Given the potential risk of AKI, ‘sick day rules’ guidance recommending the cessation of RAASi drugs during acute illness has been proposed by some groups including NICE, but this remains controversial.^{1, 10, 12, 13, 14}

Study	Country	Setting	N=	eGFR ml/min	Definition of HyperK mmol/l	Prevalence HyperK %	Mortality risk with HK
Liamis 2013 ¹⁵	Netherlands	General population (age > 55)	5179	>60	≥6.0	0.3	#OR 2.08
Chang 2016 ¹⁶	USA	Health care system – HBP (age ≥ 18)	155,695	>60	>5	10.8	NA
					>5.5	2.3	
Hughes-Austin 2017 ¹⁷	USA	Multi-ethnic general population (age ≥65)	9651	>60	≥5.0	2.8	+HR 1.41
Horne 2019 ⁹	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

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.^{6, 9, 15-19} 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.⁹ In this study, the use of RAASi was strongly associated with hyperkalaemia with an odds ratio of 13.6 - 15.9.

Hyperkalaemia is more common in patients with CKD and the incidence increases with declining renal function. 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).⁷ 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 ²⁰	USA	Renal Clinic	820	25.4	≥5.5	7.9	*HR 1.57
Sarafidis 2012 ⁷	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 ⁸	USA	CKD Registry (USA)	36,359	47	5.0 – 5.4	11	#OR 1.12
					>5.5	3.3	#OR 1.65
Turgutalp 2016 ⁶	Turkey	Elderly population (age > 65)	40,092	23-35	≥5.5	2.9	AUC values by age p< 0.001
Luo 2016 ¹⁹	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
					5.0 – 5.4	45.1	*IRR 1.1
Furuland 2018 ¹⁸	UK	Health care database	191,964	50.9	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

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

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

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Patient monitoring (Guidelines 1.1-1.2)

Guideline 1.1 – Monitoring of patients at risk of Hyperkalaemia in the community.

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

Guideline 1.2.1 – Monitoring of patients after an episode of mild hyperkalaemia detected in the community.

We recommend that the serum K⁺ is repeated within 3 days, 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⁺ ≥ 6.5 mmol/l) detected in the community are admitted for immediate assessment and treatment. (1B)

Audit measure

1. Frequency of hospital admission for severe hyperkalaemia (serum K⁺ > 6.5 mmol/l) detected on routine blood test in the community.

Rationale (Guideline 1.1 – 1.2)

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

Several observational studies have reported the frequency of blood monitoring in patients with CKD in relation to detection of hyperkalaemic events. Chang et al 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%).² In patients with an eGFR < 30ml/min who had ≥4 tests per year, hyperkalaemia was found in 30%.

The more often you test, the more often you will detect hyperkalaemia, especially in patients at risk.

Patients with CKD 4-5 have a high risk of hyperkalaemia and warrant regular testing.

Luo et al reported the frequency of blood monitoring stratified by level of renal function and level of serum K+.³ In patients with an eGFR < 30 ml/min, the mean frequency of tests per year was 1.69 ± 1.35 (serum K+ 5.5 – 5.9 mmol/l) and 1.37 ± 0.98 (serum K+ ≥ 6 mmol/l) respectively. In patients with an eGFR 50–59 ml/min, the mean frequency of tests per year was 1.34 ± 0.92 (serum K+ 5.5 – 5.9 mmol/l) and 1.21 ± 0.73 (serum K+ ≥ 6 mmol/l) respectively. Similar to Chang et al, detection of hyperkalaemia increases with frequency of testing. Overall, the frequency of monitoring in these studies was generally 1–2 times per year, with more frequent testing in patients with an eGFR < 30 ml/min.

The interval between hyperkalaemic episodes was reported in a large retrospective cohort of patients with CKD.⁴ This study utilised data from primary care records for approximately 7% of the UK population over a mean follow-up of 4.9 years. Patients experiencing at least one episode of hyperkalaemia was stratified in three groups: serum K+ 5.0 – 5.4 mmol/l (45.2%), 5.5 – 5.9 mmol/l (15.9%) and ≥ 6.0 mmol/l (4.9%). The time interval to a recurrent episode of hyperkalaemia progressively shortened in each severity group. The interval between the first to second episodes in patients with serum K+ 5.5 – 5.9 mmol/l was 0.84 years and reduced to 0.59 years between the second and third episode and 0.48 years between the third and fourth episode. The interval between recurrent episodes was shorter in patients with serum K+ ≥ 6 mmol/l (0.65, 0.41 and 0.30 years respectively).

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

The interval for blood monitoring after a hyperkalaemic event is less well documented. Horne et al 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.⁵ 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.

'Think Kidneys' have provided practical guidance on repeat testing after a hyperkalaemic episode.⁶ The timing is guided by the level of hyperkalaemia and clinical context. In patients with mild hyperkalaemia (K+ 5.5 – 5.9 mmol/l), a repeat test is recommended within 3 days if the result was unexpected or as soon as feasible if the patient is clinically stable. In patients with moderate hyperkalaemia (K+ 6.0 – 6.4 mmol/l), a repeat test is recommended within 1 working day if detected on a routine check in a stable patient, but referral to hospital should be considered if clinically unwell or if an AKI is present. Patients with severe hyperkalaemia (K+ ≥ 6.5 mmol/l) warrant urgent referral to hospital for immediate assessment and

treatment if required. The recommended interval for repeat testing after a hyperkalaemic episode is summarised in Table 4.

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

Table 4: 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

There is increasing use of point of care testing (POCT) in the hospital setting for rapid potassium measurement, but achieving rapid blood analysis in the community can be challenging. POCT has been validated in several studies in the hospital setting within the Emergency Department and Critical Care.⁷⁻¹² POCT has also been shown to improve early recognition of hyperkalaemia in patients with CKD presenting to the Emergency Department.¹³ Use of POCT in the pre-hospital setting is less well reported.^{14,15} A study of the utilisation and validation of POCT devices by community paramedics demonstrated good correlation with laboratory measurement.¹⁴ Technology is rapidly developing with the use of medical biosensors and Smart phone technology potentially making POCT easily accessible for patients.¹⁶

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Management of patients receiving RAASi drugs (Guidelines 2.1-2.7)

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

We recommend that 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.

We recommend that RAASi drugs be withheld during acute intercurrent illness (e.g. sepsis, hypovolaemia and/or AKI) at all severities of hyperkalaemia. (1D)

Guideline 2.7 – Cessation of RAASi drugs in patients with moderate or severe hyperkalaemia.

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

Audit measure

1. Frequency of blood monitoring of 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. However, hyperkalaemia frequently limits use or titration of RAASi drugs. Epstein et al conducted a large study (> 7 million of electronic patient records) to determine the impact of hyperkalaemia on the optimal versus real-world treatment with RAASi.¹ In patients for whom RAASi was recommended by treatment guidelines for cardiorenal disease, >50% were prescribed lower than recommended dose and 14-16% discontinued RAASi therapy.¹

Sub-optimal treatment for patients with heart failure and renal disease also affects patient outcome. Mortality rates have been shown to be higher in patients who receive sub-maximal dosing (8%) and in those who have discontinued RAASi (11%) compared to those who received maximal dosing (4%).² Similarly, Ouwerkerk et al demonstrated increased hospitalisation and increased mortality in patients with heart failure with reduced ejection fraction (HFrEF) who receive less than half of the recommended doses of ACE-I or ARB (HR 1.72) and beta blockers (HR 1.70) compared to patients who reached optimal doses.³ The balance between optimising treatment and compromising renal function poses a significant clinical dilemma. Monitoring of serum K⁺ in patients receiving RAASi drugs reduces the risk of adverse events. Raebel et al demonstrated that patients with diabetes who underwent potassium monitoring during the first year of treatment with RAASi drugs were less likely to experience hyperkalaemia-associated adverse events (hospitalisation, Emergency Department attendance or death) with an adjusted relative risk of 0.50 (0.37, 0.66) compared to those who were not monitored.⁴ The sub-set of patients with CKD had an adjusted relative risk of 0.29 (0.18, 0.46). Park et al conducted an observational study of hospitalised patients newly started on an ARB and demonstrated that the highest incidence of hyperkalaemia occurred on the first day and 52.4% of hyperkalaemic events occurred within the first week of initiation.⁵ In this study, hyperkalaemia also occurred earlier in patients with reduced GFR, higher baseline K⁺ level (patients with K⁺ >5.5 mmol/l were excluded) and in patients with diabetes.

The KDIGO Guideline (2012) recommends measuring serum K⁺ level within 1 week of starting RAASi drugs and after every dose increment in patients with reduced renal function.⁶ The NICE Guideline for CKD (2014) recommends measuring serum K⁺ level before starting, within 1 to 2 weeks of initiation of RAASi therapy and after every dose increment.⁷

Assess urea & electrolytes prior to initiation of RAASi drugs.

Monitor urea & electrolytes at 1 week after initiation and after each dose titration.

The NICE CKD Guideline (2014) also recommends that RAASi drugs should be withdrawn if the serum K⁺ is ≥ 6 mmol/l.⁷ However, NICE has recently 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⁺ ≥ 6 mmol/l and are not receiving an optimal dose of RAASi.^{[8][9]} 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.

The Renal Association and the British Society for Heart Failure (2019) have recently collaborated to provide consensus recommendation for the use of RAASi in patients with heart failure with reduced left ventricular ejection fraction (HFrEF).¹⁰ Monitoring of renal function is mandatory during initiation and titration of RAASi treatment. In the context of acute illness (sepsis, hypovolaemia and/or AKI), withdrawal of RAASi was advised at all severities of hyperkalaemia. 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. RAASi re-introduction was recommended after recovery and when K⁺ was < 5.5 mmol/l. Patients receiving multiple RAASi drugs and/or MRA should re-start one drug at a time. 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 Cardiology¹¹ and American Heart Association (AHA)/ American College of Cardiology (ACC)¹² guidelines provide guidance on initiation, monitoring and response to treating hyperkalaemia in patients receiving MRAs. The parameters for initiation of MRA are a serum K⁺ < 5.0 mmol/l and an eGFR > 30ml/min. Close monitoring of urea and electrolytes (U&Es) is required following initiation at 1, 4, 8 and 12 weeks. Thereafter, monitoring is required every 3 months during first year, then every 3-4 months from second year onwards. The approach to managing 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⁺ ≥ 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 SZA) and monitor U&Es

Adherence to guideline recommendations appears to be poor. In a large population-based study of new users of RAASi drugs, < 33% of patients had a K⁺ measurement within 30 days of drug initiation and only 76% had at least one measurement within the first year of treatment.¹³ 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.¹⁴ 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.¹⁵ This highlights the gap in knowledge and clinical practice.

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Threshold for treatment of hyperkalaemia (Guideline 3.1)

Guideline 3.1 – Threshold for treating Hyperkalaemia in the community.

We recommend that interventions to lower serum potassium be instituted in patients with a serum K+ \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.

Existing National guidelines recommend initiation of strategies to manage hyperkalaemia when the serum K+ rises to \geq 5.5 mmol/l.^{1,2} Data from several studies performed in the general population and in patients with CKD show an increased mortality risk in patients with a serum K+ \geq 5.5 mmol/l.³⁻⁹ Mortality risk increases

further when the serum K⁺ exceeds 6 mmol/l, therefore measures should be taken to avoid a further rise in serum K⁺ level.

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

Stop other medications known to exacerbate hyperkalaemia (e.g. oral potassium supplements, NSAIDs, trimethoprim). Other strategies for lowering serum K⁺ in the community include dietary interventions (Guideline 5.1), treating metabolic acidosis (Guideline 6.1) and controlling hyperglycaemia. Re-introduction of medications that influence K⁺ levels requires slow titration and close monitoring.

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Indications for hospital assessment (Guidelines 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

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 5, can precipitate severe hyperkalaemia.¹ Acute illness is another common antecedent to acute kidney injury and hyperkalaemia.

Drugs that potentiate risk of hyperkalaemia in patients receiving RAASi and/or MRAs

- Trimethoprim/co-trimoxazole
- Potassium supplements
- Potassium sparing diuretics
- Salt substitutes (lo-salt)
- NSAID
- Non-selective beta-blockers
- Digoxin toxicity

Table 5: Drugs that pose an additive effect on risk of hyperkalaemia in patients receiving RAASi and MRAs.

The risk of adverse events increases with worsening hyperkalaemia. Severe hyperkalaemia is an independent predictor of all-cause and in-hospital mortality as well as hospitalisation.² Therefore, defined

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

There is little evidence for a specific threshold for hospital admission for management of hyperkalaemia. Charytan et al undertook a small study (n=23) to assess the practice relating to hospitalisation of patients for hyperkalaemia.³ In this study, 11 patients with hyperkalaemia at hospital admission were compared with 12 hyperkalaemic patients managed as an outpatient. The study lacked power to determine the relative safety of location of treatment. Horne et al demonstrated the impact of hyperkalaemia on mortality and healthcare utilisation, including hospital admission, in the UK general population, but did not provide a distinct threshold warranting hospital admission.⁴ However, this study noted a significantly higher incidence rate of all-cause hospitalisation for patients with a serum K+ > 6.0 mmol/l of 28.93/ 100 person-years compared with patients with a serum K+ 5.0-5.5 mmol/l of 13.86/ 100 person-years.

The position statement for 'Think Kidneys', a collaboration of The Renal Association and British Society for Heart Failure, recommend hospital admission in all patients with severe hyperkalaemia (K+ ≥ 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.⁶ Hospital admission should be considered in patients with mild hyperkalaemia (K+ 5.5-5.9 mmol/l) if acutely unwell or have an AKI.

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

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Treatment: Dietary interventions (Guideline 5.1)

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

We recommend that a low potassium diet is instituted for patients with 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)

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

A low K+ diet is defined as a dietary intake of 2-3g/day (51-77 mmol/day)⁵. In patients with CKD with persistent hyperkalaemia (serum K+ ≥ 5.5mmol/l), a dietary K+ restriction of < 3g/ day (< 77 mmol/l)⁶ or 1 mmol/kg/IBW⁷ 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 disease⁸ 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.

A renal dietitian is skilled to provide individualised advice to patients with Stage 4-5 CKD managed by specialist renal services taking into account other factors including diabetic status, cultural needs and patient preferences. Assessment of biochemical trends would ensure that the need for ongoing dietary restrictions is reviewed. The Renal Association Guideline on Undernutrition in Chronic Kidney Disease also suggests assessment by a specialist renal dietitian when patients begin education about RRT and within one month of dialysis initiation.⁹

Although dietary intervention has become standard practice, this has not been demonstrated in a randomised controlled trial and would potentially be technically difficult to achieve. Three studies reported on dietary intervention for managing hyperkalaemia.^{10,11,12}

Ahuja et al reported a retrospective analysis of patients attending a renal clinic (n=119) to determine the predictors for development of hyperkalaemia in patients on ACE-I.⁶ Overall, 46/119 patients (38.6%) of patients developed hyperkalaemia (mean serum K+ 5.68 mmol/l). Hyperkalaemia resolved in 20/46 patients (43%) with a low K+ diet alone (<2g/day; 51 mmol/l) and in 11/46 patients (24%) with dietary advice and

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

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

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

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

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Treatment: Sodium bicarbonate (Guideline 6.1)

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

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

Rationale (Guideline 6.1)

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

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

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

The BiCARB Trial evaluated the benefits and adverse effects of sodium bicarbonate in older patients with CKD for a period of up to 2 years. This was a double-blind placebo-controlled RCT which includes 380 community-based patients in the UK aged ≥ 60 years with an eGFR < 30 ml/min and serum bicarbonate < 22 mmol/l.⁹ 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.

In the pre-dialysis setting, Sarafidis et al performed a prospective study to examine the factors influencing K⁺ metabolism in patients attending a low clearance clinic (mean eGFR 14.5 ± 4.8 mmol/l).¹⁰ This study demonstrated that patients with K⁺ ≥ 5.5 mmol/l had significantly higher urea, lower eGFR and lower serum bicarbonate levels. This sub-group also had a higher usage of sodium bicarbonate than in patients without hyperkalaemia (65.3% versus 45.4%, p=0.008).¹⁰

The potential detrimental effect of sodium load with sodium bicarbonate replacement is an important consideration, particularly in patients at risk of fluid overload. Dubey et al showed that patients with CKD 3

and 4 with co-existing diabetes, hypertension and coronary artery disease had a trend towards worsening hypertension and oedema necessitating a greater use of diuretics.⁷ Similar findings have been reported in other studies with alkali replacement in CKD patients necessitating discontinuation of sodium bicarbonate due to hypertension and oedema although these studies did not focus on management of hyperkalaemia.^{8, 11,12}

A meta-analysis of all published RCTs 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.¹³ This study did not assess potassium levels.

There remains a paucity of evidence from clinical trials on the efficacy and safety of bicarbonate therapy, therefore many existing guidelines are based on the sparse evidence and expert consensus opinion. KDOQI guidelines recommend the maintenance of serum bicarbonate level ≥ 22 mmol/l to reduce metabolic complications.¹⁴ The 2007 Cochrane Review of alkali therapy in CKD found insufficient evidence of benefit.¹⁵ The NICE CKD Guideline 2014 suggests that oral sodium bicarbonate should be considered in patients with CKD 4 or 5 with a serum bicarbonate < 20 mmol/l.¹⁶ The National Kidney Foundation 'Best Practices In Managing Hyperkalaemia in CKD' suggests the use of oral sodium bicarbonate for chronic hyperkalaemia.¹⁷

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Treatment: Diuretics (Guideline 7.1)

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

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

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.

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

Diuretic therapy has a place in the management of chronic hyperkalaemia in patients who are normovolaemic or hypervolaemic. There is little evidence to support its use in acute hyperkalaemia.⁶ A

multi-modal approach including diuretics, treatment of metabolic acidosis and dietary potassium restriction may allow the continuation of cardioprotective medications in patients with mild hyperkalaemia.

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Treatment: Calcium resonium (Guideline 8.1)

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

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

Rationale (Guideline 8.1)

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

CPS is approved for use in Europe and SPS approved for use in the USA. SPS was approved by the Food and Drug Administration (FDA) in 1958 on the basis of two small uncontrolled case series undertaken in the 1950's.³ This approval preceded the Kefauver-Harris Drug Amendment (1962) and the European Union EC/65/65 directive (1965) requiring drug manufacturers to prove the effectiveness and safety of their drug.⁴ Following multiple reports of colonic necrosis and other serious gastrointestinal adverse events (perforation,

bleeding), the FDA applied safety recommendations in 2009. The FDA also advised against the concomitant administration of sorbitol, but serious complications have also been reported without the use of sorbitol.⁵

There are 3 RCTs including SPS as an intervention. Gruy-Kapral (1998) reported a placebo-controlled randomised study of SPS in normokalaemic patients with ESRD on HD (n=6) and failed to show any significant reduction in serum K+.⁶ The size, design and insufficient baseline data renders this study weak. Nasir et al (2014) performed a RCT to compare the efficacy and safety of CPS and SPS in CKD patients (n=97) with hyperkalaemia.⁷ Although both drugs lowered serum K+, the study lacked adequate statistical analysis to substantiate the claim of equal efficacy and there was no control arm (i.e. placebo group). Of note, fewer side effects were reported with CPS than SPS. Lepage et al (2015) conducted a single centre double-blind RCT (n=33) in outpatients with CKD and mild hyperkalaemia (K+ 5.0-5.9 mmol/l) comparing efficacy of SPS 30g daily to placebo for 7 days.⁴ This study reported an absolute reduction of serum K+ level of 1.25 mmol/l ($p<0.001$), but the proportion of patients who achieved normokalaemia did not reach statistical significance ($p=0.07$). This trial lacked intermediate efficacy time points. None of these studies met the inclusion criteria for the Cochrane Review (2015).⁸

The evidence for use of SPS is otherwise sparse. Chernin et al (2012) conducted a retrospective study (n=14) to assess the efficacy of SPS in CKD patients receiving RAASi medication, and observed a reduction in serum K+ from 6.4 ± 0.3 mmol/l to 4.6 ± 0.6 mmol/l ($p<0.01$) over a median follow up of 14.5 months. The size, lack of a control group and other confounding factors rendered this study difficult to interpret. Fordjour et al (2014) conducted a prospective chart review of treatment of hyperkalaemia in hospitalised patients and found that SPS was included in 95% of treatment regimens with K+ reduction ranging from 0.7 – 1.1 mmol/l. Effectiveness was deemed to be similar among patients with CKD and those receiving dialysis. Combination regimens yielded the greatest K+ reduction. Batterink et al (2015) conducted a retrospective study (n=138) and reported that SPS reduces serum K+ by 0.14 mmol/l more than control, but concluded that this level of treatment effect may not be clinically important.⁹

The evidence for use of CPS is equally sparse. Chaaban et al (2013) conducted a retrospective study (n=70) to assess the effectiveness of calcium resonium in controlling hyperkalaemia in HD patients.¹ This study showed poor efficacy attributed to lack of adherence to the drug and dietary restrictions as well as poor tolerability. Yu et al (2017) reported a retrospective analysis of 247 CKD patients in an out-patient setting treated with low dose CPS (8.0 ± 3.6 g/day) over a variable duration from > 3 months to beyond 1 year.¹⁰ Baseline eGFR was 30 ± 15 ml/min and serum K+ was ≥ 5.0 mmol/l. Serum K+ decreased significantly from 5.8 ± 0.3 mmol/l to 4.9 ± 0.7 mmol/l ($p<0.001$) with CPS treatment without any serious adverse effects over a long period.

CPS and SPS have been used widely for decades for the non-emergency treatment of hyperkalaemia despite the lack of robust randomised clinical trials to document efficacy or safety. Tolerability and the risk of severe gastrointestinal adverse effects limit their longterm use. The availability of novel potassium binders (patiromer and sodium zirconium cyclosilicate) with a stronger evidence base for efficacy and more favourable side-effect profiles may replace CPS and SPS in clinical practice in the future. However at present, UK guidance from NICE restricts their use to specific circumstances and the Scottish Medicines Consortium (SMC) have not approved either drug. Therefore these alternatives to calcium resonium are not currently available to many patients.

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Treatment: Patiromer (Guidelines 9.1-9.3)

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

To date, 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.

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. 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.⁴⁻¹⁰ Early studies included 3 Phase I clinical pharmacology studies and 12 single dose drug-drug interaction studies as summarised in Table 6.

The PEARL-HF [11] and PEARL-HF extension⁹ studies are the only patiromer trials with all participants having a diagnosis of chronic heart failure. Fewer patients in OPAL-HK (42%)⁵ and AMETHYST-DN (35%)⁶ had heart failure (Appendix 2). In the PEARL-HF study, almost half of the patients treated with patiromer developed hypokalaemia (K+ < 4 mmol/l) which also infers a higher risk of mortality in heart failure. However, in the PEARL-HF extension study, spironolactone could be optimised with a lower starting dose of patiromer whilst reducing the incidence of hypokalaemia.

In the OPAL-HK trial, 76% of patients with HF achieved serum K+ levels within the target range with patiromer. 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 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

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 2011¹² Phase II trial	104	4 weeks	4.69	Patiromer N= 55				-0.22	
			4.65	Placebo N= 49				+0.23	
OPAL-HK Weir 2015⁶ Phase III trial	243	Phase 1 <i>Treatment</i> 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 <i>Withdrawal</i> 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 2015⁷ Phase II trial	306	52 weeks	5.3	Mild HK 5.0-5.5 N=222	-0.35	-0.51	-0.55		
				Mod HK 5.6-5.9 N=84		-0.87	-0.97		-0.92
Bushinsky 2015⁸ Prospective	25	48 hours	5.93	All	7hrs: -0.21 20hrs: -0.52 48hrs: -0.75				
TOURMALIN E Pergola 2017⁹ 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 2018¹⁰ Open-label	63	8 weeks	4.78	All		-0.13			

Table 6: Studies of efficacy of Patiromer in the treatment of 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 has approved the use of Patiromer in the treatment of chronic hyperkalaemia in patients with:

- **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.

NICE has approved the use of patiromer in the treatment of hyperkalaemia for the above indications (text box).¹³ 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).⁵ The mean serum K⁺ was 0.72 mmol/l higher in patients who were withdrawn compared with those who remained on patiromer (Phase 2). However, the study cohort did not include patients with clinically significant hyperkalaemia. The patiromer trials also did not demonstrate an improvement in quality of life or survival in patients with chronic hyperkalaemia.

The Scottish Medicines Consortium (SMC) did not approve patiromer for the treatment of hyperkalaemia in NHS Scotland.¹⁴ They concluded that there were several weaknesses and uncertainties with the economic analysis of the OPAL-HK study given its short duration and endpoints that do not readily correlate with long-term CKD or cardiovascular outcomes.

Serum K⁺ should be monitored as clinically indicated.¹ A reasonable approach would be weekly for the first month and after every dose titration, 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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Treatment: Sodium zirconium cyclosilicate (Guidelines 10.1-10.3)

Guideline 10.1 – Sodium Zirconium Cyclosilicate for the management of Hyperkalaemia

We recommend that Sodium Zirconium Cyclosilicate (SZC) is 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)

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 of the oral potassium binders is shown in Appendix 1.

SZC is generally well tolerated. The most common adverse effects are oedema (5.7%) and hypokalaemia (4.1%). SZC exchanges Na^+ for K^+ , accounting for the potential risk of worsening oedema, hypertension and heart failure. Product information and administration is described in Appendix 3E.

Three randomised controlled trials and one open label clinical trial have been reported. The first was a double-blind RCT to investigate the safety and efficacy of SZC across a range of doses over a 2-day period.⁴ A dose-dependent reduction in serum K^+ was demonstrated. The primary endpoint of rate of decline of serum K^+ was achieved at the approved dose of 10g three times daily. This was followed by two multi-national Phase III RCT trials (ZS-003, ZS-004) to evaluate the efficacy and safety of SZC over a longer duration.^{5,6} The most recent study, ZS-005, is an open-label study to assess the efficacy of SZC with longterm use (52 weeks).⁷ Patients with CKD, heart failure, diabetes mellitus and receiving RAASi medication were included in these studies. The studies were conducted in stable out-patients and excluded patients on dialysis, with life-

threatening hyperkalaemia or diabetic ketoacidosis. There was also no restriction on dietary K⁺ intake in all of SZC trials.

The key clinical trials for SZC in the treatment of hyperkalaemia are summarised in Table 7. 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 (Appendix 2).

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

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-002⁴ 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-003⁵ 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-004⁶ 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)

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-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)

Table 7: Studies of the efficacy of SZC in treatment of Hyperkalaemia

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

A meta-analysis of the SZC trials 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 recently published HARMONIZE-Global study, significantly more patients achieved normokalaemia with SZC 5mg (58.6%) and SZC 10mg (77.3%) compared with placebo (24%).⁸

Approval for SZC was delayed due to concerns about the manufacturing processes, but was granted in the EU in March 2018, followed by the FDA in May 2018. Although the marketing authorisation states SZC may be used for the ‘treatment of hyperkalaemia in adults’, the submission to NICE was limited to patients with CKD and/ or heart failure.

NICE assessed the clinical and cost effectiveness of SZC based on the ZS-004 and ZS-005 clinical trials.¹¹ A few short-falls were identified in the SZC trials including the definition of hyperkalaemia (K⁺ ≥ 5.1 mmol/l) which was lower than the Renal Association and European Resuscitation Council guidelines (K⁺ ≥ 5.5 mmol/l). The clinical trials did not compare the efficacy of SZC versus dietary restriction or any other active K⁺-lowering drug. There was also no evidence that SZC improves quality of life or extends life. However, given the strong evidence for use of RAASi drugs in patients with CKD and heart failure, the cost-effectiveness analysis suggests that the use of SZC in facilitating patients staying on RAASi drugs is a good use of NHS resources.

NICE has approved the use of SZC in the treatment of persistent hyperkalaemia in the out-patient setting under these circumstances:

- **Patients with CKD Stage 3b-5 OR Heart Failure**
AND
- **Serum K⁺ confirmed to be ≥ 6.0 mmol/l**
AND
- **Patient is receiving a sub-optimal dose of RAASi due to hyperkalaemia**
AND
- **Not on dialysis**

Initiation of SZC is restricted to secondary care.

Stop SZC if RAASi therapy is discontinued.

NICE has approved SZC in the treatment of persistent hyperkalaemia for the above indications (text box).¹¹ Safety and efficacy has been shown up to 52 weeks of therapy, but the duration of treatment in clinical practice will likely be lifelong unless RAASi is discontinued. SZC will complement, rather than replace, a low-K⁺ diet. SZC may allow less strict dietary restrictions, thereby improving quality of life for patients. 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 3E).¹ Dose titration or cessation will be led by secondary care. In real-world practice, blood monitoring will be 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

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

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Prevention (Guidelines 11.1-11.3)

Guideline 11.1 – Prevention of Hyperkalaemia in the community: monitoring

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

Guideline 11.2 – Prevention of Hyperkalaemia in the community: prescribing

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

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

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

Audit measures

1. 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)

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

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

Drugs commonly implicated in hyperkalaemia are shown below in Table 8.

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

Table 8: Drugs implicated in development of hyperkalaemia and exacerbating factors.

The Medicines and Healthcare products Regulatory Agency (MHRA) issued a safety alert, initially in June 2014, regarding the concomitant use of ACEi or ARB with MRAs (i.e. spironolactone or eplerenone) given the increased risk of severe hyperkalaemia particularly in patients with advanced renal impairment.¹ The MHRA recommend caution in co-prescription of these drugs with regular monitoring of serum biochemistry and discontinuation if hyperkalaemia develops.

NICE Clinical Guideline on 'CKD in adults: assessment and management' states that RAASi should not be routinely started in patients with a serum K+ level ≥ 5.0 mmol/l and should be discontinued if serum K+ is ≥ 6.0 mmol/l.² The NICE Clinical Guideline on 'Chronic Heart Failure in adults: assessment and management' states that serum K+ should be monitored before and after starting a RAASi or changing the dose, but does not specify the K+ level at which RAASi should be avoided or discontinued.³ Given the potential benefits of RAASi therapy in patients with CKD and heart failure, NICE has recently approved the use of Szc and patiromer to facilitate continuing RAASi therapy in selected patients.^{4,5}

Trimethoprim is a first-line antibiotic, most commonly prescribed for simple urinary tract infections (UTI). 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.⁶ An increase in serum K⁺ level of 0.36 – 1.21 mmol/l or higher can occur within 3–10 days of treatment.⁷ Treatment with RAASi or NSAIDs exacerbates hyperkalaemia.⁶

There have been multiple reports confirming the risk of hyperkalaemia and AKI in patients treated with trimethoprim.^{8–10} Antoniou et al reported a 7-fold increased risk of hospital admission for hyperkalaemia in elderly patients (age ≥ 66 years) taking trimethoprim-sulfamethoxazole compared with other antibiotics for UTI.⁸ In a large UK cohort study (n=1,191, 905) of older adults (age ≥ 65 years), Crellin et al demonstrated an increased risk of developing hyperkalaemia (OR 2.27) and AKI (OR 1.72) within 14 days of trimethoprim prescription compared with amoxicillin.⁹ The risk of hyperkalaemia has been shown in patients receiving high-dose^{11, 12} and low-dose¹⁰ trimethoprim.

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)

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.¹³ A low-K⁺ diet is usually instituted when the serum K⁺ is consistently ≥ 5.5 mmol/l and has been discussed in Guideline 5.1.

The bowel compensates for the reduction in renal K⁺ loss as renal function declines. The capacity for the bowel to secrete K⁺ is inversely related to residual renal function and becomes the main route of K⁺ excretion in patients with ESRD.^{13,14} Therefore, constipation predisposes to hyperkalaemia in patients with renal impairment.

The ‘Sick day rules’ provides information to patients taking drugs known to cause AKI and hyperkalaemia (e.g. RAASi, NSAIDs) advising temporary discontinuation of these medications during acute illness, particularly in the context of volume depletion (e.g. diarrhoea and/or vomiting, fevers/ rigors). The use of this strategy is controversial. The NICE ‘Clinical Guideline on AKI’ advocates use of sick day guidance.¹⁵ On the other hand, ‘Think Kidneys’ urges caution as the evidence-base for this guidance is weak, discontinuation of cardio-protective medication could exacerbate underlying condition and patients may not restart medication on recovery or achieve previous dosage.¹⁶ The ‘Think Kidneys’ Programme Board recommends that it is reasonable to provide sick day guidance to patients at high risk of AKI based on an individual risk assessment, but a more systematic roll-out of the ‘Sick day rules’ should be undertaken in the context of a formal evaluation.

In clinical practice, many patients admitted to hospital with an AKI at initial presentation are receiving one or more drugs that can exacerbate hyperkalaemia. It is standard practice to withhold these until renal

recovery. The Sick Day rules moves the timeline to discontinuation earlier in patients at risk of AKI and if applied appropriately, may reduce the risk of severe hyperkalaemia during acute illness.

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Treatment Algorithm: Community (Guideline 12.1)

Guideline 12.1 – Treatment Algorithm for Hyperkalaemia in the community

We recommend that the treatment of hyperkalaemia in patients in the community and out-patient setting is guided by its severity and clinical condition of the patient as summarised in the treatment algorithm. (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 5.

Patients with a serum $K^+ < 5.5 \text{ mmol/l}$ do not require any specific treatment. Patients with persistent mild hyperkalaemia ($K^+ 5.5 – 5.9 \text{ mmol/l}$) warrant a review of medication (e.g. RAASi) and dietary K^+ intake. Treatment of metabolic acidosis (serum bicarbonate $< 22 \text{ mmol/l}$) and initiation of diuretics may be helpful in chronic hyperkalaemia.

Patients with persistent moderate hyperkalaemia ($K^+ 6.0 – 6.4 \text{ mmol/l}$) who are not acutely unwell require similar considerations – medication review, treatment of metabolic acidosis and a low K^+ diet. However, some patients may be candidates for a potassium binder (Patiromer or SMC) if they meet the NICE criteria as discussed in Guidelines 9 and 10.

Patients with moderate hyperkalaemia who are acutely unwell and those with severe hyperkalaemia ($K^+ \geq 6.5 \text{ mmol/l}$) warrant referral to hospital for urgent assessment. RAASi drugs should be withheld until recovery.

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

Section 2

Management of Hyperkalaemia in Hospital

Hyperkalaemia in Hospital

Introduction

Hyperkalaemia is a potentially life-threatening medical emergency. The incidence in hospitalised patients ranges from 1 – 10%.¹⁻⁵ It is associated with increased hospitalisation and mortality.⁶⁻⁸ Despite this, there is limited evidence to guide treatment. This may account for the observed variability in the treatment of patients with hyperkalaemia, even within the same hospital.⁹ 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.⁹ The longer a patient has a high K+ level, the greater the risk of sudden deterioration.¹⁰ Urgent treatment can avoid life-threatening complications.¹¹

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.^{11-13,14} 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.¹¹

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.¹³ Intravenous calcium salts (gluconate and chloride) are life-saving, but there are no clinical trials to prove efficacy.¹³ Insulin-glucose infusion is the most effective treatment to lower serum K+, but the conventional treatment regimen was based on small historical studies mostly in dialysis patients. Beta-agonists appear to be effective in lowering serum K+, but some patients are unresponsive. Sodium bicarbonate was frequently used in clinical practice, but there is little favourable evidence of its efficacy in treating acute hyperkalaemia.¹³

Over the past 5 years, there has been some progress in the treatment of hyperkalaemia relating to management in hospitalised patients. Several retrospective studies have been conducted to investigate the incidence and causes of iatrogenic hypoglycaemia following insulin-glucose administration.¹⁵⁻¹⁹ Other studies have compared conventional versus low dose insulin regimens.²⁰⁻²² The use of variable dosing regimens of insulin and glucose in these reports is a confounding factor. Ultimately, iatrogenic hypoglycaemia appears to be multifactorial with a low pre-treatment blood glucose being a consistent risk factor. Another important development is the availability of novel potassium binders, patiromer and sodium zirconium cyclosilicate, which have both been approved by NICE for the treatment of life-threatening hyperkalaemia although their efficacy in the acute setting has not yet been reported.^{23,24}

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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Clinical assessment (Guidelines 13.1-13.2)

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 9. 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 Muscle weakness and/ or paraesthesiae may occur in severe cases.¹⁻⁴ The medication history is an important part of determining the aetiology of hyperkalaemia. Ask about current medication, recent changes and use of over the counter medications.

Risk factors for Hyperkalaemia:

- Acute Kidney Injury
- Dialysis dependency (haemodialysis or peritoneal dialysis)
- Chronic Kidney Disease Stages 4 & 5 (CKD, eGFR < 30 ml/min/1.73m²)
- 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 9: 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.⁵ The National Early Warning Score (NEWS) was developed by the Royal College of Physicians.⁶ NEWS uses several vital signs to detect abnormalities and identify acute ill patients.⁷ Baseline assessment and serial monitoring is essential in identifying patients who are deteriorating and the NEWS can facilitate timely decisions for escalation of care.

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

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ECG and cardiac monitoring (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 used to assess cardiac toxicity and risk of arrhythmias in patients with known or suspected hyperkalaemia and may be the most readily available diagnostic tool. In terms of clinical significance, the type of ECG changes 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+.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.

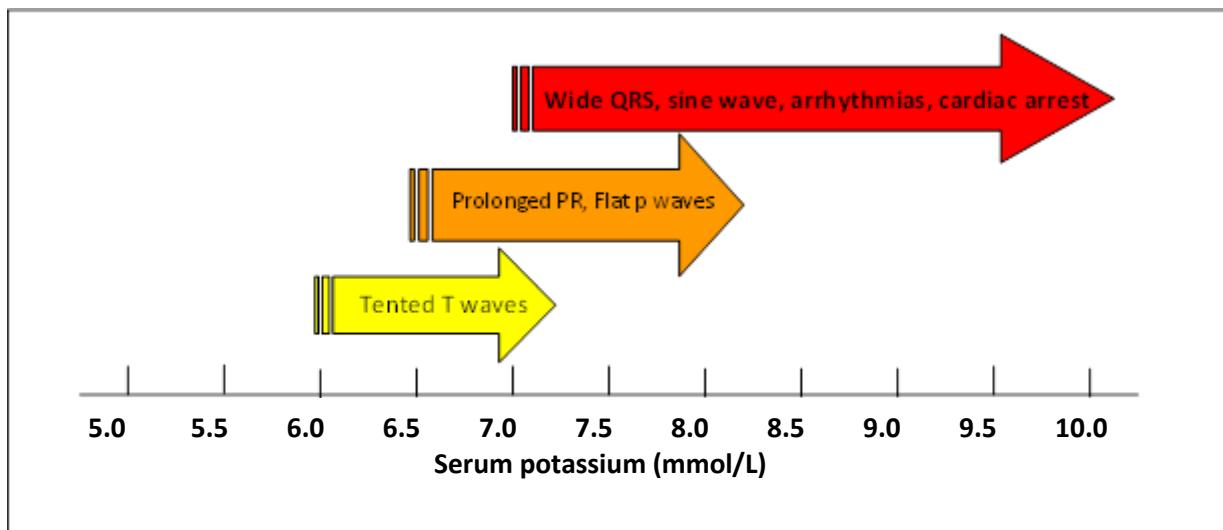


Figure 1: Progressive changes in ECG with increasing severity of hyperkalaemia.

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.^{4,5} Early studies reported the frequency of peaked T waves was 36% in hospitalised patients with hyperkalaemia.⁶ Similarly, Freeman et al reported peaked T waves at presentation in 35% of patients with a serum K+ > 6.0 mmol/l.⁷ Durfey et al also reported peaked T waves in 30% of patients with a serum K+ ≥ 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.

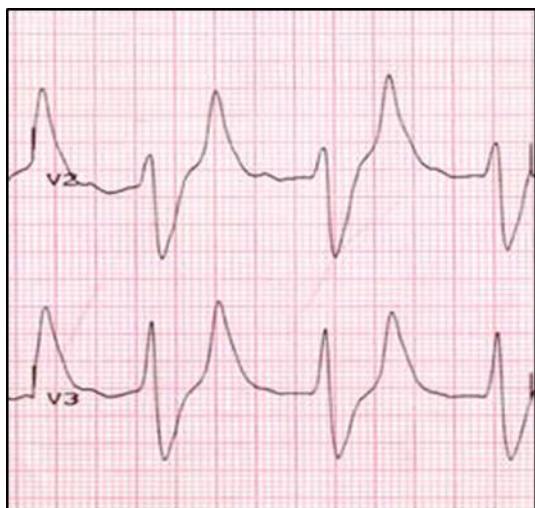


Figure 2: ECG in a patient with severe hyperkalaemia (serum K+ 9.1 mmol/l) illustrating peaked T waves (a), diminished P waves (b) and wide QRS complexes (c).

The reported utility of the ECG is variable. Some reports suggest that 50-64% of patients with a serum K+ ≥ 6.5 mmol/L show no ECG changes consistent with hyperkalaemia.⁶⁻⁸ 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, although there are reports of a normal ECG in extreme hyperkalaemia.

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.⁷ 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 in patients with severe hyperkalaemia. Durfey et al examined the ECG performed within 1 hour of K⁺ measurement in patients with severe hyperkalaemia (serum K⁺ ≥ 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 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⁺ ≥ 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⁺ ≥ 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. Physician interpretation of the ECG in hyperkalaemia is variable.^{9,10} Rafique et al reported a mean sensitivity of 0.19 (± 0.16) and specificity 0.97 (± 0.04).⁹ This suggests that the ECG can be used to rule in a diagnosis of hyperkalaemia, but not to rule it out. Secondly, the ECG may be normal even in the presence of severe hyperkalaemia.¹¹⁻¹⁵ Thirdly, the ECG appearance may be atypical with a pseudo-STEMI pattern or Brugada phenocopy.^{2,16-18} Finally, the first presentation with severe hyperkalaemia may be ventricular fibrillation or asystole.¹⁹

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.[20, 21] 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 will enable early recognition and prompt treatment of life-threatening arrhythmias in patients with hyperkalaemia. Hyperkalaemia causes arrhythmias by causing hyperpolarisation of cells, making them less able to depolarise when necessary.²² Arrhythmias can occur at any time in the patient's presentation without prior toxic ECG changes.²³ All arrhythmias have been reported in patients with hyperkalaemia, including atrial fibrillation,²⁴ bradycardia,²⁵⁻³² and ventricular tachycardia.^{33,34} Some typical arrhythmias are shown in Figure 3.

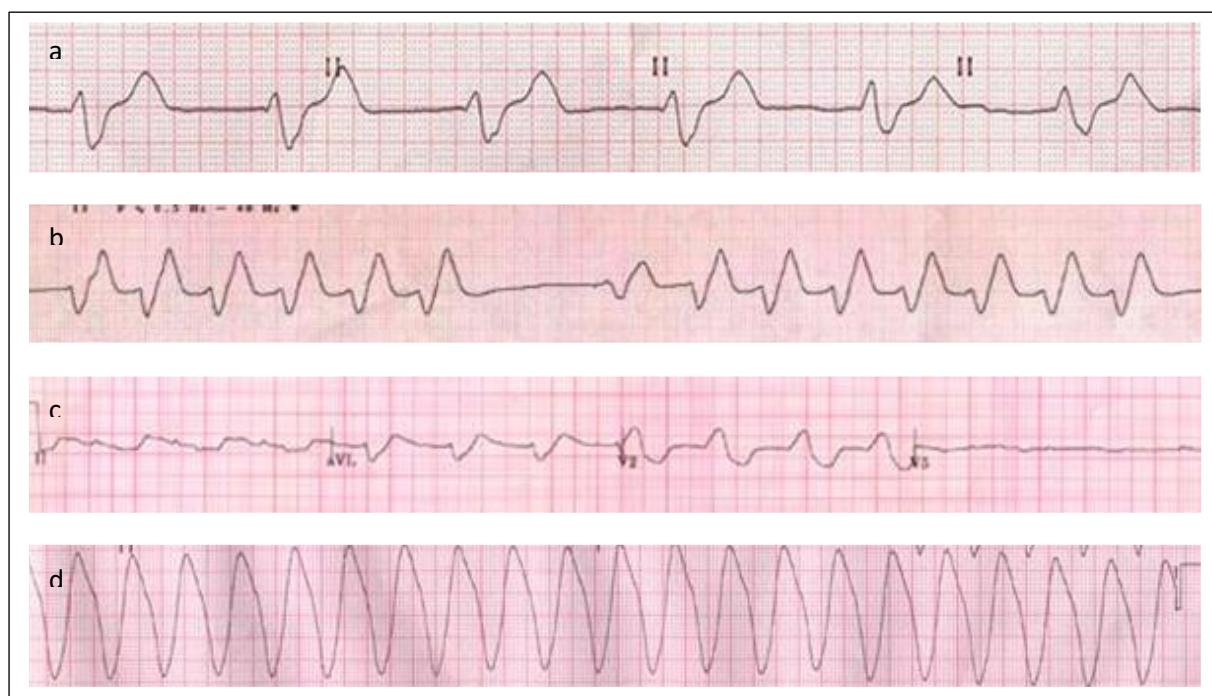


Figure 3: Arrhythmias in patients with severe hyperkalaemia illustrating bradycardia with wide QRS [K+ 9.6 mmol/L] (a), sine wave with pause [K+ 9.3 mmol/L] (b), sine wave without pause [K+ 8.4 mmol/L] (c), and ventricular tachycardia [K+ 9.1 mmol/L] (d).

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.^{23,28} Negatively chronotropic drugs (e.g. beta blockers) exacerbate bradycardia in hyperkalaemic patients.²⁹⁻³² The BRASH (Bradycardia, renal failure, atrioventricular node blockers, shock and hyperkalaemia) syndrome is a recently coined term to describe refractory bradycardia and haemodynamic instability in the context of hyperkalaemia and in patients receiving rate controlling drugs.²⁹⁻³¹ 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.^{27,35,36}

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Laboratory analysis (Guidelines 15.1-15.3)

Guideline 15.1 – Hyperkalaemia: Laboratory tests

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

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.¹¹⁻¹⁵ Point of care testing in the ED can also reduce length of stay and improve patient flow.¹⁵

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).¹⁶ 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, first reported in 1955, describes the finding of a raised serum (clotted blood) K⁺ value concurrently with a normal plasma (non-clotted blood) K⁺ value.¹ The clotting process releases K⁺ from cells and platelets increasing the serum K⁺ concentration by an average of 0.4 mmol/L.

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

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

Send FBC to exclude a haematological disorder.

Pseudo-hyperkalaemia is present if:

$$[\text{Serum K}^+] - [\text{Plasma K}^+] > 0.4 \text{ mmol/l}$$

The most common cause of pseudo-hyperkalaemia is a prolonged transit time to the laboratory or poor storage conditions. Other causes of pseudo-hyperkalaemia include difficult venepuncture, a high platelet count, haemolysis, erythrocytosis, prolonged storage time of clotted samples, or cold storage conditions. When using evacuated tubes for blood collection, if the order of draw is wrong, the sample can be contaminated with potassium EDTA (for full blood count).^{3,4} Another common cause of contamination is sampling from the arm into which potassium-containing fluids are being infused. An inverse relationship between ambient temperature and potassium concentration has been reported with higher K⁺ values in the winter months and has been termed 'seasonal' pseudo-hyperkalaemia.⁵

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

The importance of recognition of pseudo-hyperkalaemia is the avoidance of unnecessary treatment which could cause harm.⁶

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Treatment (Guidelines 16.1-16.6)

Guideline 16.1 – Hyperkalaemia: Summary of treatment strategy

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

Rationale (Guideline 16.1)

The treatment of hyperkalaemia currently varies considerably. A systematic approach, as shown in Figure 4, takes into account clinical priorities, may reduce variability, enhance patient outcome and reduce adverse events related to hyperkalaemia and its treatment.¹

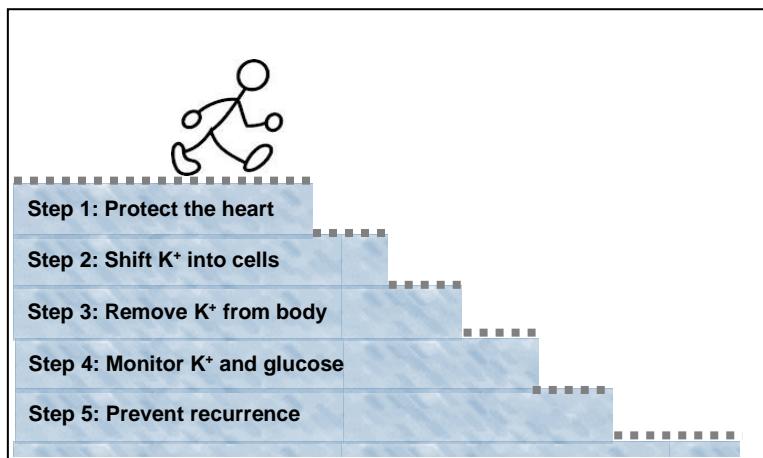


Figure 4: There are five key steps in the treatment of hyperkalaemia (*never walk away without completing all of these steps*).

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 10.

STEP 1	Protect the heart	IV Calcium Gluconate or Chloride
STEP 2	Shift potassium into cells	Insulin-Glucose Salbutamol
STEP 3	Remove potassium from the body	Sodium Zirconium Cyclosilicate Cation-exchange resins

Table 10: Mechanism of action of drugs used in treatment of hyperkalaemia.

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Guideline 16.2 – Hyperkalaemia: STEP 1 - Protect the heart; intravenous calcium salts

We recommend that intravenous calcium chloride or calcium gluconate, at an equivalent dose (6.8mmol), is given to patients with hyperkalaemia in the presence of ECG evidence of hyperkalaemia. (1C)

Audit Measures

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

Rationale (Guideline 16.2)

The use of intravenous (IV) calcium in the treatment of hyperkalaemia is well established in clinical practice but is based on sparse evidence. The toxic effects of potassium on the heart and antagonism by calcium was first demonstrated in an animal model in 1883¹ 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. It is effective within 3 minutes at improving adverse ECG appearances (e.g. narrowing of the QRS complex).^{4, 7-9} The dose should be repeated if there is no effect within 5-10 minutes. The duration of action is only 30-60 minutes, so further doses may be necessary if hyperkalaemia remains uncontrolled. As IV calcium does not lower serum K⁺, other interventions are urgently required.

$$10 \text{ ml } 10\% \text{ Calcium Chloride} = 6.8 \text{ mmol Ca}^{2+}$$

$$10 \text{ ml } 10\% \text{ Calcium Gluconate} = 2.26 \text{ mmol Ca}^{2+}$$

Table 11: Calcium content of IV calcium salts used in treatment of hyperkalaemia.

The choice of calcium salt (chloride or gluconate) is guided by practicalities such as availability, local practice and the clinical condition of the patient. There are some important differences between the two available solutions. Both preparations, calcium chloride¹⁰ and calcium gluconate¹¹, are available in the form of 10ml of 10% solution but calcium chloride contains 3 times more calcium than calcium gluconate as shown in Table 11. The bioavailability of both preparations appear to be similar with a study in patients with poor liver function (pre-transplant) demonstrating that calcium gluconate does not require hepatic activation to become effective.¹² Calcium gluconate is less irritant to the skin than calcium chloride, but both salts can cause tissue necrosis. Calcium chloride has been recommended in the setting of haemodynamic instability, including cardiac arrest.¹³

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

- tissue necrosis if extravasation occurs
- hypotension, peripheral vasodilation, hot flushes and/or chalky taste (mainly after too rapid infusion)
- bradycardia, arrhythmias (frequency unknown)

Report all adverse events via the Yellow Card system.

Historical evidence suggests that the administration of intravenous calcium may potentiate digoxin toxicity, but this is limited to case reports^{14,15,16}. 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 calcium¹⁷, but some methodological concerns in this paper has been highlighted.[18] In instances where digoxin toxicity was unrecognised at presentation, no adverse event after IV calcium administration was reported.^{19,20}

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

1. A single dose of 10ml 10% calcium gluconate is often administered irrespective of the response which may have been inadequate.
2. The 12-lead ECG is frequently not repeated after administration to assess response. Look for a narrowing of the QRS complex (Figure 5), reduction in T wave amplitude (Figure 5), increase in heart rate if bradycardic or reversal of arrhythmia.
3. IV calcium can cause bradycardia, therefore there may be reluctance to administer if the patient's heart rate is already slow. IV Calcium remains indicated and may be life-saving in hyperkalaemia-induced bradycardia.²¹
4. The relatively short duration of action of IV calcium (30-60 minutes) may not be considered in patients with prolonged hyperkalaemia. Repeat ECG and consider a further dose if patient remains hyperkalaemic.
5. IV calcium may not be deemed necessary when emergency dialysis is planned or being initiated for severe hyperkalaemia, but this remains essential.

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

- life-threatening ECG changes (absent P waves, wide QRS, sine-wave pattern)^{3,13}

- cardiac arrhythmias¹³
- cardiac arrest^{13,22}

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

- isolated peaked T waves
- normal ECG

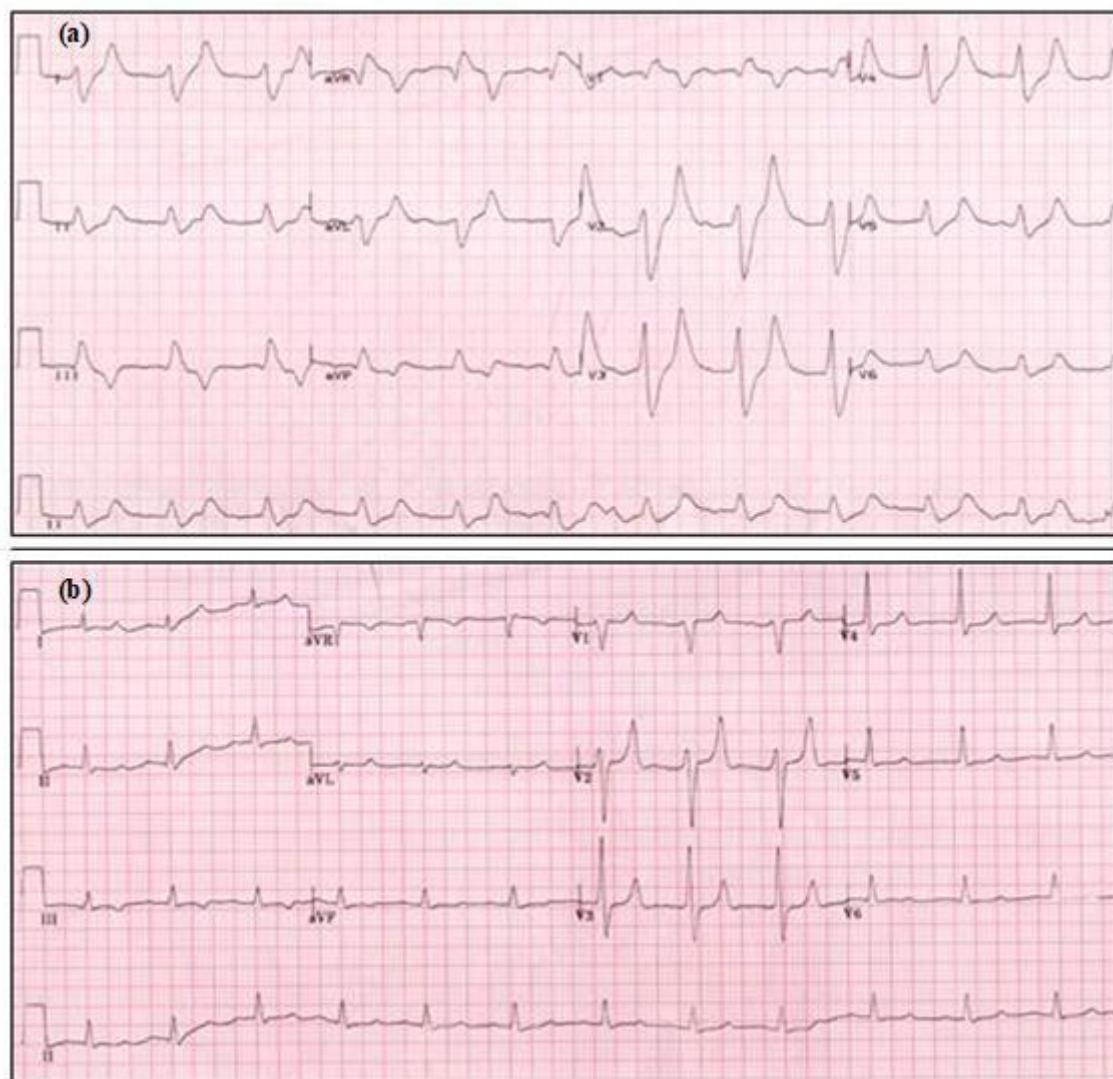


Figure 5: ECG on admission (a) and following 20ml 10% calcium gluconate IV (b) in a patient with serum K⁺ 9.3 mmol/L who presented with generalised weakness.

In summary, IV calcium has been widely recommended for the treatment and prophylaxis of arrhythmias in patients with hyperkalaemia. The use of IV calcium buys time for other interventions to take effect. Given that 1) the ECG is the best tool for assessing cardiac toxicity, 2) the effect of IV calcium is assessed by an improvement in ECG appearance, and 3) IV calcium is not without risk, it seems reasonable to reserve IV

calcium for patients with ECG changes of hyperkalaemia. When 10% calcium gluconate is used, sequential doses of 10ml solution are often required whereas a single dose of calcium chloride is more likely to be effective. Therefore, we recommend an equivalent dosage of calcium chloride or gluconate (6.8 mmol) for initial therapy.

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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 ($K+ \geq 6.5 \text{ mmol/l}$). (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 ($K+ 6.0 - 6.4 \text{ mmol/l}$). (2C)

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

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

Audit measure

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

Rationale (Guidelines 16.3.1 – 16.3.4)

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 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 minutes²⁻³, 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:

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

Iatrogenic Hypoglycaemia after Insulin-glucose therapy

Hypoglycaemia is the most serious complication of treatment with insulin-glucose for acute hyperkalaemia. Over the last decade, several observational studies, using variable treatment regimens, have highlighted this risk as shown in Table 12.^{10-14,15} In one of these studies, Boughton et al used the UK Renal Association Hyperkalaemia Guideline (2014) protocol, however 10 units insulin was given in 100ml 20% glucose (~ 20g), slightly lower than the guideline recommendation of 125 ml 20% glucose (25g). This may have influenced hypoglycaemic events.¹⁴

Study	Country	N=	Baseline Blood glucose (BG)	Time Interval to Hypo (hrs)	Hypo (%)	*Severe Hypo (%)	Risk factors for Hypo
#Schafers 2012 ¹⁰	US	219	8.6 (No hypo group) 6.7 (Hypo group)	3.0	8.7	2.3	Low pre-treatment blood glucose Renal impairment
#Apel 2014 ¹¹	US (ESRD)	221	9.0 (no hypo group) 5.8 (hypo group)	2.0	13	5.9	Low pre-treatment blood glucose No history of diabetes
#Estep 2015 ¹⁴	US	86	8.3 (No hypo group had BG 2.4 mmol/l higher than hypo group)	1.45	17.4	3.5	Low pre-treatment blood glucose
Coca 2017 ¹²	Spain	164	8.5 (No hypo group) 6.2 (Hypo group)	3.5	6.1	1.2	Low pre-treatment blood glucose
#Scott 2019 ¹³	US (ED)	409	7.3 (Hypo occurred in 34% of patients with baseline BG < 5.6)	NA	17	8	Low pre-treatment blood glucose Lower glucose dose Higher insulin dose
Boughton 2019 ¹⁴	UK	662	8.7 (No hypo group) 5.8 (Hypo group)	NA	17.5	7.1	Low pre-treatment blood glucose Older age Low body weight

Table 12: Incidence and risk factors associated with iatrogenic hypoglycaemia after insulin-glucose infusion for treatment of hyperkalaemia.

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

#Studies without a standardised Insulin-glucose protocol

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

These studies demonstrate that the most consistent factor contributing to hypoglycaemia after insulin-glucose treatment is a low pre-treatment blood glucose level (< 7 mmol/l). This is an important consideration in designing a safe and effective treatment protocol.

Insulin and Glucose dose: Efficacy

The evidence-base for efficacy of insulin-glucose in the treatment of acute hyperkalaemia is heterogeneous consisting of variable study designs, insulin doses, glucose doses, method of administration (bolus or infusion), and study populations as shown in Table 13.

Early prospective studies^{2,3,5,6,16,17} and one more recent study¹⁸, were performed predominantly in stable haemodialysis patients and included small patient cohorts. Few prospective studies included patients with acute kidney injury.^{4,8,19}

Retrospective studies reported over the past decade have attempted to address the optimal regimen to reduce the risk of hypoglycaemia without compromising efficacy.^{12,20-25} Some studies have considered reduced insulin dose (5 units)^{20,22,23}, higher glucose dose (50g)^{10,12,21,22,24}, body weight^{21,25}, glycaemic status²⁶ and level of renal function^{20,26} 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.

Efficacy		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 ⁴	10	10			40	6.7	1.0	
Allon 1990 ²	12	10		25		5.48	0.65	
Ljutic 1993 ⁵	9	10		25		6.33	0.76	
Allon 1996 ³	8		0.5 U/kg/min		60	4.28		0.85
Duranay 1996 ¹⁶	20	10			30	6.71	0.99	
Kim 1996 ⁶	8		0.5 U/kg/min		40	6.3		0.7
Ngugi 1997 ⁸	70	10		25		6.9	1.14	
Mahajan 2001 ¹⁷	30		12	25		6.59		0.83
Mushtaq 2006 ²³	15	10		25		6.5	0.8	
Chothia 2014 ¹⁸	10	10	0		50	6.01 [10 units] 6.23 [0 units]	0.83	0.50
Pierce 2015 ²⁰	149	10	5	25		6.3	1.08	1.1
Wheeler 2016 ²¹	132	10	0.1 U/kg		50	6.1	#NI	#NI
La Rue 2017 ²²	675	10	5	25 + 25 ± 25		6.4	1.0	1.0
Coca 2017 ¹²	164	10			50	6.85	1.18	
Garcia 2018 ²³	401	10	5	25	0, 12.5, 50	6.15 [10 units] 6.24 [5 units]	0.90	0.81
Farina 2018 ²⁴	240	10		25	50	6.5 [25g] 6.3 [50g]	1.0 [25g] 1.1 [50g]	

Table 13: Prospective and Retrospective studies of Insulin-glucose therapy.

Insulin dose – Conventional Regimen: Insulin 10 units in 25g glucose

The majority of the prospective studies used a dose of 10 units of soluble insulin as shown in Table 14.^{2, 4, 5, 8, 16, 18, 23, 19} The most commonly used dose of glucose was 25g.^{2, 5, 8, 23, 19} The mean baseline serum K⁺ ranged from 5.48 – 6.9 mmol/l in patients treated with this conventional regimen. The efficacy demonstrated in these studies showed a reduction in serum K⁺ ranging from 0.65 – 1.14 mmol/l as shown below in Table 14. This evidence formed the basis of the historical recommendation to treat acute hyperkalaemia with insulin 10 units and glucose 25g. Recent observational studies have shown similar efficacy (0.9-1.08 mmol/l) with this regimen.^{20, 23, 24}

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=70)⁸	10	25	6.9	1.14	NA	NA	20
Mushtaq 2006 (n=15)²³	10	25	6.5	0.8	NA	7.5	0
Pierce 2015 (n=149)²⁰	10	25	6.3	1.08	55	NA	16.7
Garcia 2018 (n=401)²³	10	25	6.15	0.9	36.2	8.7	10.7
Farnia 2018 (n=240)²⁴	10	25	6.5	1.0	26.7	7.0	15.8

Table 14: Efficacy and risk of hypoglycaemia with conventional regimen - 10 units Insulin with 25g glucose (studies without efficacy data excluded)

DM – Diabetes Mellitus. BM – Blood glucose. *all patients non-diabetic.

Insulin dose – 5 versus 10 units

Three retrospective studies, consisting of large cohorts of up to 675 patients, have compared the efficacy and hypoglycaemic risk with regimens using 5 versus 10 units of insulin in patients with renal impairment as shown in Table 15.^{20,22,23} The K⁺-lowering achieved using 10 units insulin was 0.9 – 1.08 mmol/l compared with 0.81 – 1.1 mmol/l using 5 units insulin.

Interpretation of the data in these studies is confounded by the low proportion of patients receiving 5 units insulin in two of the studies^{22,23}, the use of variable glucose regimens which may have influenced the incidence of hypoglycaemia, and the use of concomitant K⁺-lowering drugs which may have influenced

efficacy. Albuterol, a beta-agonist, was used in more patients treated with 5 units insulin in two of the reports^{22,23} and was not stated in the other report.²⁰

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 2015²⁰ (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 2017²² (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 2018²³ (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

Table 15: Comparison of studies performed using 5 versus 10 units insulin (studies without efficacy data excluded).

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

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

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

p = 0.03

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

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 reported a post-hoc analysis of patients with a serum K⁺ ≥ 6.0 mmol/l and showed a trend towards higher K⁺-lowering in patients treated with 10 units insulin compared with those treated with 5 units insulin. (difference -0.238 mmol/l; p=0.018).²³ This observation has been shown more definitively in a recent large study (n=700).

Moussavi et al reported significantly greater K⁺-lowering in patients treated with 10 units insulin (1.11 ± 0.8 mmol/l, p=0.008) compared with those treated with < 10 units insulin (0.94 ± 0.71 mmol/l).²⁷

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 conducted using 10 units of insulin (Table 13) was compared between patients with a mean K⁺ ≥ 6.5 mmol/l (n=6) vs those with a mean K⁺ < 6.5 mmol/l (n=6). Interestingly, this showed a trend towards higher K⁺-lowering in studies with more severe hyperkalaemia (mean reduction 1.02 mmol/l vs 0.87 mmol/l; difference -0.15 mmol/l). The extent of this correlation may be affected by the narrow range in K⁺ level as no studies exceeded a mean K⁺ level of > 7.0 mmol/l, however this observation suggests that the higher the serum K⁺, the greater the efficacy of insulin.

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

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

Insulin dose – Conventional regimen

The studies conducted prior to 2010, using a regimen of 10 units of insulin with 25g glucose, showed a wide variation in incidence rate of hypoglycaemia ranging from 11 – 20% in two studies,^{5,8} no episodes in one study¹⁹ and as high as 75% in a study including only patients without diabetes.² Similarly, over the past decade, the incidence of hypoglycaemia reported using this regimen ranged from 5 - 28%.^{10, 11, 14, 20, 23, 24, 26}

Insulin dose – Low dose regimen

Studies assessing the hypoglycaemic risk using regimens of 5 vs 10 units of insulin were confounded by the proportion of patients who received 5 units insulin (range 20 – 48%) and the variable glucose dosing (Table 15).^{20, 22, 23} Pierce et al, the only study with almost equal study arms, showed no significant difference in incidence of hypoglycaemia between conventional vs low-dose insulin treatment groups (16.7% vs 19.7%, p=0.79).

McNicholas et al conducted as a 2-part audit comparing the incidence of hypoglycaemia in patients treated with 5 vs 10 units insulin with 25g glucose based on level of renal function.²⁶ Adherence to the treatment protocol improved in Audit 2 with a higher number of patients with CKD/ESRD receiving 5 units insulin resulting in a reduction in hypoglycaemic events from 28% to 11% with no severe episodes.

Insulin dose – Weight-based regimen

Tailoring insulin dose to body weight is another potential strategy as shown in Table 16.^{3, 6, 21, 25} 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.²¹ 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.²⁵ In clinical practice, a weight-based regimen would be difficult to safely and reliably implement in a medical emergency.

Table 16: Comparison of studies performed using weight-base Insulin regimen.

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 1996³ (n=8)	5 mU/kg/min	60	4.28	0.85	0	4.8	0	0
Kim 1996⁶ (n=8)	5 mU/kg/min	40	6.3	0.7	NA	NA	0	0
Wheeler 2016²¹ (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 2018²⁵ (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

*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.

Glucose dose

Studies assessing the effect of glucose dose (25g vs 50g) on hypoglycaemic risk are shown in Table 17. Farnia et al reported a trend towards a lower incidence of hypoglycaemia at 60 minutes in patients treated with 50g glucose.²⁴ Sub-group analysis of patients with a baseline blood glucose < 6.1 mmol/l and those without diabetes showed a significant reduction in hypoglycaemic events when treated with 50g glucose. Coca et al delivered an infusion of 50g glucose with 10 units insulin over 240 minutes and showed a low hypoglycaemic rate at 6.1% with this strategy.¹²

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 ¹⁸ (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 ²¹ (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 ¹² (n=164)	-	-	-	-	-	-	-	-
	50	10	6.85	1.18		8.3	6.1	1.2
Garcia 2018 ²³ (n=401)	0	5 (2%)	6.24	0.81	29	7.6	8.7	
	25	5 (16%)						
	50	5 (5%)						
Garcia 2018 ²³ (n=401)	0	10 (4%)	6.15	0.9	36	8.8	10.7	
	25	10 (63%)						
	50	10 (9%)						
Farnia 2018 ²⁴ (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 17: 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.^{18, 28} 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).¹⁸ 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.^{1,29} This approach also risks a paradoxical worsening of hyperkalaemia by causing a shift of K⁺ out of cells.³⁰⁻³² This strategy is not recommended.

Other risk factors

Several risk factors have been identified that may contribute to hypoglycaemia after insulin-glucose treatment. Patient-related factors are listed below in Table 18. Insulin has a longer half-life in patients with renal failure making them more at risk of hypoglycaemia.³³⁻³⁵ The reported incidence of hypoglycaemia in patients with ESRD is up to 33%.^{10, 20, 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 (≤ 25 g glucose)

Table 18: Risk Factors for Hypoglycaemia following treatment with Insulin-Glucose

Most of the patient-related factors are not modifiable with the exception of the baseline blood glucose. Based on the available studies, a pre-treatment blood glucose < 7 mmol/l appears to be the threshold for identifying patients potentially at risk of hypoglycaemia.^{10-14, 18, 21-25} Both treatment-related factors are modifiable.

Tailoring the treatment protocol to address one or more of these risk factors will increase complexity and likely affect adherence as seen in two reports.^{22, 26} However, a single protocol to fit all will continue to risk hypoglycaemia.

Summary

Historical evidence has guided the development of previous guidelines with the conventional regimen of 10 units soluble insulin with 25g glucose being standard practice for decades.^{36, 37, 38} The incidence of hypoglycaemia following this treatment regimen remains high, therefore recent studies have been comprehensively reviewed to determine if a change in practice is warranted. Unfortunately, the available evidence is limited by small cohort sizes in the early prospective studies, retrospective design in recent studies and use of multiple insulin-glucose treatment regimens.

The risk of hypoglycaemia is increased in patients without diabetes and in patients with a pre-treatment blood glucose < 7 mmol/l. In a sub-group of patients without diabetes, hypoglycaemia developed in 7.9% within 1 hour.²⁴ Reducing the dose of insulin alone is insufficient to reduce hypoglycaemic events which remains at 8.7-19.7% with low-dose insulin, although it does appear to reduce the incidence of severe hypoglycaemia in some studies. There appears to be more evidence that increasing the dose of glucose more consistently reduces hypoglycaemic events with the larger studies (with efficacy data) reporting rates of 6.1-8.3%.^{12, 24}

The method of administration of glucose may be important. LaRue et al attempted sequential doses of 25g glucose (i.e. second dose after 1 hour and third dose after 3 hours if the blood glucose < 3.9 mmol/l), but

non-adherence to the protocol resulted in a lower dose of glucose administered (34 - 39g).²² Coca et al administered 50g glucose with insulin over a 4-hour infusion and reported a low rate of hypoglycaemia (6.1%) and the lowest rate of severe hypoglycaemia (1.2%), but this strategy delays assessment of efficacy.¹² Another approach is the initiation of a continuous infusion of 10% glucose at 50ml/hr following initial treatment with 25g glucose.^{30,39} 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, titration of the infusion guided by blood glucose level and avoids the transient hyperglycaemia after a 50g glucose dosing.

Achieving a lower hypoglycaemic rate without compromising efficacy is the ultimate goal. Although most studies have shown that reducing the dose of insulin does not appear to compromise efficacy, two reports have highlighted a dose-dependent effect with 10 units insulin showing greater efficacy than 5 units insulin.^{23,27} There also appears to be a trend for greater efficacy with increasing severity of hyperkalaemia in patients treated with 10 units insulin.

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 appears to out-weigh the risk of hypoglycaemia in the setting of life-threatening hyperkalaemia. Further study is required before a reduction in insulin dosage to 5 units can be recommended.

The KDIGO statement (2019) on the management of acute hyperkalaemia acknowledges that there is limited evidence, but has recommended the administration of 5 units in place of 10 units insulin.⁴⁰ This document also advocates other treatment options without a clear evidence base including sodium bicarbonate (if acidosis present) and diuretics. The implications of this change in dose of insulin to patients in whom a multi-modal treatment approach may not be feasible (i.e. peri-arrest or cardiac arrest) does not appear to have been considered.

The current Renal Association guideline (2020) 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. 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.⁴¹

Administration will depend on the concentration of glucose solution chosen (Appendix 3B). The use of 50% glucose has reduced in recent years in view of the potential risk of extravasation injury.⁴⁰ 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.

Insulin-glucose protocol for treatment of hyperkalaemia

- Check blood glucose prior to insulin administration.
- **Give 10 units soluble Insulin with 25 g glucose.**
- **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.

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. A further area for study is the use of potassium binders in place of insulin-glucose therapy in moderate hyperkalaemia in the hospital setting.

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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 ($K+ \geq 6.5 \text{ mmol/L}$) 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 ($K+ 6.0\text{-}6.4 \text{ mmol/L}$) 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)

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 19: Efficacy of Nebulised Salbutamol.

The effect of salbutamol is dose-dependent as shown above in Table 19. The onset of action is within 30 minutes and duration of action is for at least 2 hours as shown below in Table 20.^{2, 3, 6-11} The peak effect of 10mg nebulised salbutamol is seen at 120 minutes and at 90 minutes for the 20mg nebulised dose.⁴ The degree of potassium lowering is variable and 20-40% of patients have a decline in serum K⁺ < 0.5 mmol/L.¹²

The combination of salbutamol with insulin-glucose is more effective than either treatment alone.^{9, 13} The peak K⁺ lowering effect with combination therapy at 60 minutes was 1.5 mmol/L with intravenous beta-agonist therapy¹³ and 1.2 mmol/L with nebulised beta-agonist therapy⁹. Mild hyperglycaemia (2-3 mmol/L increase) has also been reported and this may partly protect against insulin-induced hypoglycaemia.

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 1994	17	10 mg	5.8	0.88	90	>60
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	1200µg (via MDS-I)	5.5	0.4	60	ns

Table 20: Studies investigating efficacy of nebulised salbutamol in hyperkalaemia.

*children (aged 5-18 years)

ns – not stated

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

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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 salbutamol⁵, others have not demonstrated any additional benefit from bicarbonate administration when added to insulin-glucose¹ or salbutamol^{1,6}. The combination of all three treatments was the most effective strategy in one study.⁶

Prolonged administration of sodium bicarbonate may lower K+, but at the expense of a sodium load.³ A randomised controlled trial conducted by Jaber et al assessed the effect of using hypertonic sodium bicarbonate (4.2%) in critically ill patients with severe metabolic acidosis (pH < 7.2).⁷ There was no difference in the primary outcome (composite of death from any cause by day 28 or 1 organ failure at day 7), however the bicarbonate group had significantly lower K+ levels and a lower requirement for renal replacement therapy. A recent retrospective study of the use of bicarbonate infusion in patients with sepsis reported improved survival in the sub-group of patients with severe acidosis associated with AKI stage 2 or 3.⁸

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

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

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

We recommend that Sodium Zirconium Cyclosilicate is used as an option in the emergency management of acute life-threatening hyperkalaemia (serum K+ \geq 6.5 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.

Rationale (Guideline 16.6.1)

Until recently, there had been no new advances in treatment of acute hyperkalaemia for decades. Sodium Zirconium Cyclosilicate (S2C) 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 S2C is up to 9 times greater than that of SPS.²

The S2C clinical trials have been discussed in detail in Guidelines 10.1-10.3 and include three RCTs [3-5] and one open label clinical trial.[6] Major limitations are that all studies were performed in the stable out-patient setting and the threshold for treatment was lower than standard practice with few patients having a serum K+ \geq 6.0 mmol/l.

Acute Phase	ZS-003 [4]	ZS-004 [5]	ZS-005 [6]
24 hours		66%	66%
48 hours	86.4%	88%	75%
72 hours			78%

Table 21: 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 The median time to normalisation of serum K+ is 2.2 hours and SZC lowers serum K+ by 1.1 mmol/l within 48 hours.⁵ The ZS-003 and ZS-004 trials also demonstrated a greater K+-lowering effect with increasing severity of hyperkalaemia.^{4,5} In patients with a serum K+ > 6.0 mmol/l, SZC lowers serum K+ by 1.5 mmol/l within 48 hours. The efficacy of SZC over the first 24-72 hours (Table 21), demonstrates that 66% of patients achieved normokalaemia within 24 hours.^{5,6}

NICE has approved the use of SZC as an option in the treatment acute life-threatening hyperkalaemia alongside standard care in hospitalised patients.

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

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

The ENERGIZE trial is an ongoing Phase 2 (NCT03337477), multi-centre randomised, double-blind placebo controlled study to evaluate SZC as an adjunct to insulin-glucose in treatment of acute hyperkalaemia for normalisation of serum K+.⁸ The primary outcome is the mean absolute change in serum K+ from baseline until 4 hours after starting SZC/ placebo. The study will include patients with a serum K+ \geq 5.8 mmol/l, although this is below the current treatment threshold (K+ \geq 6.0 mmol/l) for insulin-glucose. Patients will be randomised to receive SZC 10g three times daily over 10 hours (at 0, 4, and 10 hrs) or placebo during the treatment period of 24 hours alongside standard care with insulin (0.1 units/kg) and glucose 25g. Further study is warranted to determine whether SZC could be used as an alternative to insulin-glucose in patients with moderate hyperkalaemia. The main advantage of this strategy would be reducing the risk of hypoglycaemia in patients who are at a lower risk of arrhythmias.

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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 life-threatening hyperkalaemia (serum K+ \geq 6.5 mmol/l). (1C)

Audit Measures

1. The proportion of patients with acute severe hyperkalaemia (serum K+ \geq 6.5 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. A role for patiromer in the acute setting has not been investigated as all major clinical trials were performed in stable out-patients.¹⁻⁶ The onset of action is slow (4-7 hours),⁷ therefore its contribution to rapid control of serum potassium (within the first 4 hours) may be limited in the acute setting. Patiromer also has the potential to bind to some co-administered drugs, therefore it cannot be taken within 3 hours of other medications.² However, patiromer is generally better tolerated than calcium resonium.

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).¹ The mean serum K+ was 0.72 mmol/l higher in patients who were withdrawn compared with those who remained on patiromer (Phase 2). The patiromer studies initiated treatment at a lower threshold compared with routine medical practice. Given that most patients did not have clinically significant hyperkalaemia, the efficacy of patiromer in the context of life-threatening hyperkalaemia is not known.

The first study to assess the efficacy of patiromer in the acute setting was a pilot study within an Emergency Department.⁸ 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). 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 in serum K+ at 6 hours (6.32 mmol/l vs 5.81 mmol/l, p=0.155) compared with standard care.

NICE has approved the use of patiromer as an option in the treatment acute life-threatening hyperkalaemia alongside standard care in hospitalised patients.

NICE has approved patiromer for treating patients with life-threatening hyperkalaemia alongside standard medical therapy including insulin and glucose.⁹ Patiromer should not be used instead of standard treatment, but could replace calcium resonium. 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 16.6.3 – Hyperkalaemia: STEP 3 – Remove K+ from body; Cation-exchange resin

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

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 Ca²⁺. The most common resin used in hospitals in the UK is CPS, Calcium resonium®.¹ The onset of action is slow (> 4 hours) and efficacy is unpredictable excluding its use in emergencies. It is also poorly tolerated due to taste and constipation. The most serious adverse effect of resins is intestinal necrosis.^{2,3}

Evidence in support for the use of cation-exchange resins in the treatment of hyperkalaemia is very limited and these drugs were approved before evidence-based practice was established.^{4,5} It is unclear whether the resins have a K⁺-lowering effect in isolation or whether this is caused by the induction of diarrhoea by cathartics. Multiple doses are required over several days, with the effect on lowering the serum K⁺ noted over 1 to 5 days.^{6,7} The Cochrane Review for the acute management of hyperkalaemia included no studies on resins.[8] Resins play no role in the emergency management of severe hyperkalaemia.^{8,9} The use of resins in chronic hyperkalaemia is discussed in Guideline 8.1.

Resins may be considered in patients with moderate hyperkalaemia in the acute setting (with no or mild ECG changes) where slower reduction in serum K⁺ may not compromise the patient.⁹ Nasir et al demonstrated equal efficacy of SPS and CPS in lowering serum K⁺ over a 3-day period in patients with CKD.¹⁰ Resins may also be used in combination with other strategies (i.e. insulin-glucose, low K⁺ diet), as an alternative to treating patients who are poor candidates for dialysis, or when dialysis is delayed.

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Blood monitoring (Guidelines 17.1-17.2)

Guideline 17.1.1 – Hyperkalaemia: STEP 4 - Blood monitoring; serum potassium

We recommend that the serum K+ is monitored closely in all patients with hyperkalaemia to assess efficacy of treatment and to monitor for rebound hyperkalaemia after the initial response to treatment wanes. (1B)

Guideline 17.1.2 – Hyperkalaemia: STEP 4 - Blood monitoring; serum potassium

We suggest that serum K+ is assessed at least 1, 2, 4, 6 and 24 hours after identification and treatment of moderate or severe hyperkalaemia. (2C)

Audit measures

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

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 infusion and nebulised salbutamol are the most effective treatments in reducing serum K+ levels in current practice. The time to peak effect with insulin-glucose ranges from 30-60 minutes¹⁻⁵ 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 and the median time to normalisation of serum K⁺ is 2.2 hours.¹¹ 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 assessed at 1-2 hours. Therefore, measure serum K⁺ at 1 and 2 hours after initial treatment to determine if the K⁺ level has decreased sufficiently.

Further monitoring at 4 and 6 hours is required to assess for any rebound in serum K⁺ as the effects of 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.

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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, 15, 30, 60, 90, 120, 180, 240, 360, 480 and 720 minutes) up to 12 hours after administration of insulin-glucose infusion in all patients with hyperkalaemia. (1C)

Audit measure

1. The proportion of patients who have at least one blood glucose test performed within 1 hour of completion of insulin-glucose infusion [Audit Standard: 100%].
2. The frequency of hypoglycaemia occurring in patients receiving treatment with insulin-glucose for hyperkalaemia.

Rationale (Guideline 17.2)

Hypoglycaemia, defined as a blood glucose of < 4.0 mmol/L, is the most common adverse event following insulin-glucose infusion for the treatment of hyperkalaemia.¹⁻⁵ Even mild hypoglycaemia is associated with an increased risk of mortality in hospitalised patients.[6] 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.⁷ The impact of hypoglycaemia is independent of diabetic status and adverse outcomes have been shown in patients with diabetes mellitus or without diabetes.^{7,8} One mechanism by which hypoglycaemia may be detrimental is by reducing myocardial blood flow in patients with diabetes and as well as in healthy adults.^{9,10}

Iatrogenic hypoglycaemia is a significant patient safety concern, therefore should be anticipated with regular blood glucose monitoring. Risk factors for hypoglycaemia are shown in Table 12; Guideline 16.3. The incidence of hypoglycaemia appears to be lower in patients treated with 50g vs 25g glucose as initial treatment as discussed in Guideline 16.3.¹¹

The majority of hypoglycaemic events occur between 2.0 to 3.5 hours after insulin-glucose infusion (Table 12; Guideline 16.3).^{1,4,5,12} Apel et al demonstrated that 75% of hypoglycaemic episodes occurred within 3 hours of insulin administration (median 2 hours) and persist for a median of 2 hours.⁴ However, in patients without diabetes, hypoglycaemia may occur within 1 hour.¹¹ The risk of hypoglycaemia persists for as late as 6 hours after administration of IV insulin.^{1,4,5,12,13} The Joint British Diabetes Societies for inpatient care has advised blood glucose monitoring for 12 hours after insulin-glucose infusion for treatment of hyperkalaemia: at least 3 times in the first hour followed by at least 6 further measurements over the subsequent 11 hours.

Recent studies suggest that variables related to treatment (dose of insulin, dose of glucose) and the baseline clinical parameters (e.g. pre-treatment glucose) have a greater influence on the rate of hypoglycaemia than non-modifiable baseline patient characteristics.^{2,5} Therefore, this is a potentially preventable adverse event. The current guideline recommendation provides an increased glucose dose to the patients anticipated to be at the greatest risk of hypoglycaemia (i.e. pre-treatment blood glucose < 7.0 mmol/l). This criteria will likely overlap with other patient groups at risk including patients with low body weight, advanced age or renal failure. Frequent blood glucose monitoring remains the cornerstone of preventing hypoglycaemia.

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Treatment of hyperkalaemia in haemodialysis patients (Guidelines 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 patients¹⁻⁶ and was shown to be responsible for 3-5% of deaths.^{1,4} Factors contributing to hyperkalaemia in HD patients are summarised in Table 22. The risk of hyperkalaemia in longterm HD patients is influenced by 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 MainENace HemoDialysis) observational study in the USA 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 \leq 2mmol/l and 21% in patients dialysing on a dialysate K+ \geq 3mmol/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
- Dietary K⁺ intake
- Dialysate K⁺ concentration
- Problems with dialysis access - poor blood flow, recirculation
- Poor dialysis adequacy
- Medication
- Diabetic status – glycaemic control
- Constipation
- Compliance – poor attendance, shortened treatment time

Table 22: 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 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 23. 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 K ⁺ CONCENTRATION (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; switch to 2 mmol K ⁺ when serum K ⁺ < 7)

Table 23: 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 hypokalemic 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.

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⁺ dialysate solutions. Novel potassium binders may provide an additional strategy.²⁹ Patiromer and SZA 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⁺ ≥ 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 Ca²⁺ 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 trial [NCT03740048] is an ongoing pilot trial of twice versus thrice weekly HD in patients with incident ESRD to investigate whether patiromer can have a dialysis-sparing effect.³³ Patients randomised to twice-weekly regimen will receive a loop diuretic and sodium bicarbonate with the addition of patiromer if they develop hyperkalaemia during the 6 week study period.

SZC: The DIALIZE trial was a Phase IIIb RCT (NCT03303521) designed to evaluate SZC in controlling hyperkalaemia in haemodialysis (HD) patients.³⁴ This is 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).

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Referral to specialist services and escalation of care (Guidelines 19.1-19.6)

Guideline 19.1 - Hyperkalaemia: Specialist Referral

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

Guideline 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)

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

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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Minimum standards for patient transfer (Guidelines 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 the referring hospital is less complicated, but still requires good communication and coordination. Cardiac monitoring and resuscitation equipment are essential for the transfer of patients with hyperkalaemia, either within or between hospitals.

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

Pre-transfer stabilisation is essential for all patients.^{1,3} Following appropriate medical therapy for hyperkalaemia, the response to treatment should be assessed with repeat observations, biochemistry, blood glucose and ECG prior to transfer. We suggest that a patient should not, in general, be transferred between hospitals if the serum K⁺ is ≥ 6.5 mmol/L, though other factors (in

particular, the location of intensive care and dialysis facilities) will occasionally over-ride this consideration. Critical care review is essential for patients with any concern regarding oxygenation, ventilation or haemodynamic instability.

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 nebulises, 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 appropriate records
10. Maintaining patient dignity
11. Hand-over to receiving team
12. Return of transfer staff and equipment

Table 24: Minimum standards for safe patient transfer.

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

The organisation of the patient transfer itself requires a coordinated approach and liaison with the receiving team to ensure that they are prepared for the patient's arrival.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 27.

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

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Prevention (Guidelines 21.1-21.4)

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)

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 reduced renal blood flow and ultimately AKI with hyperkalaemia. Patients may present with hyperkalaemia at the time of hospital admission or it may develop after hospital admission in patients in whom the K⁺ level was normal on arrival. Clinicians should be alert to the potential development of hyperkalaemia in the context of intercurrent illness in patients receiving drugs known to exacerbate hyperkalaemia. Early recognition and treatment of AKI can reduce morbidity and mortality.

Hyperkalaemia often occurs after hospital admission. A study of in-patients with hyperkalaemia showed that 33.3% of cases developed after hospital admission.⁴ Most cases were mild, but 15.4% were moderate or severe (K⁺ ≥ 6.0 mmol/l). AKI was present in 73% of cases with a pre-renal cause in 50% of these. The aetiology was often multifactorial, but hyperkalaemia was more common in the elderly and patients with diabetes and/or CKD. Prescribed medication was implicated in 76% of patients receiving potentially hyperkalaemia-inducing drugs (e.g. RAASi) and 55% of these patients were taking two or more of such medications.⁵ Furthermore, this study demonstrated that the severity of hyperkalaemia was found to be significantly correlated ($p < 0.01$) with the number of potentially hyperkalaemia-inducing drugs used concurrently. Medications frequently implicated in hyperkalaemia are summarised in Table 25.

Hospital acquired hyperkalaemia is common in the elderly, aged 75 years or more. Robert et al investigated the factors predisposing to the development of hyperkalaemia occurring 3 or more days after hospital admission in an elderly cohort.⁵ Hyperkalaemia developed during 4.5% of hospital admissions and 27% of episodes were considered severe (K⁺ ≥ 6.0 mmol/l). AKI was present in 51% of cases and hyperkalaemia-inducing drugs were implicated in 80.5% of cases.⁵ Overall, 79.9% of hyperkalaemic events were potentially avoidable.

Drugs that affect aldosterone secretion
<ul style="list-style-type: none"> • ACE inhibitors • Angiotensin Receptor Blockers • Non-steroidal anti-inflammatory drugs • Calcineurin inhibitors • Heparins • Antifungals (e.: ketoconazole, fluconazole and itraconazole)
Drugs that block aldosterone binding to mineralocorticoid receptor (MRA)
<ul style="list-style-type: none"> • Spironolactone • Eplerenone • Drospirenone
Drugs that inhibit activity of epithelial sodium channel
<ul style="list-style-type: none"> • Potassium sparing diuretics (e.g. amiloride and triamterene) • Trimethoprim; Co-trimoxazole • Pentamidine
Drugs that alter transmembrane potassium movement
<ul style="list-style-type: none"> • β-blockers • Digoxin • Intravenous cationic amino acids • Hyperosmolar solutions (e.g. mannitol, glucose) • Suxamethonium
Potassium containing agents
<ul style="list-style-type: none"> • 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 25: Drugs commonly associate with hyperkalaemia (Adapted from [2, 3]).

Hyperkalaemia is particularly common in patients with CKD. Furuland et al reported hyperkalaemia ($K+ > 5.0 \text{ mmol/l}$) in 48.4% of patients admitted with renal impairment with multiple episodes occurring in 28.8% of patients with CKD Stage 3-5.⁶ The main risk factors for recurrence were decline in renal function, diabetes and treatment with RAASi drugs. Patients with hyperkalaemia were shown to have a longer duration of hospital stay and higher mortality risk than those without hyperkalaemia.⁶

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

Dietary intervention is a further preventative measure in hospitalised patients with moderate or severe hyperkalaemia. Institution of a low potassium diet may help to control hyperkalaemia and avoid recurrence. This requires provision of a renal menu and restrictions on food items brought in by family members. A formal assessment by a renal dietician would ensure appropriate guidance is given.

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.⁹ Risk increases in the presence of impaired renal function, use of drug combinations that can exacerbate hyperkalaemia or in patients with a higher baseline K⁺ level.⁹ Patient education and community monitoring should be in place before hospital discharge.

Re-instating RAASi or other medication following an acute illness associated with hyperkalaemia is another important consideration. This decision balances the risk-benefit ratio and original indication of the drug (e.g. heart failure).¹⁰ It is reasonable to consider re-introduction and re-titration of the drug, on recovery, in patients who previously had stable renal function and K⁺ 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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Treatment Algorithm: Hospital (Guidelines 22.1)

Guideline 21.1 – Hyperkalaemia; Algorithm in Hospital

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

Rationale (Guideline 21.1)

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

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

The 2019 algorithm provides guidance for the new treatment recommendations:

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

Section 3

Management of Hyperkalaemia in Resuscitation

Hyperkalaemia in Resuscitation

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 acute kidney injury. Patients receiving long-term haemodialysis (HD) are most at risk of hyperkalaemia. Cardiac arrest can occur in hospital, within an out-patient dialysis unit or out of hospital, but hyperkalaemia should be considered in all settings in patients at risk. Patients on long-term HD are one of the highest risk groups for out-of-hospital cardiac arrest, occurring 20 times more frequently than in the general population.³

The reported incidence of in-hospital hyperkalaemic cardiac arrest is variable. Wallmuller et al found hyperkalaemia as the primary aetiology in only 1% of in-hospital cardiac arrests (n=1041) although it was the most common metabolic cause (47%).⁴ In contrast, Wang et al⁵ reported an incidence of 12% (n=1114) and Saarinen et al⁶ 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 m² compared with the general population without CKD.⁷ Cardiovascular disease is also highly prevalent in the dialysis population. The added insult of hyperkalaemia in patients with pre-existing heart disease may contribute to sudden death in dialysis patients, presumably from cardiac arrest.

Pre-dialysis hyperkalaemia and hypokalaemia have both been shown to be associated with higher all-cause mortality.⁸ 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.⁹ There was no advantage of using a low K+ dialysate. The intermittent nature of HD treatment is a further consideration. Bleyer et al demonstrated that HD patients are susceptible to SCD in the first 12 hours from start of the HD session, but the highest risk period is the last 12 hours of the 2-day inter-dialytic interval.[10] In this study, hyperkalaemia (K+ ≥ 6.0 mmol/l) was present in 6.5% of patients with SCD.

Optimising and controlling K+ levels in dialysis patients is challenging. Kovesdy et al demonstrated greater survival in maintenance HD patients with a pre-dialysis serum K+ of 4.6 – 5.3 mmol/l.⁸ 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.¹¹

This section of the guideline will cover:

1. special considerations in the resuscitation of patients receiving dialysis 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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Hyperkalaemic cardiac arrest – Special circumstance (Guidelines 23.1-23.2)

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. Recognition of hyperkalaemia as the aetiology cardiac arrest may be pre-arrest or during the resuscitation attempt. Early detection of

hyperkalaemia before cardiac arrest provides a window of opportunity to prevent arrhythmias or cardiac arrest, but delays in treatment are well recognised.

The National Patient Safety Alert resource for hyperkalaemia (2018) highlighted 35 cases of cardiac arrest in patients with hyperkalaemia which were reported due to concerns related to treatment and/ or monitoring.¹ Wang et al (2016) reported that 20% (5/25) of dialysis patients who suffered a hyperkalaemic cardiac arrest did not receive either intravenous calcium or sodium bicarbonate.² Saarinen et al (2011) investigated the impact of appropriate treatment in cases where a reversible cause of cardiac arrest was identified and found that no patients received appropriate treatment when the aetiology was hyperkalaemia.³ The ECG may be helpful in assessing the risk of cardiac arrest in patients with hyperkalaemia. However, the progressive ECG changes frequently described may not be present and the first sign of hyperkalaemia may be cardiac arrest. An et al reported that approximately 20% of patients presented with cardiac arrest at the time of diagnosis of hyperkalaemia.⁴ Durfey et al demonstrated that arrhythmias or cardiac arrest occurred within 6 hours of the presenting ECG in 15% of patients with serum K+ ≥ 6.5 mmol/l before IV calcium was administered and before K+-lowering treatment was initiated in all but one patient.⁵

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 cardiac monitoring is essential for all patients with severe hyperkalaemia. Prompt treatment of hyperkalaemia can avoid arrhythmias and cardiac arrest. Avoid delays in treatment and seek specialist help early.

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Resuscitation strategy in dialysis patients (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 incidence of cardiac arrest in dialysis patients is higher than in the general population, therefore vigilance and staff training is essential. The incidence of cardiac arrest in the out-patient setting ranges from 3.4 – 7.8 / 100,000 HD sessions as shown in Table 26.¹⁻³ Sparse data is available on the incidence of in-hospital cardiac arrest in patients on long-term HD. Wong et al reported a rate of 1.4 events per 1000 in-hospital days with a survival to hospital discharge of 22%.⁴ An early study of in-hospital CPR in patients with ESRD showed a survival to hospital discharge of only 8%.⁵

Study	Number of HD sessions	Number of cardiac arrests	Incidence of CPR /100,000 dialysis sessions	Survival to Hospital Discharge
Karnik 2001 ¹	5, 744,708	400	7	NA
La France 2006 ³	307,553	24	7.8	75%
Davis 2008 ²	2, 611,119	110	3.4	24%

Table 26: 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 27. Karnik et al reported that the mean time into dialysis at cardiac arrest was 123 ± 77 minutes.¹ The mean time to cardiac arrest was shorter in patients with central venous catheters compared with arteriovenous fistulas.¹ Electrolyte and fluid shifts may also play a role in the timing of events.

Study	N=	Before HD	During HD	After HD
Karnik 2001¹	400	7%	81%	12%
Davis 2008²	152	10%	70%	20%
La France 2006³	38	8%	78%	14%

Table 27: Timing of cardiac arrest during dialysis in out-patient centres.

HD – haemodialysis

Shockable cardiac arrest rhythms (pulseless VT or VF), have been reported to be more common in the dialysis population than non-shockable rhythms (PEA or asystole). Davis et al demonstrated a shockable primary arrest rhythm in 65% of arrests.² Karnik et al reported the arrest rhythm in only 16% of cases but of these, the initial rhythm was VF in 42%, VT in 20% and asystole in 15%.¹ 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).³

Study	PEA/Asystole			VF/VT		
	Events %	ROSC Achieved (%)	Survival to D/C (%)	Events %	ROSC Achieved (%)	Survival to D/C (%)
Davis 2008² HD patients Out-pt HD unit n= 152	35	37	11	65	51	31
La France 2006³ HD patients Out-pt HD unit n= 24	*50	NA	NA	*50	NA	NA
Meaney 2010⁶ US gen pop IHCA n= 51,919	76	42	11	24	64	37
Nolan 2014⁷ UK gen pop IHCA n= 23,554	72	26	11	17	76	49

Table 28: 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 28. 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.^{6, 7} 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.⁸

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

Survival after cardiac arrest is better with shockable rhythms.

Modifications to ALS in Renal Failure

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

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

Special considerations during resuscitation in dialysis patients is shown in Table 29. The cardiac arrest team may have little knowledge of these considerations in dialysis patients, therefore expert help is essential for optimising care and safety.

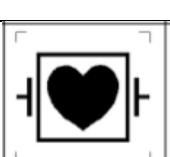
The practice of defibrillation in HD units is variable across the UK and many staff are unaware of the safety considerations.⁹ The ERC Guidelines (2015) recommends disconnection from dialysis equipment prior to defibrillation, unless defibrillator-proof, in keeping with the International Electrotechnical Committee (IEC) standards 60601-2-4.¹⁰ Most haemodialysis equipment is not defibrillator-proof.

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 symbol 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

Table 29: 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) recommended that all dialysis facilities should have on-site capability of defibrillation and the use of AEDs is the simplest and most cost effective device.¹¹ The implementation of AEDs within dialysis facilities was mandated within one year of this guideline. Shortly thereafter, Lehrich et al investigated the use of AEDs in dialysis centres and reported that the presence of AEDs alone did not independently improve survival and suggested that further measures are required to affect outcome.¹²

The impact of dialysis unit staff initiating resuscitation before arrival of paramedics has recently been reported to assess outcomes of staff-led CPR and AED use. In this study of OHCA in out-patient dialysis clinics (n=398 events), dialysis staff initiated CPR in 81% of events, but applied an AED before paramedics arrived in only 52.3%.¹³ The timing of events in relation to dialysis is not available. When dialysis staff were the first to apply the AED, there was a greater proportion of shockable rhythms (41% vs 25%), reinforcing

early application of AED. The odds of survival to hospital discharge was 3-fold higher with staff-initiated CPR, but there was only a non-significant trend towards improved survival to discharge with staff-initiated AED. This may be explained by the low usage of AED by nursing staff.

Cardiac arrest in dialysis centres are witnessed events.

CPR should be initiated by nursing staff.

First responders require regular training in use of an AED.

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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Treatment: Calcium chloride (Guidelines 25.1)

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)

This guideline extrapolates from management in the non-arrested patient, recognising the sparsity of evidence for the use of specific medical interventions in hyperkalaemic cardiac arrest. Intravenous calcium is widely recommended for treatment of hyperkalaemia in the context of toxic ECG changes, arrhythmias and cardiac arrest.¹⁻³ However, in the absence of hyperkalaemia or other specific indication, IV calcium can have deleterious effects in cardiac arrest with coronary vasospasm and worsening cerebral hypoxic damage.

The quality of evidence for the general use of IV calcium in cardiac arrest was reviewed using the 2010 International Liaison Committee on Resuscitation (ILCOR) evidence evaluation process.⁴ Only 10 studies were adequate for inclusion and only two studies had a blinded randomised design. The analysis was further limited by the wide variation in sample size, reported data and outcomes. The conclusion was that there is no evidence that IV calcium during CPR improves survival after cardiac arrest. Its role in specific settings of hyperkalaemia, calcium channel blocker intoxication, hypocalcaemia and hypermagnesaemia remain unclear due to limited data.

More recently, Wang et al (2016) have reported the outcome of IV calcium in hyperkalaemic IHCA.⁵ In this study, 56% of patients received IV calcium either alone (4/ 109; 4%) or more frequently in combination with sodium bicarbonate (57/ 109; 52%). ROSC was achieved in only one patient who received IV calcium alone (1/4; 25%), but this patient did not survive > 24 hours. In comparison, ROSC was achieved in a higher proportion of patients who received both drugs (12/57; 21%).

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

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Treatment: Insulin-glucose (Guidelines 25.2)

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 standard (10 units) vs low dose (5 units) insulin, Garcia et al 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 also demonstrated significantly greater K+-lowering with 10 units insulin compared with low-dose insulin.⁷ 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 have historically recommended the use of insulin-glucose for hyperkalaemic cardiac arrest based on treatment in the non-arrested patient.⁸⁻¹⁰ 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.^{11, 12} Subsequent ERC guidelines (2010, 2015) altered the dose of glucose to 25g based on the available evidence and the Cochrane review on the emergency interventions for hyperkalaemia published in 2005.^{10, 13, 14}

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.¹⁵ Therefore, hyperkalaemia frequently occurs after cardioplegia.^{15, 16} 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.¹⁵

The optimal dose of insulin and glucose during cardioplegia is unclear. Morgan et al suggested 30-50g per 10 units of insulin.¹⁷ 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.¹⁸ Kocoglu et al suggested 2g of glucose for 1 unit of insulin, but hypoglycaemia was common and required treatment with 10% glucose.¹⁶ 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.¹⁶

The current RA Hyperkalaemia guideline (2020) 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.¹⁹ 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.²⁰

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Treatment: Sodium bicarbonate (Guidelines 25.3)

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 over the past few decades. The rationale for using sodium bicarbonate (SB) is to counteract the worsening metabolic acidosis in cardiac arrest as a result of hypoxia, poor perfusion and increased lactate production. The potential deleterious effects of using 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 ($\text{pH} < 7.1$), 2) prolonged cardiac arrest ($> 10\text{-}20$ minutes), 3) hyperkalaemia and 4) overdose of tricyclic antidepressants.² More recently, Weng et al (2013) showed no benefit of sodium bicarbonate during prolonged CPR.³ 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

Clinical practice is guided by international resuscitation guidelines. The 2010 ACLS Guidelines for adults published by the American Heart Association stated that 'the routine use of sodium bicarbonate is not recommended for patients in cardiac arrest', but supported its use in hyperkalaemia and tricyclic overdose with or without cardiac arrest.⁴ Similarly, the European Resuscitation Council (ERC) guidelines (2015) have also recommended the use of SB for these specific indications.⁵

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%).⁶ SB was administered early in the course of resuscitation (within 10 minutes) and ROSC was achieved in 47% of patients who received SB alone and 21% who received both drugs.

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

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Treatment: Initiation of dialysis during cardiac arrest (Guidelines 25.4)

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 cardiac arrest. 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 alter serum K+ level and there is little evidence that sodium bicarbonate significantly lowers serum K+. Therefore, the only drugs administered during CPR which may lower the serum K+ are insulin-glucose and adrenaline.

In the largest study of hyperkalaemic cardiac arrest (n=109), dialysis was not instituted during CPR.¹ Patients were analysed by the severity of hyperkalaemia - K+ 6.5 – 7.9 mmol/l (72/ 109; 66%), K+ 7.9 – 9.4 mmol/l (30/109; 28%) and K+ > 9.4 mmol/l (7/ 109; 6%). Overall, ROSC > 20 minutes was achieved in 37% of patients, but only 4 patients (3.7%) survived to hospital discharge. The incidence of ROSC declined with increasing severity of hyperkalaemia and was achieved in: 32/72 (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 30.²⁻¹⁴ 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 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 rewarming in accidental hypothermia without cardiac arrest¹⁵⁻¹⁷ and in cardiac arrest.^{18, 19} In one of these cases, manual CPR was performed for 5.5 hours and CVVH was achieved with no technical difficulties for over 3 hours.¹⁸ 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 is 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.

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 1981²	36	Asystole	9.7	70	HD	75	6.6	Full recovery
Torrecilla 1989³	53	Asystole	10.2	15	HD	90	6.5	Full recovery
Lin 1994⁴	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 1994⁵	57	Asystole	9.6	15	HD	95	7.2	Survived (3 days)
Lee 1994⁶	11	Asystole	10.2	140	HF on CPB	ns	ns	Full recovery
Jackson 1996⁷	16	Asystole	9.8	165	PD	60	4.3	Full recovery
Kao 2000⁸	68	VT	8.3	150	HD	40	5.1	Full recovery
Schummer 2000⁹	68	ns	9.0	ns	HDF	15	ns	Full recovery
Iwanczuk 2008¹⁰	53	ns	8.5	ns	HD	40	5.4	Full recovery
Chiu 2014¹¹	66	VF	8.6	ns	CVVH on VA-ECMO	ns	ns	Full recovery
Tijssen 2017¹²	17	Asystole	8.3	ns	CRRT on ECMO	ns	ns	Full recovery
Kim 2019¹³	13	Sine wave	9.6	90	HF on VA-ECMO	ns	ns	Full recovery
Klingkowski 2019¹⁴	5	VF	9.2	ns	CVVH and ECMO	25 (ECMO prolonged)	4.2	Full recovery

Table 30: Outcome of hyperkalaemic cardiac arrest with RRT during CPR.

(ns = not specified)

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 30 reveals that the mean serum K+ at the time of cardiac arrest was 9.2 mmol/l (range 8.3-10.2 mmol/l). The mean serum K+ at ROSC was 6.1 mmol/l (range 4.2-7.6 mmol/l) in patients who received a haemodialysis modality. Therefore, the mean reduction in K+ required to achieve ROSC was 3.01 mmol/l (range 1.3-5.0 mmol/l) and this would be difficult to achieve with drugs alone.

The term ‘extreme hyperkalaemia’ has been used in the literature.[20-22] It has been defined as a serum K+ > 9.0 mmol/l.²³ 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 30), 9/15

(60%) had a serum K⁺ > 9.0 mmol/l and 7/9 (78%) 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.

The ERC Guidelines (2015) suggest considering dialysis initiation for hyperkalaemic cardiac arrest resistant to medical therapy.²⁴ This recommendation was based on several considerations:

- Firstly, the reports of successful outcomes of hyperkalaemic cardiac arrest have demonstrated that it is technically feasible to dialyse during CPR. With the aid of the blood pump, a blood flow rate of up to 200 ml/min can be achieved with a chest compression rate of 100/min.
- Secondly, it seems logical to 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 in refractory hyperkalaemia.
- Fourthly, survival in patients with extreme hyperkalaemia is very low without the initiation of dialysis during CPR.
- Lastly, the evidence base for other interventions for hyperkalaemia, particularly calcium salts, is also limited, but has become standard medical practice. 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. There may also be a reluctance to consider dialysis during CPR with the anticipation of technique failure. The resuscitation team will rely on 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.²⁵ An update and summary of the procedure is outlined in Table 31.

Once CPR is underway, initiate medical treatment for hyperkalaemia and seek expert help early. If hyperkalaemia is suspected, 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.

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

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. Consider the use of mechanical devices to perform chest compressions (e.g. LUCAS2, Autopulse). Where available, use ECMO to optimise perfusion during prolonged cardiac arrest management.^{6, 11-14}

Given that defibrillation is frequently unsuccessful until the serum K⁺ is controlled, analogous to rewarming for hypothermic cardiac arrest, RRT should be considered for refractory hyperkalaemic cardiac arrest if deemed clinically appropriate and suitable facilities and staff are available.

*“Like most things in life, you may not always succeed, but failure is usually guaranteed if you do not try.”*²⁶

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 31: Summary of procedure for initiation of dialysis during CPR.

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Prevention (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 is the best approach. Primary measures to prevent the development of hyperkalaemia in patients at risk is a key step. Patients with renal failure, heart failure and/ or diabetes have a high risk, particularly when treated with RAASi drugs. Cautious prescribing and blood monitoring is essential in these patients.

Preventing cardiac arrest in patients who have become hyperkalaemic is dependent on prompt recognition and treatment. The initial clinical presentation may be overshadowed by the acute illness, but severe hyperkalaemia is likely to be more immediately life-threatening. Limb weakness is an ominous sign. Look for toxic ECG changes which may precede cardiac arrest - wide QRS complex, bradycardia or sine wave (Guidelines 14.1-14.2; Figure 3), but some patients may have a normal ECG despite severe hyperkalaemia. The rationale for cardiac monitoring is to detect arrhythmias before cardiac arrest ensues, therefore a higher level of care is required.

Delays in treatment are well recognised and has resulted in patient harm.^{1,2} The potential for clinical deterioration may not be appreciated by medical or nursing staff prior to cardiac arrest. Time is frequently lost whilst awaiting repeat bloods to confirm hyperkalaemia even in the presence of renal failure and ECG changes. Refer for specialist advice early in patients with severe hyperkalaemia with ECG changes, end-stage renal disease, oliguric AKI, and in patients who do not respond to medical treatment.

Treat severe hyperkalaemia as a medical emergency.

IV calcium is a crucial step in the prevention of arrhythmias and cardiac arrest in hyperkalaemia.³ It is important to re-assess the ECG after administration of IV calcium as a further dose may be necessary if toxic changes persist. Vigilance is also required as toxic ECG changes may recur when the effects of the drug have worn off after approximately 30-60 minutes. IV calcium may buy time, but does not lower the serum K+. Therefore, other therapeutic measures should not be delayed.

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

The lack of blood monitoring after initiating medical treatment is a common pitfall in the management of hyperkalaemia. If the serum K+ is not repeated at approximately one hour after treatment when the drugs have taken its maximum effect, then the efficacy of treatment cannot be assessed. Patients who are refractory to medical treatment are potentially at risk of cardiac arrest. Furthermore, there is a tendency for rebound hyperkalaemia once the effects of insulin-glucose and salbutamol have worn off. Failure to repeat the serum K+ at 4-6 hours will miss this rebound and could result in arrhythmias or cardiac arrest. Rebound may also occur after dialysis and may be exaggerated if temporising drugs have been used.⁵

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.[6, 7]
- 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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Treatment Algorithm: Resuscitation (Guideline 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 (Guideline 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 7.

Lay summary

Hyperkalaemia is a medical disorder in which the potassium (K^+) level in the blood is raised. The higher the level, the greater the risk of life-threatening consequences. Hyperkalaemia may be mild ($K^+ 5.5 – 5.9 \text{ mmol/l}$), moderate ($K^+ 6.0 – 6.4 \text{ mmol/l}$) or severe ($K^+ \geq 6.5 \text{ mmol/l}$). Severe hyperkalaemia can affect muscle function in the limbs causing weakness, or in the heart causing potentially fatal heart rhythms. Therefore early recognition and treatment of hyperkalaemia can save lives.

The kidneys are largely responsible for removing potassium from the body, therefore the most common cause of hyperkalaemia is impaired kidney function. Some commonly prescribed drugs used to treat heart failure, kidney disease and diabetes mellitus can also contribute to hyperkalaemia, therefore regular blood monitoring is required.

Hyperkalaemia can occur in the community or in the hospital. Most cases of mild or moderate hyperkalaemia can be managed without the need for hospital admission unless it occurs in the setting of an acute illness. Hospital assessment is required for severe hyperkalaemia as prompt treatment may prevent adverse events. Hyperkalaemia detected in hospital may be present at the time of hospital admission or occur during the course of admission, therefore vigilance is required during acute illness.

The treatment for hyperkalaemia is evolving. Two new oral potassium lowering drugs (sodium zirconium cyclosilicate and patiromer) have recently been approved for specific indications by the National Institute for Health and Care Excellence (NICE). Insulin and glucose infusion remains the most effective emergency treatment, but hypoglycaemia (low blood glucose) is a common adverse event. A continuous infusion of glucose in patients with a low pre-treatment blood glucose level ($< 7 \text{ mmol/l}$) is now recommended.

Treatment algorithms are useful in many medical emergencies and have been applied to the treatment of hyperkalaemia in the community, in hospital and in resuscitation. Prevention of hyperkalaemia is the best approach. This requires careful drug prescribing, blood monitoring, a low potassium diet when indicated and the provision of patient information and education. Standardised protocols will provide a more consistent approach to treating hyperkalaemia and improve patient safety.

Appendices

- 1. Oral potassium lowering drugs**
- 2. Summary of clinical trials of oral potassium lowering drugs**
- 3. 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
- 4. ECG in Hyperkalaemia – sine wave.**
- 5. Algorithm – Management of Hyperkalaemia in the Community.**
- 6. Algorithm – Management of Hyperkalaemia in Hospital.**
- 7. Algorithm – Management of Hyperkalaemia in Resuscitation.**

Appendix 1: 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	2.5-30 g/day
Onset of effect	>4 hours	4-7 hours	1 hour
Efficacy	Unpredictable and variable	-1.01 mmol/l in 4 weeks [OPAL-HK]	- 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	1958	2015	2018
NICE Appraisal status	N/A	Pending	Approved

Comparison between potassium-binding agents for treatment of hyperkalaemia.

Appendix 2: Summary of clinical trials of 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

Appendix 3A: Drug administration and safety - IV calcium preparations

Calcium Chloride	
Available as	<ul style="list-style-type: none"> Calcium chloride 10% pre-filled syringe 10mL (contains 6.8mmol of calcium in 10mL)
Preparation	<ul style="list-style-type: none"> Can be used undiluted
Flush solutions	<ul style="list-style-type: none"> Flush well with sodium chloride 0.9% to reduce vein irritation. Incompatible with many solutions (including sodium bicarbonate and phosphate).
Administration	<ul style="list-style-type: none"> Give by intravenous injection over 3-5 minutes. Give as a bolus injection during resuscitation. Preferably administer via a central venous device (if already in-situ). For peripheral administration, choose a large vein and monitor closely for phlebitis. Ensure patient is supine and closely observed during injection. Monitor ECG and blood pressure.
Specialist technical information	<ul style="list-style-type: none"> Extravasation can cause tissue damage because of the high osmolarity.
Cautions and side effects	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Calcium gluconate 10% ampoules (contains 2.2mmol of calcium in 10mL)
Preparation	<ul style="list-style-type: none"> Can be used undiluted.
Flush solutions	<ul style="list-style-type: none"> Flush well with sodium chloride 0.9% or glucose 5% to avoid vein irritation. Incompatible with many solutions (including sodium bicarbonate and phosphate).
Administration	<ul style="list-style-type: none"> The rate of administration should not exceed 2mL per minute (equivalent to 10mL of undiluted injection over 5 minutes). For peripheral administration, choose a large vein and monitor closely for phlebitis. Ensure patient is supine and closely observed during injection. Monitoring ECG and blood pressure.
Specialist technical information	<ul style="list-style-type: none"> Extravasation can cause tissue damage because of the high osmolarity.
Cautions and side effects	<ul style="list-style-type: none"> Cautions: - Hypercalcaemia. Digoxin. Side-Effects: - Administer slowly to minimise peripheral vasodilation, cardiac depression and circulatory collapse

References

1. Electronic Medicines Compendium (2018) 'Summary of Product Characteristics – Calcium Gluconate Injection BP – Hameln Pharmaceuticals Ltd'. Available at <https://www.medicines.org.uk/emc/product/6264/smpc>. Accessed on 06.05.19.
2. Injectable Medicines Guide. Monograph for Calcium gluconate. Version 6 05.02.2019. Available at <http://www.injguide.nhs.uk/IVGuidePrint.asp?Drugno=3225&format=3>. Accessed 06.05.2019
3. Guidelines and Audit Implementation Network (2014) Guidelines for the treatment of hyperkalaemia in adults. Belfast, GAIN.
4. Injectable Medicines Guide. Monograph for Calcium chloride. Version 5 22.06.2016. Available at. <http://www.injguide.nhs.uk/IVGuidePrint.asp?Drugno=2562&format=3> Accessed 06.05.2019
5. Electronic Medicines Compendium (2018) 'Summary of Product Characteristics – Calcium Chloride Intravenous Infusion 10% w/v – Martindale Pharma'. Available at <https://www.medicines.org.uk/emc/product/4126/smpc> Accessed 06.05.2019
6. University College London Hospitals NHS Foundation Trust. Injectable Medicines Administration Guide. 3rd edition. 2010. Wiley-Blackwell. Chichester.

Appendix 3B: 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	<ul style="list-style-type: none"> 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.
Concentration of final solution	10 units soluble insulin in 50mL
Dilution/flush solutions	Sodium chloride 0.9% - flush well to reduce vein irritation
Administration	<p>IV Injection: Administered over 5-15 minutes intravenously into a large vein</p> <p>Monitor for phlebitis if 50% glucose is given peripherally.</p>
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	<ul style="list-style-type: none"> 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.

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 (2017) '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>. Accessed 29.04.2019
2. Electronic Medicines Compendium (2018) '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>. Accessed 29.04.2019
3. Guidelines and Audit Implementation Network (2014) Guidelines for the treatment of hyperkalaemia in adults. Belfast, GAIN.
4. Injectable Medicines Guide. Monograph for Insulin (soluble) Human. Version 5 22.01.2019. Available at <http://www.injguide.nhs.uk/IVGuidePrint.asp?Drugno=2612&format=3>. Accessed 29.04.2019

Appendix 3C: Drug administration and safety - Salbutamol

Salbutamol Nebulised Solution	
Available as	<ul style="list-style-type: none"> • 2.5mg/2.5mL nebuliser solution • 5mg/2.5mL nebuliser solution
Administration	<ul style="list-style-type: none"> • 10mg DOSE <ul style="list-style-type: none"> = 10ml of 2.5mg/2.5mL nebuliser solution. = 5ml of 5mg/2.5mL nebuliser solution. • 20mg DOSE <ul style="list-style-type: none"> = 10ml of 5mg/2.5mL nebuliser solution. • Use a face mask or T-piece.
Cautions and side effects	<ul style="list-style-type: none"> • Cautions: <ul style="list-style-type: none"> – Consider only giving 10mg in patients with ischaemic heart disease. – Tachyarrhythmia – Open angle glaucoma • Side-Effects: <ul style="list-style-type: none"> – Tremor – Tachycardia – Headache

References

1. Guidelines and Audit Implementation Network (2014) Guidelines for the treatment of hyperkalaemia in adults. Belfast, GAIN.
2. Electronic Medicines Compendium (2016) 'Summary of Product Characteristics – Ventolin Nebules – GlaxoSmithKline UK. Available at <https://www.medicines.org.uk/emc/product/8256/smpc>. Accessed 06.05.2019

Appendix 3D: Drug administration and safety – Patiromer

▼ Patiromer	
Available as	8.4g, 16.8g and 25.2g sachets
Preparation	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Apple juice or cranberry juice can be used instead of water to prepare the mixture (be aware of potential interactions with cranberry juice). Other liquids should be avoided due to potential potassium content. Should be taken with food. Administration should be separated by 3 hours from other medicines.
Storage and handling	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Cautions – Hypercalcaemia, hypomagnesaemia, GI disorders, contains sorbitol. Side-effects – Hypomagnesaemia, constipation, diarrhoea, abdominal pain and flatulence

▼ Black label medicine subject to additional monitoring to allow quick identification of new safety information. Report all suspected adverse reactions.

References

1. Electronic Medicines Compendium (2017) ‘Summary of Product Characteristics – Veltassa (Patiromer) – Vifor Fresenius Medical Care Renal Pharma UK Ltd’. Available at <https://www.medicines.org.uk/emc/product/779> accessed 03.05.2019.
2. Joint Formulary Committee. *British National Formulary* (online) London: BMJ Group and Pharmaceutical Press. Available at <http://www.medicinescomplete.com> accessed 03.05.2019

Appendix 3E: Drug administration and safety – Sodium zirconium cyclosilicate

▼ Sodium Zirconium Cyclosilicate	
Available as	5g, 10g sachets (powder oral suspension)
Preparation	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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 if hypokalaemia develops (serum K⁺ < 4.0 mmol/l)
Cautions and side effects	<ul style="list-style-type: none"> Cautions – can cause QT interval lengthening as a result of a reduction in serum potassium. May be opaque to X-rays – consider if having abdominal X-rays. Side effects – Hypokalaemia, oedema, gastrointestinal disorders.

▼ Black label medicine subject to additional monitoring to allow quick identification of new safety information. Report all suspected adverse reactions.

References

1. Electronic Medicines Compendium (2019) 'Summary of Product Characteristics – Lokelma 10g powder for oral suspension – AstraZeneca UK Limited'. Available at <https://www.medicines.org.uk/emc/product/10074/smpc>. Accessed 03.05.2019.

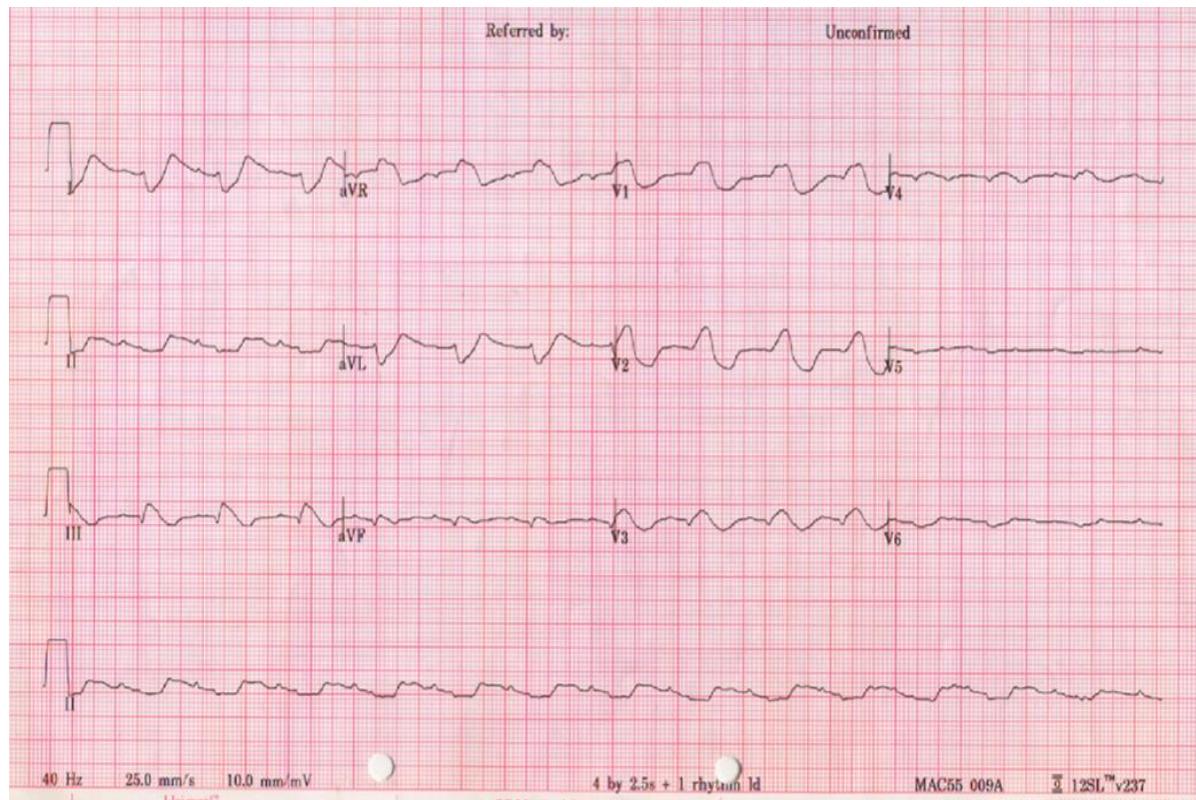
Appendix 3F: Drug administration and safety – Calcium resonium

Calcium Resonium	
Available as	Calcium Resonium Powder (99.934%)
Preparation	<ul style="list-style-type: none"> • Oral administration:- <ul style="list-style-type: none"> ○ 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 <ul style="list-style-type: none"> ○ 30g of resin should be mixed with 150mL of water or glucose 10% as a daily retention enema.
Administration	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Contra-indicated in hypercalcaemia or in obstructive bowel disease. • Concomitant use with sorbitol is not recommended due to gastrointestinal stenosis and intestinal ischaemia.

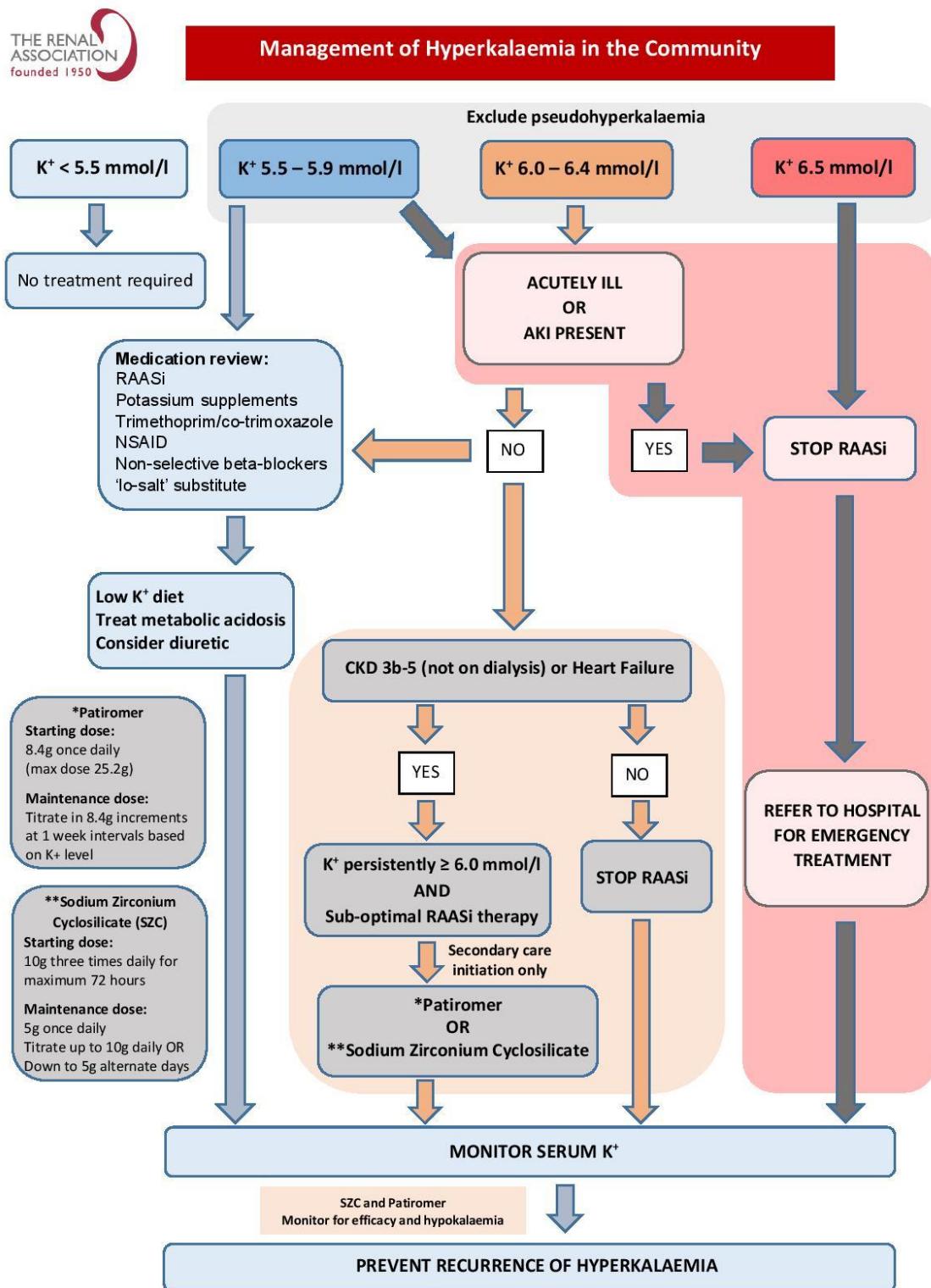
References

1. Electronic Medicines Compendium (2018) '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>. Accessed 06.05.2019

Appendix 4 – Sine wave ECG



Appendix 5 – Hyperkalaemia Algorithm - Community

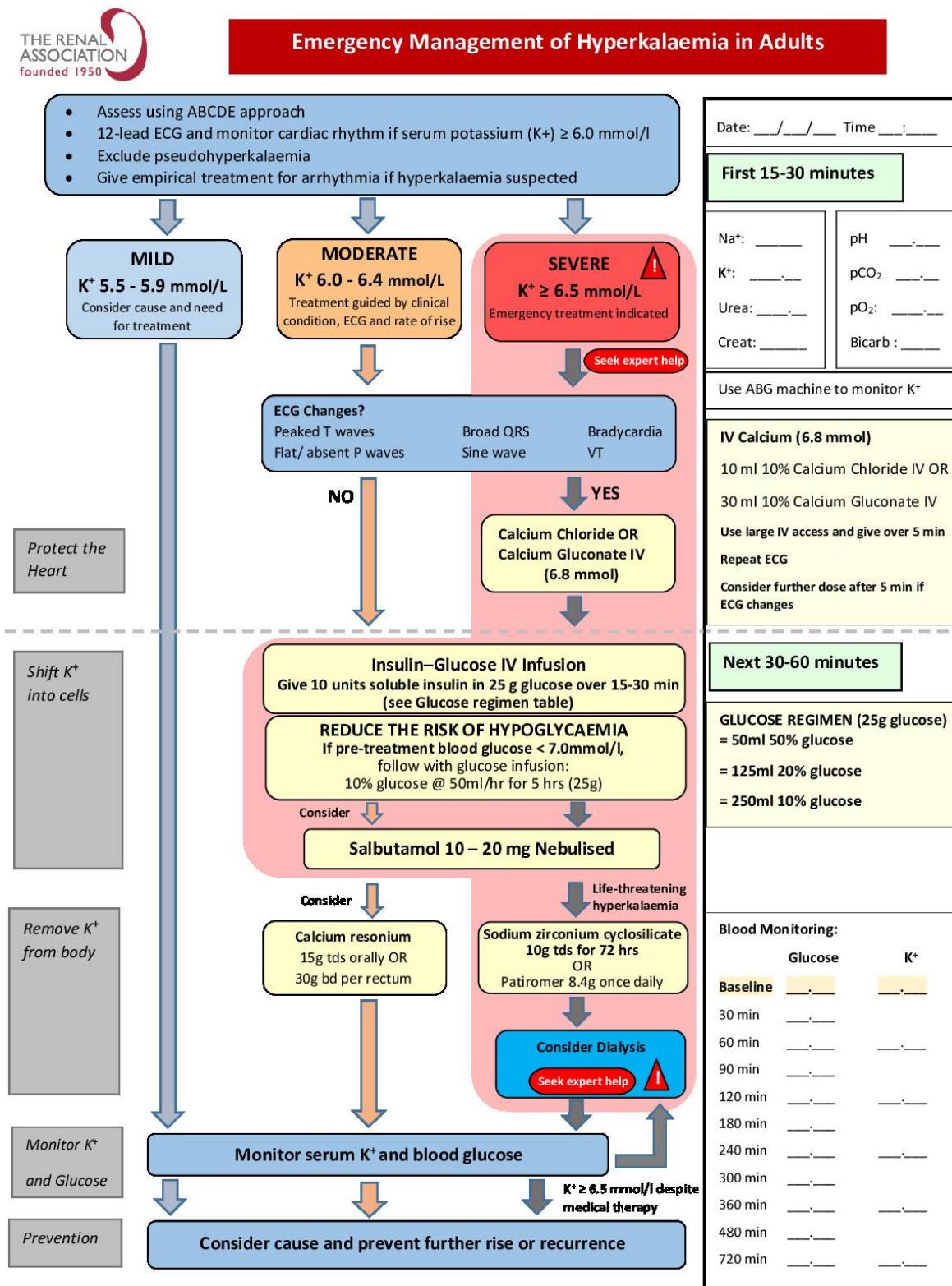


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The Renal Association UK

Appendix 6 – Hyperkalaemia Algorithm – Hospital



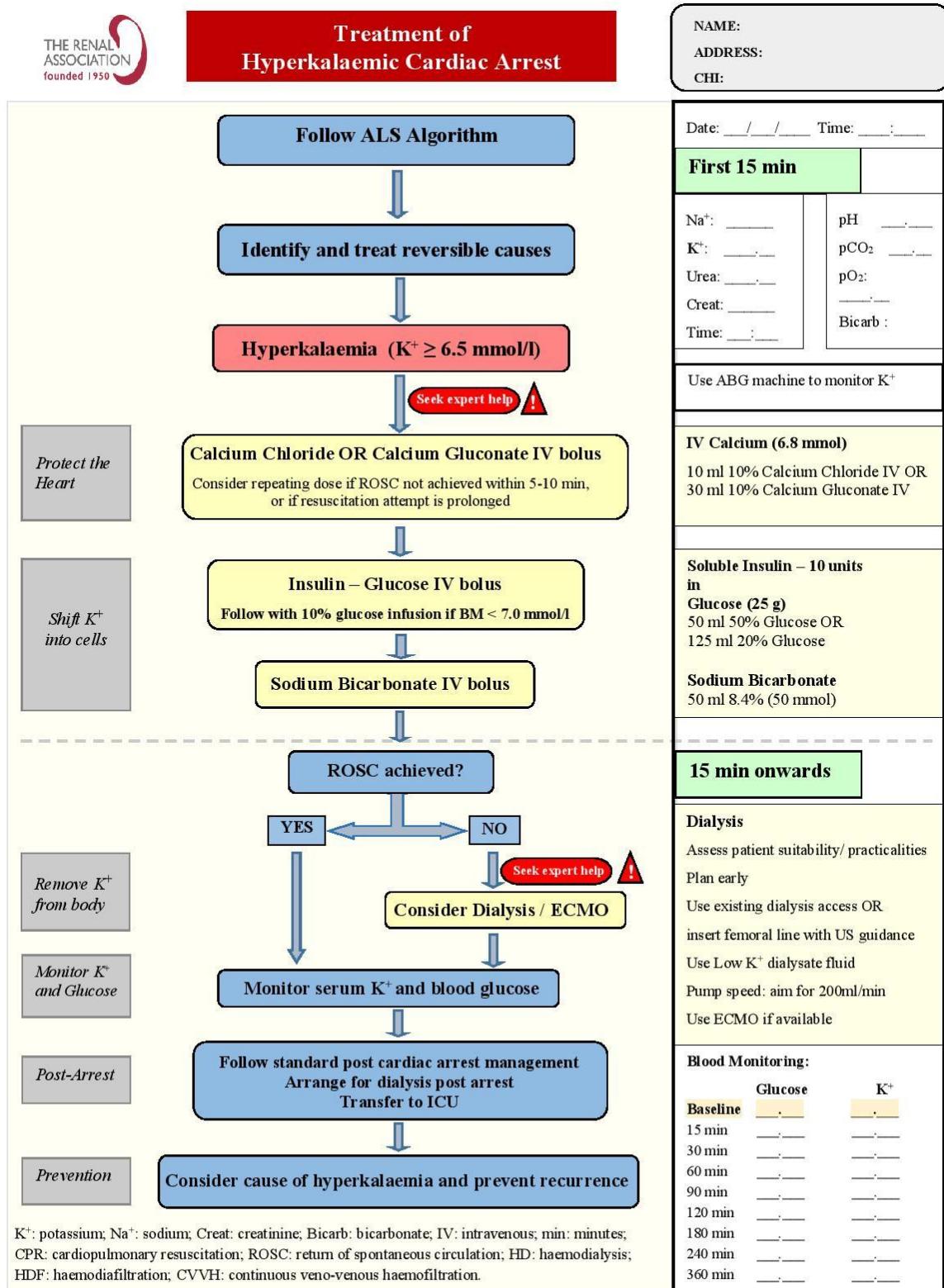
K^+ : potassium; Na^+ : sodium; Creat: creatinine; Bicarb: bicarbonate; max - maximum

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The Renal Association UK

Appendix 7 – Hyperkalaemia Algorithm – Resuscitation



K⁺: potassium; Na⁺: sodium; Creat: creatinine; Bicarb: bicarbonate; IV: intravenous; min: minutes; CPR: cardiopulmonary resuscitation; ROSC: return of spontaneous circulation; HD: haemodialysis; HDF: haemodiafiltration; CVVH: continuous veno-venous haemofiltration.

Publication Date: 1.07.20

Review Date: 1.07.25

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
FICM	Faculty of Intensive Care Medicine
GCS	Glasgow coma scale
GFR	Glomerular filtration rate
HBP	Hypertension
HD	Haemodialysis
HDF	Haemodiafiltration
HDU	High dependency unit
HF	Haemofiltration
HFrEF	Heart failure with reduced ejection fraction
HK	Hyperkalaemia
HR	Hazard ratio
Hypo	Hypoglycaemia
ICS	Intensive Care Society
ICU	Intensive Care Unit
IEC	International Electrotechnical Committee
IHCA	In-hospital cardiac arrest
IHD	Intermittent haemodialysis
ILCOR	International Liaison Committee on Resuscitation
IV	Intravenous
K ⁺	Potassium ion
KDOQI	Kidney Disease Outcomes Quality Initiative
MET	Medical emergency team
Mg ⁺	Magnesium ion
MHRA	Medicines and Healthcare products Regulatory Agency
MRA	Mineralocorticoid receptor antagonist
Na ⁺	Sodium ion
NA	Not available
NCEPOD	National Confidential Enquiry into Patient Outcome and Death.

NEWS	National Early Warning Score
NHS	National Health Service
NI	Not included
NICE	National Institute for Health and Care Excellence
NSAIDS	Non-steroidal anti-inflammatory drugs
OHCA	Out-of-hospital cardiac arrest
OR	Odds ratio
PEA	Pulseless electrical activity
POCT	Point of care testing
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
USA	United States of America
USRDS	United States Renal Data System
VF	Ventricular fibrillation
VT	Ventricular tachycardia