

Current treatment and unmet needs of hyperkalaemia in the emergency department

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Hyperkalaemia is a common electrolyte abnormality and can cause life-threatening cardiac arrhythmia. Even though it is common in patients with diabetes, heart failure, and kidney disease, there is poor consensus over its definition and wide variability in its treatment. Medications used to treat hyperkalaemia in the emergent setting do not have robust efficacy and safety data to guide treatment leading to mismanagement due to poor choice of some agents or inappropriate dosing of others. Moreover, the medications used in the emergent setting are at best temporizing measures, with dialysis being the definitive treatment. New and old k binder therapies provide means to excrete potassium, but their roles are unclear in the emergent setting. Electrocardiograms are the corner stones of hyperkalaemia management; however, recent studies show that they might manifest abnormalities infrequently, even in severe hyperkalaemia, thus questioning their role. With an aging population and a rise in rates of heart and kidney failure, hyperkalaemia is on the rise, and there is a need, now more than ever, to understand the efficacy and safety of the current medications and to develop newer ones.

Introduction

Hyperkalaemia is a potentially life-threatening electrolyte disorder, most commonly occurring in patients with chronic kidney disease (CKD), diabetes mellitus (DM), and heart failure (HF).^{1,2} It is present in up to 10% of hospitalized patients, where it is most often associated with renal failure or drugs that alter potassium excretion.³⁻⁶ Hyperkalaemia is a common cause for emergency haemodialysis and is associated with increased risk of sudden cardiac death in patients with end-stage renal disease.⁷

There is no agreed definition of hyperkalaemia. Levels above 5.0 mmol/L are associated with increased mortality, and serum potassium greater than 5.5 mmol/L is generally

accepted as the level which requires immediate intervention.⁸ What constitutes moderate or severe hyperkalaemia has been inconsistently defined in the literature.⁹ The European Resuscitation Council recommends the stratification of hyperkalaemia into mild (5.5-5.9 mmol/L), moderate (6.0-6.4 mmol/L), and severe (>6.5 mmol/L) to aid clinical decision-making.¹⁰ Although the presence of moderate hyperkalaemia is often asymptomatic, severe hyperkalaemia can impair cardiac function and have life-threatening consequences.^{5,11-13} Hence, serum potassium levels of greater than 6.5 mmol/L, or any elevated level associated with the electrocardiogram (ECG) manifestations of hyperkalaemia are recommended as thresholds for initiation of emergency therapy.^{14,15}

Emergency treatment approaches are largely based on small studies and anecdotal experience leading to wide

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variability in the choice of drug and the dosages to use. In one study evaluating hyperkalaemia therapy, more than 140 different therapeutic strategies were utilized.¹⁶ Moreover, despite hyperkalaemia being a potentially life-threatening condition encountered commonly in both out- and inpatient settings, there is limited randomized evidence to guide treatment. This may explain the observed variability in the treatment of patients with hyperkalaemia.⁶ Uniform guidance on the treatment of hyperkalaemia based on the best available evidence is therefore needed.

This article reviews the common medications used to treat acute hyperkalaemia, the role of the ECG in its management, highlights the variability in practice patterns, and the lack of guidelines for the treatment of acute hyperkalaemia. Lastly, an acute hyperkalaemia emergency treatment algorithm is proposed, incorporating the most contemporary data.

Current treatments of hyperkalaemia

The current treatment of hyperkalaemia in the emergency department (ED) varies considerably because available pharmacologic agents have limited data supporting their efficacy.^{6,17} A recent Cochrane review of ED management of hyperkalaemia highlighted the limitations of the available studies and the lack of large data sets to support robust recommendations.¹⁸ Nonetheless, the United Kingdom Renal Association has developed clinical practice guidelines for the treatment of acute hyperkalaemia.¹³ Following are the commonly used agents for the treatment of hyperkalaemia in the emergent setting. In essence, a three-fold approach to the treatment of hyperkalaemia is currently adopted by clinicians:

- (1) Stabilization of the cardiac membranes using intravenous calcium. The immediate goal of acute management in hyperkalaemia is the stabilization of the membrane potential, with or without changing the serum potassium concentration;
- (2) Redistribution of potassium using intravenous insulin and beta-2 agonist. These pharmacologic therapies induce temporary but rapid redistribution of potassium into the intracellular space; and
- (3) Elimination of potassium from the body via haemodialysis, sodium-potassium exchange resin binders and diuretics.

Calcium

The effect of potassium on myocytes is counter balanced by the concurrent calcium concentration such that intravenous calcium antagonizes hyperkalaemia induced cardiac membrane excitability and protects the heart against arrhythmias.¹⁹ It is usually effective within minutes, as noted by an improvement in the ECG appearance or reversal of ECG abnormality. It is generally accepted that intravenous (IV) calcium is indicated for potentially life-threatening ECG changes (absent P waves, wide QRS, sine-wave pattern),^{10,18,20-22} arrhythmias, or cardiac arrest.²³ The dose can be repeated, if there is no effect within 5-10 min.

The use of IV calcium for treating fatal arrhythmias in the setting of hyperkalaemia is well published, but is not

based on robust evidence. The toxic effects of potassium on myocytes, and its reversal by calcium, were first demonstrated in animal models.^{24,25} Later, IV calcium was shown to be effective in treating patients with acute kidney injury during the Korean War.²⁶ Although the bulk of evidence supporting the use of calcium comes from case reports and anecdotal experience,²⁷ there is little doubt that calcium is an important and life-saving agent in the emergency treatment of hyperkalaemia.

Some adverse effects of intravenous calcium are peripheral vasodilation, hypotension, bradycardia, and arrhythmias.²⁸ A more serious adverse effect of IV calcium is tissue necrosis if extravasation occurs. This can be avoided if calcium gluconate is used, which is considered less toxic on peripheral veins. Historically, caution has been advised with administration of IV calcium in patients with known or suspected digoxin toxicity because of case reports of death in this context.²⁹⁻³¹ On the contrary, there are also reports showing no adverse effects of IV calcium administration in the presence of unrecognized digoxin toxicity.^{32,33} Furthermore, a recent retrospective study of 23 patients receiving IV calcium in the setting of digoxin toxicity has shown no increased risk of arrhythmia or mortality.³⁴

Insulin/dextrose

A combination of insulin and glucose is the mainstay of hyperkalaemia treatment in the acute setting. Insulin lowers serum potassium by activating sodium-potassium ATPase (Na-K ATPase) and by moving sodium out of the cell in exchange for the movement of potassium into the cell.³⁵ Serum potassium concentration can start to decrease within 15 min of administering insulin.^{21,36} Multiple small studies have shown the efficacy of insulin in treating hyperkalaemia, and that its effect may last several hours.^{18,37-41}

The main risk of insulin-glucose therapy is hypoglycaemia. This risk is dependent on the dose of insulin and glucose administered, with the incidence of hypoglycaemia ranging from 11% to 75%.^{21,38,39,42-46} A recent ED study found the rate of symptomatic hypoglycaemia occurring as a result of insulin therapy for hypoglycaemia was 17%.¹⁶ While uraemia may blunt the hypoglycaemic effect of insulin,⁴⁷ because of renal insulin metabolism, patients with kidney failure may experience hypoglycaemia up to 6 h after treatment.⁴⁸⁻⁵⁰ Therefore, glucose monitoring is recommended for several hours after insulin administration in patients with renal failure.⁵⁰

Beta-2 agonists

Beta-2 adrenergic receptor agonists promote the translocation of potassium into the cell by activation of the Na-K ATPase pump. Salbutamol and other beta-agonists are equally effective given intravenously or via a nebulizer.^{18,51,52}

The effect of intravenous or nebulized salbutamol is dose-dependent,⁴³ with an onset of action within 30 min, and a peak effect within 60 min. Nebulized salbutamol is given in doses of 10 or 20 mg. It decreases serum potassium by approximately 1 mmol/L^{36,38,43} and lasts for at least 2 h.^{43,52,54}

Salbutamol may be ineffective in some hyperkalaemic patients, for which the mechanism of resistance is not understood.^{36,43} Non-selective beta-blockers may prevent the hypokalaemic response to salbutamol,⁴⁴ although, one study showed that even in the absence of beta-blocker use, up to 40% of patients may not respond to salbutamol.⁴⁵ Common side effects are tremor, palpitations, and headache. Mild hyperglycaemia has also been reported,^{36,42,53} and thus there may be a protective role against insulin-induced hypoglycaemia when used simultaneously.³⁸

Sodium bicarbonate

Sodium bicarbonate infusion promotes uptake of potassium into skeletal muscle by favouring sodium bicarbonate cotransport and sodium-hydrogen exchange which, by increasing intracellular sodium, increases Na-K ATPase activity.⁵⁴

In 1959, Schwarz *et al.*⁵⁵ showed that an infusion of sodium bicarbonate lowered serum potassium in four patients with severe acidosis. Since then, bicarbonate has often been the first-line treatment for acute hyperkalaemia.⁵⁶ More recent studies have demonstrated little effect on potassium in stable haemodialysis patients, and thus it has fallen out of favour.^{21,57-60} However, bicarbonate therapy may be beneficial for patients with metabolic acidosis.^{61,62} Overall, there is currently insufficient evidence to support the use of intravenous sodium bicarbonate for the acute treatment of hyperkalaemia and should be used with caution since it can cause sodium and fluid overload.¹⁸

Cation-exchange resin

Cation-exchange resins are cross-linked polymers with negatively charged structural units that can exchange bound sodium or calcium for cations, including potassium. They are taken orally or introduced rectally and excreted via the gastrointestinal tract. Since the cation exchange is based on competitive binding, the resin works most effectively in the colon where there is an abundance of potassium. Thus, treatment with resins is effective only in the chronic setting because of the prolonged transit time to the colon where it binds potassium optimally. However, because of the lack of options to excrete potassium in the anuric patients their use is prevalent.

Sodium polystyrene sulfonate (SPS)

There is limited prospective data on the use of SPS. In 1961, Scherr *et al.*⁶³ evaluated 32 hyperkalaemic patients and reported 23 had mean potassium reduction of 1.0mmol/L in the first 24h of treatment. Nasir and Ahmad⁶⁴ randomized 97 CKD patients to SPS or calcium polystyrene sulfonate (CPS) and reported a 1.5 and 1mmol/L potassium decrease after 3 days of treatment with SPS and CPS, respectively. Lastly, Lepage *et al.*⁶⁵ evaluated 33 mildly hyperkalaemia CKD patients in a double-blind randomized trial and found 30g of SPS administered o.d. for 7 days was superior to placebo in reducing serum potassium within 1 week.

Common adverse events of SPS are nausea, vomiting, diarrhoea, abdominal bloating and cramps, anorexia, electrolyte imbalance (e.g. hypokalaemia), and possibly

elevated diastolic blood pressure.^{64,66} A drug-drug interaction is another concern. A more serious adverse event is bowel necrosis and subsequent death. Although this is rare and actual rate of occurrence is unknown, a systematic review documented 58 cases of bowel necrosis, with 33% mortality associated with SPS use.^{67,68}

Patiromer

Patiromer is the newest resin cleared by the FDA. It is a calcium exchange resin with more robust data to show efficacy and safety as compared to SPS. PEARL-HF was a double-blinded, placebo-controlled study, whose focus was on HF patients with an indication to start spironolactone.⁶⁹ Patiromer lowered potassium levels and also enabled more patients to be on 50 mg of spironolactone compared to the placebo group.

OPAL-HK was a 12-week evaluation of the efficacy and safety of patiromer in patients with CKD on Renin-Angiotensin-Aldosterone-System inhibitor (RAASI) therapy and with hyperkalaemia.⁷⁰ At the end of the study, more patients on patiromer (94% vs. 44%) were able to be continued on RAASI therapy compared to placebo. AMETHYST-DN was a 52-week safety and efficacy evaluation of patiromer in patients with hyperkalaemia and diabetic nephropathy.⁷¹ This multicentre, dose-titration study evaluated the optimal starting and maintenance doses of patiromer and reported a superior potassium reduction from baseline to Week 4 in all groups.

Patiromer is generally well tolerated both acutely and on a long-term basis.^{68,72} Common adverse symptoms are related to the gastrointestinal system, with constipation occurring in 7.2% and hypomagnesaemia occurring in 5.3%.⁷³ Lastly, animal data showed that patiromer may interact with certain positively charged drugs and reduce their bioavailability by 30%.^{73,74} This was further investigated in healthy adults, and it was determined that patiromer when co-administered decreased the bioavailability of three drugs: ciprofloxacin, levothyroxine, and metformin. However, there was no interaction with patiromer if these drugs were taken 3 h apart.⁷³

Role of electrocardiogram in hyperkalaemia treatment

The myocardial membrane potential is established by the potassium concentration gradient across the cellular membrane. Hence, rise in extracellular potassium concentration has profound effects upon myocyte function.⁷⁵ Hyperkalaemia decreases the transmembrane potassium gradient leading to increased potassium conductance, and this shortens the duration of the action potential.⁷⁶ In turn, the repolarization time is shortened which is responsible for some of the early ECG manifestations of hyperkalaemia, such as ST-T segment depression, peaked T waves, and Q-T interval shortening.^{77,78} As potassium levels continue to rise, prolongation of the PR and QRS duration occur.⁷⁶⁻⁷⁸ Other common ECG manifestations include a diminished P-wave, QRS widening, and ultimately a wide-complex 'sine-wave' that may progress to asystole or ventricular fibrillation.⁷⁹⁻⁹⁰ Because of these observations, it is recommended

to obtain an ECG early in the evaluation of patients with hyperkalaemia.^{13,79,91}

Although the ECG is useful in assessing hyperkalaemia, the relationship between electrocardiographic changes and clinical outcomes is not clear.⁹²⁻⁹⁵ Acker *et al.* evaluated patients with serum potassium ranging between 6 and 9.3 mmol/L and found only 46% of ECGs had findings consistent with hyperkalaemia, and no patient experienced serious arrhythmias.⁶ Moreover, there are multiple case reports of patients with markedly elevated potassium levels, as high as 8.3 mmol/L without significant ECG changes.^{92,96} Attempts to quantify ECG alterations associated with hyperkalaemia by analysing various ECG parameters have provided mixed results.^{93,97-101} While most clinicians tend to believe that the inconsistent ECG manifestations are due to myocyte adaption from chronic hyperkalaemia, a recent study has shown that acute and chronic hyperkalaemia may have similar rates of ECG abnormalities.¹⁰² Finally, Wrenn *et al.* showed that physician interpretation of the ECG resulting in the diagnosis of hyperkalaemia has a sensitivity of less than 50%.¹⁰³ In light of all these studies, the clinical role of the ECG is poorly defined. It is recommended to obtain an ECG to evaluate for arrhythmia; however, a lack of changes consistent with hyperkalaemia should not preclude treatment.^{13,17}

Unmet need

There is mounting evidence that hyperkalaemia is associated with an increase in all-cause mortality.^{5,104} In one retrospective analysis of 245 808 veterans, Einhorn *et al.*⁵ found an increased risk of mortality within 1 day of a hyperkalaemic event. In another study, Goyal *et al.* analysed the Cerner Health Facts database of 38 689 patients with confirmed acute myocardial infarction (AMI). Potassium was found to have a U-shaped distribution with in-hospital mortality.¹⁰⁵ Mean post-admission serum potassium between 3.5 and 4.5 mmol/L resulted in the lowest mortality, while mortality was twice as high for potassium of 4.5 to <5.0 mmol/L and even greater for higher potassium levels. Finally, Singer *et al.*¹⁰⁶ reported a similar U-shaped mortality curve on 100 260 ED visits as shown in *Figure 1*.

Even though hyperkalaemia is associated with increased mortality in and out of hospital, there is no accepted guideline and treatment in the ED is provider dependent.^{16,107} A recent multicentre study in the United States found that 43 different treatment combinations were used in the first 4 h of treatment of hyperkalaemia in the ED.¹⁶ This underscores the lack of treatment protocols and the consequent variability in hyperkalaemia treatment.

It is worth noting that, with the exception of haemodialysis and resin therapy, medical management only translocates serum potassium to the intracellular space and does not eliminate it from the body. This is helpful to protect the patient from potential arrhythmia but is only a temporizing measure. Moreover, there is sparse data on these agents in terms of efficacy, safety, dosing, and duration of action. Hence, more studies are needed to understand the current anti-hyperkalaemia agents and also develop newer agents to eliminate potassium in the emergent setting.

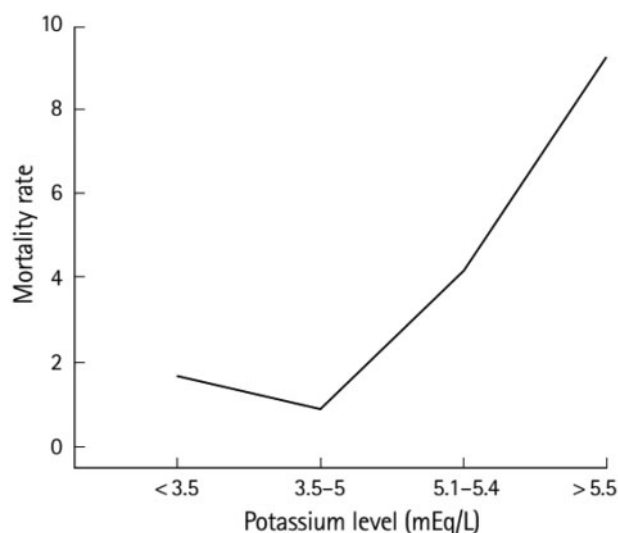


Figure 1 Association between potassium level and mortality. Adapted from Singer *et al.*¹⁰⁶ This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial Licence.

Clearly, there is an unmet need for better and safer treatment options for acute hyperkalaemia.

Hyperkalaemia protocol

Even though hyperkalaemia can cause potentially fatal arrhythmias, its treatment varies considerably because of lack of standardized guidelines. A systematic approach synthesizing the current evidence may reduce the variability seen in hyperkalaemia treatment, optimize patient outcomes, and reduce adverse events. Here, we propose an algorithm that is adapted from recently published algorithms^{107,108} and guidelines¹³ and also incorporates the most up to date evidence available on oral binders and hypoglycaemia rates from insulin use. It is divided into four steps:

- (1) Assess pre-test probability (verify results)
- (2) Assess severity (determine myocardial involvement)
- (3) Provide treatment
- (4) Reassess.

The treatment algorithm (*Figure 2*) emphasizes several key points. First, the verification of results and the decision to treat should depend on pre-test probability of hyperkalaemia and be independent of ECG findings which are insensitive to serum potassium. Evaluating the potassium level in the context of the disease burden (pre-test probability) will help distinguish true from pseudo-hyperkalaemia resulting from haemolyzed samples. Second, assessment of myocardial involvement should include both depolarization (PR amplitude, PR length, QRS duration, bundle branch, and fascicular blocks) and repolarization (ST segment, T wave amplitude, and shape) aspects of the ECG and not just peak T-wave and wide QRS. Third, if myocardial involvement is found, calcium should be given immediately and repeated till ECG changes improve, since the adverse effect from hypercalcemia is potentially less

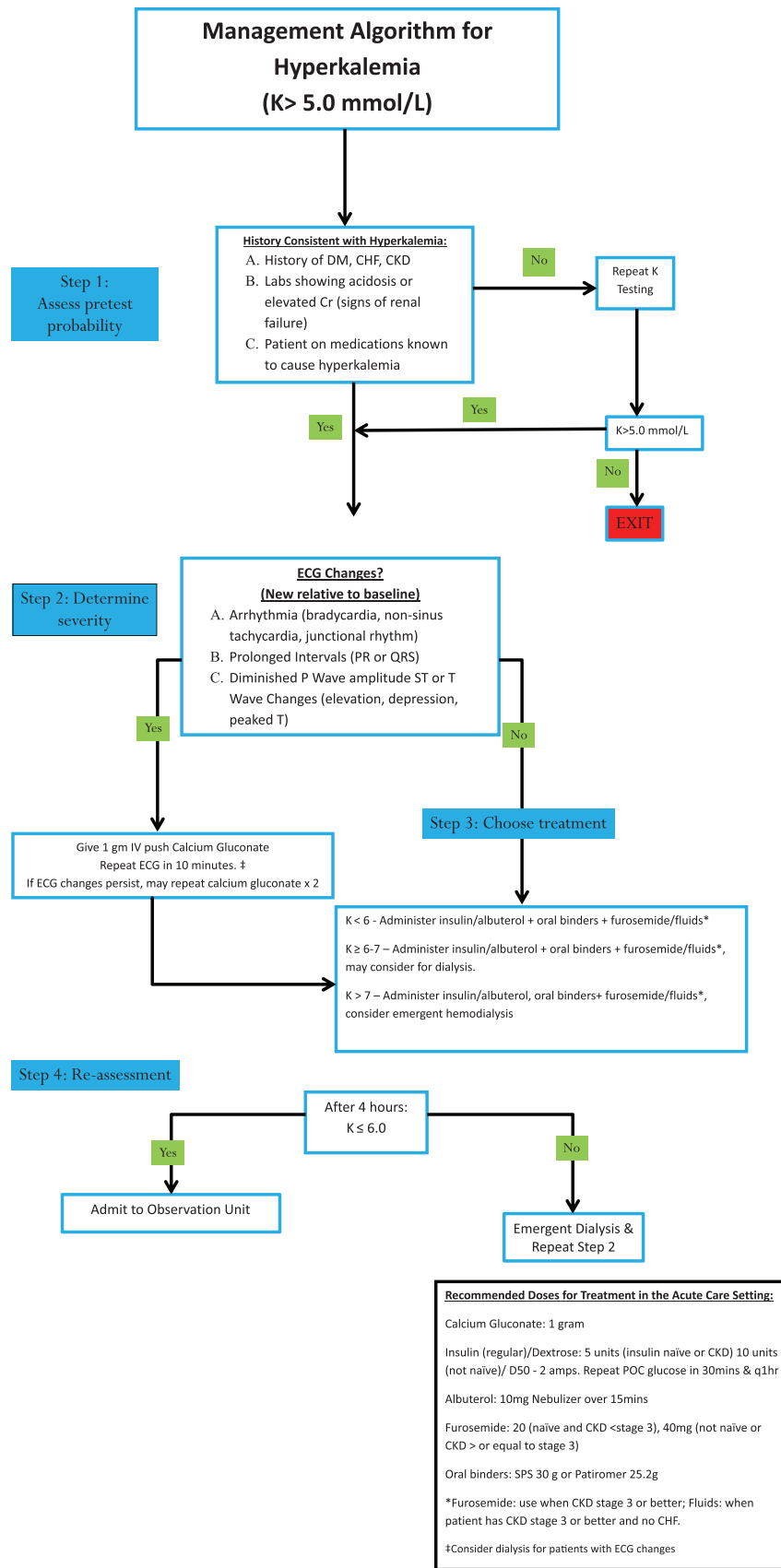


Figure 2 Hyperkalaemia management algorithm proposed by authors. CHF, congestive heart failure; CKD, chronic kidney disease; Cr, creatinine; DM, diabetes mellitus; ECG, electrocardiogram; K, potassium.

Table 1 Duration of effect of insulin in the treatment of hyperkalaemia

Author of study	Insulin dose (units)	Glucose dose (g)	Duration of effect (min)
Ngugi <i>et al.</i> ³⁸	10	25	>360
Lens <i>et al.</i> ³⁹	10	40	>360
Duranay <i>et al.</i> ⁴⁰	10	30	>360
Mahajan <i>et al.</i> ⁴¹	12	25	>360

severe compared to impending life-threatening arrhythmia from hyperkalaemia. Fourth, sodium bicarbonate has limited utility in acute treatment of hyperkalaemia since current evidence does not support its use in the absence of acidosis. Fifth, lower amount of insulin or higher dextrose content is recommended to reduce hypoglycaemia. Furthermore, hypoglycaemia should be monitored for up to 6 h after insulin use in patients with CKD.⁵⁰ Sixth, a combination therapy of insulin and albuterol may reduce serum potassium to a greater extent and also reduce the risk of hypoglycaemia.¹⁸ Seventh, as the hypokalaemic effects of insulin and albuterol decline by 4 h, reassessment and repeat treatment may be necessary. Although, the precise duration of effect of insulin has been controversial, several studies have shown the insulin may be effective in excess of 6 h (Table 1).³⁸⁻⁴¹ Lastly, a key limitation of this algorithm, just like any other published algorithms or guidelines,^{13,107,108} is the fact that it has no outcome data and even though we incorporated the most up to date evidence, it should be followed with the same caution as used with the other ones.

Summary

Hyperkalaemia is a common electrolyte abnormality in patients with CKD, HF, and DM and is reported in up to 10% of hospitalized patients.⁶ Recent studies suggest that hyperkalaemia may be an independent predictor of mortality.^{5,105,106} Hyperkalaemia may be regarded as the 'silent killer'¹⁰⁹ since the symptoms are non-specific,⁷⁹ and the ECG is often non-diagnostic.^{94,103}

Current therapeutic options in the acute setting are limited to shifting potassium, and do not provide definitive treatment. Moreover, the lack of robust efficacy and safety data, together with paucity of guidelines, has left hyperkalaemia treatment up to individual practitioners with much variability and without consistency. This has allowed not only the use of agents like sodium bicarbonate and SPS (which have little value in the acute setting) but also inappropriate doses of insulin and albuterol resulting in decreased efficacy or increased side effects. Therefore, more studies examining the existing therapies and evaluating new therapies are needed for the ED management of hyperkalaemia.

The protocol proposed here incorporates the most up to date evidence on therapeutic options available in the ED. If clinicians adopted one and treated hyperkalaemia uniformly that would be a significant leap forward in

understanding the efficacy and safety of current options and optimizing their use. The rising prevalence of HF, DM, and CKD and the increasing use of RAASIs and MRAs have increased the incidence of hyperkalaemia,¹¹⁰⁻¹¹² and have made the need for therapeutic options more urgent. There is clearly a need to understand the current options and develop better and safer treatment for acute hyperkalaemia.

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