REVIEW PAPER

Potassium disorders—clinical spectrum and emergency management[☆]

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Summary   Potassium disorders are common and may precipitate cardiac arrhythmias or cardiopulmonary arrest. They are an anticipated complication in patients with renal failure, but may also occur in patients with no previous history of renal disease. They have a broad clinical spectrum of presentation and this paper will highlight the life-threatening arrhythmias associated with both hyperkalaemia and hypokalaemia. Although the medical literature to date has provided a foundation for the therapeutic options available, this has not translated into consistent medical practice. Treatment algorithms have undoubtedly been useful in the management of other medical emergencies such as cardiac arrest and acute asthma. Hence, we have applied this strategy to the treatment of hyperkalaemia and hypokalaemia which may prove valuable in clinical practice.
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Introduction

Potassium (K) is the most abundant cation in the body. Under normal circumstances, only 2% of total body potassium stores are found in the extracellular space and serum potassium concentration is tightly regulated between 3.5 and 5.0 mmol/l.[1] Therefore, there is normally a large potassium concentration gradient between intracellular and extracellular fluid compartments and it is the magnitude of the potassium gradient across cell membranes that contributes to the excitability of nerve and muscle cells, including the myocardium.[2]

Potassium homeostasis is largely regulated by the kidney accounting for excretion of 90% of daily potassium loss.[1] Therefore patients with renal failure, acute or chronic, who have impaired regulatory mechanisms are prone to hyperkalaemia. Patients with normal renal function eliminate only 5—10% of their daily potassium load through the gut. However, in patients with end-stage renal failure (ESRF), gut elimination is increased and accounts for up to 25% of daily potassium elimination.[3]

Potassium disorders are common in clinical practice and may be life-threatening. Before approaching the treatment of these conditions, it is impor-tant to understand the basis of potassium home-ostasis and to recognise that these disorders may present with a diverse clinical spectrum including symptoms, ECG abnormalities and/or arrhythmias. There remains little consistency in treatment of hyperkalaemia and hypokalaemia, therefore treatment algorithms have been developed to assist emergency management.

Hyperkalaemia

Hyperkalaemia is the most common electrolyte disorder associated with potentially life-threatening arrhythmias and cardiopulmonary arrest. It is defined as a serum potassium concentration above 5.0 mmol/l[2] and may be classified as mild (K 5.0—5.9 mmol/l), moderate (K 6.0—6.4 mmol/l) or severe (K $\geq$ 6.5 mmol/l). A potassium concentration above 10.0 mmol/l is usually fatal unless emergency treatment is readily instituted, however survival with extreme hyperkalaemia (K 14 mmol/l) has been reported.[4] There are a number of potential causes of hyperkalaemia which are listed in Table 1, but most commonly it is the result of impaired excretion by the kid-

Table 1   Causes of Hyperkalaemia

Drugs	ACE-inhibitors — e.g. ramipril, captopril
	Angiotensin Receptor Blockers — e.g. losartan
	NSAIDs — e.g. ibuprofen, diclofenac
	Beta-blockers — e.g. atenolol
	K^+ supplements — e.g. oral or IV replacement
	K^+ sparing diuretics — e.g. spironolactone
	Antibiotics — e.g. trimethoprim
	Anaesthetic agents — e.g. suxamethonium
Renal and metabolic diseases	Acute renal failure
	Chronic renal failure
	Type 4 renal tubular acidosis
	Metabolic acidosis
Diet	Foods with high potassium content
	Fasting — relative lack of insulin
	Salt substitute — 'Lo salt'
Endocrine disorders	Addison's Disease
	Hyporeninaemia
	Insulin deficiency/Hyperglycaemia
Haematological disorder/Massive Cell Death	Tumour lysis syndrome
	Rhabdomyolysis
	Massive blood transfusion
	Massive haemolysis — mechanical cell damage
Others	Hyperkalaemic periodic paralysis
	Pseudo-hyperkalaemia
	Abnormal erythrocytes
	Thrombocytosis
	Leucocytosis

ACE: angiotensin converting enzyme; K^+: potassium; NSAIDs: non-steroidal anti-inflammatory drugs; IV: intravenous.

neys or increased release of potassium from cells.[2]

Clinical spectrum of presentation of hyperkalaemia

Symptoms
Patients may present with weakness progressing to flaccid paralysis, paraesthesia, depressed deep tendon reflexes or respiratory difficulties.[1—3] However, these symptoms usually only occur in severe cases, are not specific to hyperkalaemia and are often over-shadowed by the primary illness precipitating hyperkalaemia. On the other hand, the absence of these symptoms should not lead to a false sense of security if the clinical history suggests a high risk of an electrolyte disturbance. In any event, more information is required to guide medical management and the most useful tests are serum biochemistry and ECG.

ECG abnormalities
The first indicator of hyperkalaemia may be the presence of ECG abnormalities, arrhythmias,

or cardiac arrest. The effect of hyperkalaemia on the ECG depends on the absolute serum potassium as well as the rate of increase.[3,5,6] There is great variability in the level of serum potassium which results in ECG changes, but most patients appear to show ECG abnormalities at a serum potassium level above 6.7 mmol/l.[3] In rare instances, the ECG may be normal even in extreme hyperkalaemia and this should raise the possibility of pseudo-hyperkalaemia.[7,8] In the context of diabetic ketoacidosis, hyperkalaemia may also present with ECG changes suggestive of myocardial ischaemia or pseudo-infarction.[9] The presence of other metabolic disturbances, such as hypocalcaemia, hyponatraemia, and acidaemia, may exacerbate the effects of hyperkalaemia.[3]

Cardiac sensitivity to hyperkalaemia is maximal in the atrium, and later in decreasing order, the ventricular cells, His cells, sinoatrial node and inter-atrial tracts.[10] This may help to explain the progressive changes seen in the ECG with increasing severity of hyperkalaemia (Table 2). As serum potassium rises above 5.5—6.5 mmol/l, tall peaked

Table 2 ECG changes associated with the severity of hyperkalaemia

Potassium (mmol/l)	MAJOR ECG CHANGES
5.5	Tall, peaked (tented) T waves [T wave larger than R wave in more than 1 lead]
6.5	
7.0	Prolonged PR interval
7.5	Flattened or absent P waves
8.0	
8.5	Widened QRS [greater than 0.12 seconds]
>9.0	Sine wave pattern (S and T waves merging) — High risk of Cardiac arrest
	Bradycardia
	Ventricular tachycardia

There is some degree of overlap of ECG features in hyperkalaemia. As serum potassium rises above 7 mmol/l, more than one abnormality may be present. The risk of cardiac arrest increases with rising serum potassium and the presence of ominous ECG signs indicated above.

Figure 1 Life-threatening ECG changes in hyperkalaemia. (a) Illustrates tented T waves, loss of P waves and a wide QRS complex in a patient presenting with paralysis and acute renal failure (serum K 9.3 mmol/l). (b) Illustrates a sine-wave pattern in a patient with acute renal failure and digoxin toxicity (serum K 9.3 mmol/l). (c) Illustrates a severe bradycardia at a rate of 28 beats/min in a haemodialysis patient presenting with syncope (serum K 8.1 mmol/l). (d) Illustrates ventricular tachycardia in a haemodialysis patient presenting with generalised weakness (serum K 9.1 mmol/l). The paper speed is 25 mm/s.

T waves may appear. However, only 20% of hyper-kalaemic patients show the classical symmetrically narrow peaked T waves, while the others show large amplitude T waves.[11] As serum potassium rises to 6.5—7.5 mmol/l, the PR interval becomes prolonged and the P wave becomes flattened and eventually lost. This is followed by prolongation of the QRS complex when serum potassium rises to 7.0—8.0 mmol/l. In severe hyperkalaemia, many of these features may occur simultaneously as shown in Figure 1a. Untreated, the QRS complex merges with the T wave to form a sine-wave pattern with impending cardiac arrest (Figure 1b).

The effect of hyperkalaemia on the ECG in patients with end-stage renal failure is less well understood. Early investigators suggested that patients with ESRF have a tolerance to hyper-kalaemia and thereby do not manifest the usual neuromuscular and cardiac features.[7,12] More recently, it has been postulated that the absence of typical ECG changes may be partly explained by changes in serum calcium.[6] Nevertheless, the ECG remains central to the management of hyper-kalaemia in all patients, including those with renal failure.

Arrhythmias associated with hyperkalaemia

In addition to the ECG changes, virtually any arrhythmia or conduction disturbance can occur in the presence of hyperkalaemia. In some instances, treatment may be delayed as the rhythm distur-bance may not be immediately related to the elec-trolyte disorder. The following is a review of the spectrum of arrhythmias associated with severe hyperkalaemia.

Bradycardia. Bradycardia is an ominous complica-tion of hyperkalaemia, but there are few reports in the literature.[13—15] Patients presenting with a severe bradycardia in the context of hyper-kalaemia, as shown in Figure 1c, pose several dilem-mas. Firstly, there is no widely available guidance for the use of calcium salts for bradycardia induced by hyperkalaemia. As bradycardia is listed as a potential adverse effect of calcium salts, there may be further reluctance to use calcium salts even in the context of severe hyperkalaemia. However, the administration of calcium to patients with AV block may avert progression to asystole while potassium lowering drugs take effect and definitive treatment is being planned.[16]

Secondly, the response to atropine is usually poor and a cardiology opinion is often sought. In this sit-uation, it may seem compelling to pace the heart prior to haemodialysis. Indeed there is one report of temporary pacing for complete heart block induced by hyperkalaemia (K 7.99 mmol/l), in which pacing improved the haemodynamic status and appeared to facilitate an uneventful haemodialysis.[15] In this case report, the ECG returned to normal sinus rhythm after haemodialysis. However, temporary pacing is not without risk, may not be effective and delays definitive treatment of the underlying dis-order. Furthermore, proceeding with haemodialysis without pacing may have led to the same outcome, which is often the case in our own clinical experi-ence.

Thirdly, there is some evidence to suggest a reduced efficacy of temporary pacing. In severe hyperkalaemia, there is elevation of the stimu-lation threshold at the electrode tissue interface during cardiac pacing which can lead to failure of ventricular depolarisation.[17] This was evident in a case report of a post-operative patient who progressed to asystole due to hyperkalaemia (K 10.2 mmol/l) despite the presence of a function-ing temporary pacemaker inserted at the time of cardiac surgery.[18] Similarly, transvenous pacing was unsuccessful in a 16-year-old patient with severe hyperkalaemia (K 9.8 mmol/l) despite good wire position on screening.[19] In terms of safety, in addi-tion to the usual risks of central venous cannu-lation, temporary pacing may be complicated by arrhythmias as hyperkalaemia increases myocardial excitability.

Lastly, patients with permanent pacemakers are not protected from the cardiac consequences of hyperkalaemia. Loss of atrial capture has been reported in patients with dual-chamber pac-ing devices who become hyperkalaemic.[17,20] It is postulated that the high atrial myocardial sensitivity to hyperkalaemia may be responsi-ble for the atrial unresponsiveness observed dur-ing dual-chamber pacing.[17] In another report, hyperkalaemia-induced 2:1 AV block in a patient with a dual-chamber pacemaker.[21] Other mech-anisms by which hyperkalaemia may affect the paced heart include prolongation of intraventric-ular conduction manifesting as a very wide QRS complex[17,22] and pacemaker latency which is an increase in the interval between the pacemaker stimulus artefact and the onset of the paced beat.[23] Treatment of hyperkalaemia leads to resolution of conduction abnormalities and narrowing of the QRS complex.

A universal recommendation is difficult in the face of little evidence, but haemodialysis per-formed without initial ultrafiltration and with appropriate cardiac monitoring, usually resolves the bradycardia without the need for cardiac inter-vention. A defibrillator with external pacing facil-ities should be available although this is rarely needed. Persistent bradycardia when the serum

potassium becomes normal requires further investigation and management.

Asytole. The outcome of asystolic cardiac arrest due to hyperkalaemia is usually fatal unless the serum potassium can be returned to normal. One explanation is that severe hyperkalaemia causes myocardial conductivity and excitability to decrease eventually, thereby blocking cardiac conduction globally and maintaining cardiac standstill.[10] Despite this, there are several reports of successful resuscitation in patients presenting with or developing asystole as a result of severe hyperkalaemia.[13,18,19,24] Dialysis was necessary during the course of cardiopulmonary resuscitation (CPR) in most of these cases to lower the serum potassium. All of the resuscitation attempts were prolonged and notably, the only patient managed medically without dialysis was reported to make a spontaneous recovery 8 min after termination of resuscitation.[24] This suggests that the effects of medical therapy may be delayed in the context of a cardiac arrest. Hyperkalaemia-induced asystole is thought to be more common in chronic than in acute hyperkalaemia,[11] however, one of the above cases illustrated acute hyperkalaemia (K 9.8 mmol/l) induced by suxamethonium in the presence of otherwise normal renal function.[19]

Ventricular tachycardia. Ventricular tachycardia (VT) is a recognised manifestation of hyperkalaemia,[25,26] but it is more commonly reported in association with hypokalaemia.[11] It has also been suggested that the presence of a broad complex tachycardia induced by hyperkalaemia may be misinterpreted as VT instead of a sine-wave pattern.[24] However, pulseless VT has been documented as the presenting cardiac arrest rhythm[4,27−29] or may occur during the resuscitation attempt of another primary rhythm[19,24,30] in the presence of hyperkalaemia. VT in the presence of a cardiac output may also be a manifestation of severe hyperkalaemia in children[31] as well as adults,[32] and this is confirmed by our own observations as shown in Figure 1d.

Ventricular fibrillation. Ventricular fibrillation (VF) is often presented as the natural transition from a sine-wave pattern in the presence of extreme hyperkalaemia (K > 8.0 mmol/l).[1,3,11,32] However, in another report, ventricular arrhythmias or cardiac arrest was said to occur at any time point along the transition from peaked T waves to the sine-wave pattern.[6] In reality, a sine-wave pattern is a rare phenomenon probably because it gives rise to VF fairly rapidly, although it can also progress to VT or asystole.[24] Additionally, the threshold for VF in hyperkalaemic patients is likely to be variable and may be influenced by the presence of other electrolyte disorders. Therefore to pre-empt cardiac arrest, it is important to recognise all warning signs (Table 2), institute treatment early and to be vigilant at all times. Analogous to resuscitation for hypothermia, it is important to recognise that defibrillation is frequently unsuccessful until the serum potassium is controlled and CPR should be prolonged.

Pulseless electrical activity (PEA). Any electrolyte disorder may present as PEA, including hyperkalaemia. There are few reports in the literature of successful resuscitation with PEA as the presenting rhythm of cardiac arrest. In each case, prolonged resuscitation was required.[24,33,34]

Pseudohyperkalaemia

Pseudohyperkalaemia, also known as spurious hyperkalaemia, is defined as a difference between serum and plasma potassium greater than 0.4 mmol/l.[35] It should be suspected in patients with hyperviscosity syndromes such as polycythemia rubra vera,[35] in the absence of ECG changes despite severe hyperkalaemia,[7,8] and when sample storage has been prolonged or inadequate.[36] Arterial blood sampling is common practice in intensive care settings, but rarely pseudohyperkalaemia may occur due to malposition of the arterial cannula resulting in a high shear rate and haemolysis.[37] Recognition of pseudohyperkalaemia may avoid potentially hazardous medical intervention, but the rapid detection and treatment of true hyperkalaemia remains of paramount importance.

Emergency treatment of hyperkalaemia

There is currently no standardised treatment strategy for the emergency management of hyperkalaemia in clinical practice largely because there is no agreement on a treatment threshold. This has resulted in much confusion, over or under treatment, late specialist referral and patient deaths. Despite its clinical importance, the first systematic review of the treatment of hyperkalaemia was published only this year.[26] To date, management has been recommended on the basis of the severity of hyperkalaemia and the effect on the ECG, but clear guidelines on the basis of the clinical circumstances has been lacking, particularly in the event of cardiac arrest. Before developing a treatment algorithm, several factors have been considered including the evidence for the therapeutic strategies currently available, the influence of the degree of renal impairment on management and the approach to resuscitation in the event of cardiac arrest.

Table 3 Summary of therapeutic agents for the management of hyperkalaemia

Therapy	Dose	Mechanism	Onset (min)	Duration (h)
Calcium chloride	10 ml of 10% IV	Antagonise	1—3	0.5—1
Insulin/50% glucose	10 units in 25 g IV	Shift	15—30	4—6
Salbutamol	0.5 mg IV 20 mg Neb	Shift	15—30	4—6
Sodium bicarbonate	1 mmol/kg IV	Shift	15—30	Several
Calcium resonium	15—30 g PO/PR	Removes	Variable	4—6

IV: intravenous; Neb: nebulised; PO: oral; PR: per rectum; min: minute.

The drugs available to treat hyperkalaemia have not changed for several decades and despite extensive investigation of their individual and combined efficacy, their remains much variability in how these agents are used in clinical practice. In general, the choice of agents is influenced by the severity of hyperkalaemia and the presence of ECG changes or concurrent metabolic disturbances. In most instances, more than one agent is often required for adequate control and some agents (salbutamol and sodium bicarbonate) are not suitable as monotherapy. A brief summary of the important drugs used to treat hyperkalaemia is given below and the mechanism of action, rate of onset and duration of action of these agents are shown in Table 3.

Protecting the heart

Calcium chloride. Although there are no clinical studies assessing the efficacy of calcium salts in the emergency management of hyperkalaemia, there remains little doubt of their importance in emergency management even in patients with normal serum calcium. Both calcium salts, calcium chloride and calcium gluconate, antagonise the cardiac membrane excitability and have been widely recommended for the treatment and prophylaxis of arrhythmias due to hyperkalaemia when life-threatening ECG changes (absent P waves, wide QRS, sine-wave pattern) are present[24—26] or when cardiac arrest occurs. Some reports also suggest the use of calcium salts for isolated peaked T waves which is an early ECG manifestation of hyperkalaemia.[16,25,38] This approach seems appropriate since the transition period from peaked T waves to broad QRS complex is unknown and is likely to be highly variable from patient to patient. As peaked T waves are a frequently recollected sign of hyperkalaemia, it may also prompt earlier recognition and treatment.

The decision of which calcium salt should be used, chloride or gluconate, is largely guided by practicalities such as availability and local practice. Calcium chloride contains more calcium (6.8 mmol in 10 ml) than calcium gluconate (2.2 mmol in 10 ml)

and has greater bioavailability, but is more likely to cause tissue injury if extravasation occurs. In some institutions, calcium gluconate is the preferred option in a non-arrested patient, but it is important to bear in mind that a higher dose may be necessary to block the toxic effects of hyperkalaemia on the heart.

- *Efficacy*: calcium chloride and calcium gluconate do not lower serum potassium.
- *Cautions*: known or suspected digoxin toxicity. Rate of administration should be slower (over 30 min) in patients taking digoxin as calcium salts may contribute to toxicity.[38,39]
- *Adverse effects*: bradycardia, arrhythmias, tissue necrosis if extravasation occurs.

Shifting of potassium into cells

Insulin—glucose therapy. Several studies have evaluated the efficacy of insulin with glucose for the treatment of hyperkalaemia.[40—42] Insulin enhances cellular uptake of potassium by stimulating the sodium—potassium (Na—K) adenosine triphosphatase (ATP) pump.[38] This effect is independent of its effect on cellular glucose uptake.[3] Administration of glucose without insulin is not recommended in non-diabetics as endogenous insulin release may be insufficient and paradoxically could increase serum potassium further.[43] It is important to note that the potassium lowering effect of insulin is preserved in renal failure, but uraemia attenuates the hypoglycaemic response.[38]

- *Efficacy*: insulin reduces potassium by 0.65—1 mmol/l within 60 min of administration.[3,16,38,40]
- *Cautions*: regular (soluble) insulin should be used.
- *Adverse effects*: hypoglycaemia. This may be delayed (30—60 min post-infusion) if less than 30 g glucose is given.[38]

Sodium bicarbonate. Sodium bicarbonate decreases the concentration of H^+ in the extracellular fluid compartment which increases intracellular Na^+ via the Na^+/H^+ exchanger and facilitates K^+ shift into cells via the Na—K—ATPase pump. However, bicarbonate does not lower serum

potassium in the absence of metabolic acidosis.[43] Disappointingly, there is limited evidence for the use of sodium bicarbonate in the treatment of hyperkalaemia.[3,41,42,44,45]

- *Efficacy*: no study has shown an independent potassium lowering effect within 60 min,[26] but when used in combination with insulin—glucose or salbutamol, it lowered potassium by 0.47 ± 0.31 mmol/l at 30 min.[42]
- *Cautions*: calcium salts and sodium bicarbonate should not be administered simultaneously via the same route to avoid precipitation of calcium carbonate.
- *Adverse effects*: hypernatraemia; pulmonary oedema due to large sodium load; tetany in patients with coexistent hypocalcaemia.

Salbutamol. Beta agonists have been widely studied for the treatment of hyperkalaemia.[40–51] Salbutamol binds to beta-$_2$ receptors stimulating adenylase cyclase which converts ATP to 3'5' cyclic adenosine monophospate. This results in stimulation of the Na—K ATP pump and intracellular potassium uptake.[38]

- *Efficacy*: salbutamol lowers serum potassium by 0.87—1.4 mmol/l after intravenous administration[46,50] and by 0.53—0.98 mmol/l after administration in the nebulised form.[40] The response is dependent on the dose administered as greater efficacy was reported in patients receiving 20 mg versus 10 mg of nebulised salbutamol.[26] It is important to note that beta-blockers may affect the response to treatment and up to 40% of patients with ESRF do not respond to salbutamol.[3]
- *Cautions*: beta-agonists may exacerbate tachycardia in patients with tachyarrhythmias.
- *Adverse effects*: tachycardia, tremor, anxiety and flushing.

Removing potassium from the body
Exchange resins. Cation exchange resins are cross-linked polymers with negatively charged structural units which exchange calcium (calcium resonium) or sodium (sodium polystyrene sulphonate; Kayexalate) for potassium across the intestinal wall.

- *Efficacy*: resins do not appear to increase faecal potassium excretion above the effect of induction of diarrhoea with laxatives.[52,53] These studies have reported no reduction in serum potassium at 4 h.[26,53]
- *Cautions*: slow acting, therefore unsuitable for urgent management of hyperkalaemia. Co-administration of laxative is recommended.

- *Adverse effects*: constipation, intestinal necrosis.

Diuretics. The theoretical basis for the use of diuretics in the treatment of hyperkalaemia is to enhance urinary potassium excretion. However, there are no clinical trials to support their use in the treatment of hyperkalaemia.[26]

Intravenous fluids. Although there is no clinical trial to support fluid replacement,[26] it is advisable to administer 0.9% saline intravenously if there is clinical evidence of volume depletion with the aim of improving renal perfusion and enhancing urinary potassium excretion.

Dialysis. Dialysis is the most immediate and reliable way of removing potassium from the body. The principle mechanism of action is the diffusion of potassium across the transmembrane gradient. Haemodialysis can remove 25—40 mmol/h of potassium[54] and is more effective than peritoneal dialysis. The typical decline in serum potassium is 1 mmol/l in the first 60 min, followed by 1 mmol/l over next 2 h.[3] The efficacy of haemodialysis in lowering serum potassium can be improved by performing dialysis with a low potassium concentration in the dialysate,[55] a high blood flow rate[56] or a high dialysate bicarbonate concentration.[57]

Influence of degree of renal impairment on management

Hyperkalaemia may occur in the context of acute (ARF), chronic (CRF) or end-stage renal failure (ESRF). The aetiology may vary depending on the degree of renal impairment. Drugs are the most common cause of hyperkalaemia in ARF and CRF. In patients with severe CRF (GFR < 30 ml/min) or ESRF, additional factors including dietary potassium intake become important. Non-compliance with the haemodialysis schedule can also result in lethal hyperkalaemia. Hyperkalaemia has been reported to be the indication for emergency dialysis 24% of the time in patients on maintenance haemodialysis in one centre.[58]

The clinical sequelae of hyperkalaemia may be influenced by the rate of onset of hyperkalaemia and the frequency of its occurrence. In ARF, hyperkalaemia often develops rapidly and is usually poorly tolerated, therefore prompt aggressive treatment is warranted. It has been suggested that the slower onset of hyperkalaemia in CRF is better tolerated and ECG signs may be absent despite a serum potassium of 7.0—7.5 mmol/l.[24] A relative tolerance to hyperkalaemia has also been postulated in patients with ESRF who experience frequent mild hyperkalaemia,[12] however

there remains little evidence to support this theory as 3–5% of deaths in dialysis patients may be attributable to hyperkalaemia.[59] Therefore, the effects of hyperkalaemia should not be underestimated in patients with advanced renal impairment.

Most studies investigating the therapeutic effects of pharmacological agents for the treatment of hyperkalaemia have been performed in patients with ESRF as this model provides a significant cohort of patients with mild hyperkalaemia who pass little urine, thereby making interpretation of treatment efficacy much easier.[26] The therapeutic options are the same irrespective of the nature and severity of the underlying renal disease. However in ESRF, sodium bicarbonate has been found to be less effective,[3,26] and medical measures only provide temporary relief until dialysis can be initiated. Overall, the main difference in approach to treatment may be the urgency for correction of serum potassium of mild-moderate severity, but prompt treatment is warranted for severe hyperkalaemia irrespective of the degree of renal impairment.

Interventions in cardiopulmonary arrest

The focus so far has been averting cardiac arrest with prompt treatment of hyperkalaemia. However, cardiac arrest may occur if treatment of known hyperkalaemia has been sub-optimal or ineffective. In other cases, hyperkalaemia is discovered only after the resuscitation is underway. When hyperkalaemia is suspected to be the primary precipitant of cardiac arrest, resuscitation should not be terminated until serum potassium is controlled, by any means necessary, unless there are extenuating circumstances. Hyperkalaemia may also arise during the resuscitation attempt as a result of metabolic changes and hypoxia but does not usually require specific intervention.[39]

During CPR, adrenaline (epinephrine) should be the first drug to be administered irrespective of the cause of cardiac arrest. Adrenaline is a powerful sympathomimetic amine with both alpha- and beta-adrenergic activity which helps to drive potassium into cells, thereby lowering serum potassium.[24] Next, calcium chloride should be administered to antagonise the toxic effects of hyperkalaemia. Sodium bicarbonate should be considered in the context of a metabolic acidosis. Insulin–glucose is thought to be ineffective during CPR,[39] however it is unlikely to cause harm and should begin to have effect with minutes of return of spontaneous circulation. There is no literature available on the use of intravenous salbutamol in this scenario. Optimising ventilation during CPR can avoid compounding aci-

dosis and further extracellular shift of potassium. This approach is summarised in Figure 2.

Haemodialysis during resuscitation
In cardiac arrest, dialysis modalities have been used effectively for the rewarming of hypothermic patients, but there is relatively little experience in its use for hyperkalaemia. It seems ironic that the indication for which dialysis is intended is rarely implemented during resuscitation, particularly when medical therapy may be less effective. The hesitancy to initiate dialysis during CPR is largely because technique failure is anticipated. The general perception is that haemodialysis cannot be achieved during CPR as the extracorporeal circuit will clot due to inadequate blood pressure. However, there is evidence to suggest that dialysis can be effective despite reduced circulation. With the aid of the blood pump, a blood flow rate of up to 150 ml/min can be achieved with external chest compressions at a rate of 60/min[27] and up to 200 ml/min at a rate of 80–100/min.[28]

There are several reports of patients treated successfully with dialysis during CPR for cardiac arrest secondary to hyperkalaemia.[13,18,19,29,30,60,61,62] In many of these reports, resuscitation combined with dialysis has been successful even after prolonged CPR (in excess of 90 min) with no neurological sequelae. The dialysis mode used was dependent on local availability and practice, but success has been reported with haemodialysis, veno-venous haemofiltration or veno-venous haemodiafiltration,[62] and also with peritoneal dialysis.[19] This growing series of reports over the last two decades suggests that external cardiac compression can support adequate blood flow for haemodialysis. Ultimately, if the blood clots in the circuit, it would be reasonable to try again as there is little to lose. Haemodialysis is undoubtedly the most effective treatment for managing life-threatening hyperkalaemia.

Post-resuscitation care
If the resuscitation attempt is successful, attention should turn to maintaining the circulation, performing further investigations, deciding on the timing for haemodialysis and planning after-care. Insulin–glucose may be more effective for persistent hyperkalaemia.[39] If vascular access for dialysis has not been achieved during resuscitation, this may now be possible with the return of spontaneous circulation. Femoral access is usually fast and uncomplicated. Early specialist input will ensure the preparation of a dialysis machine to avoid further delay.
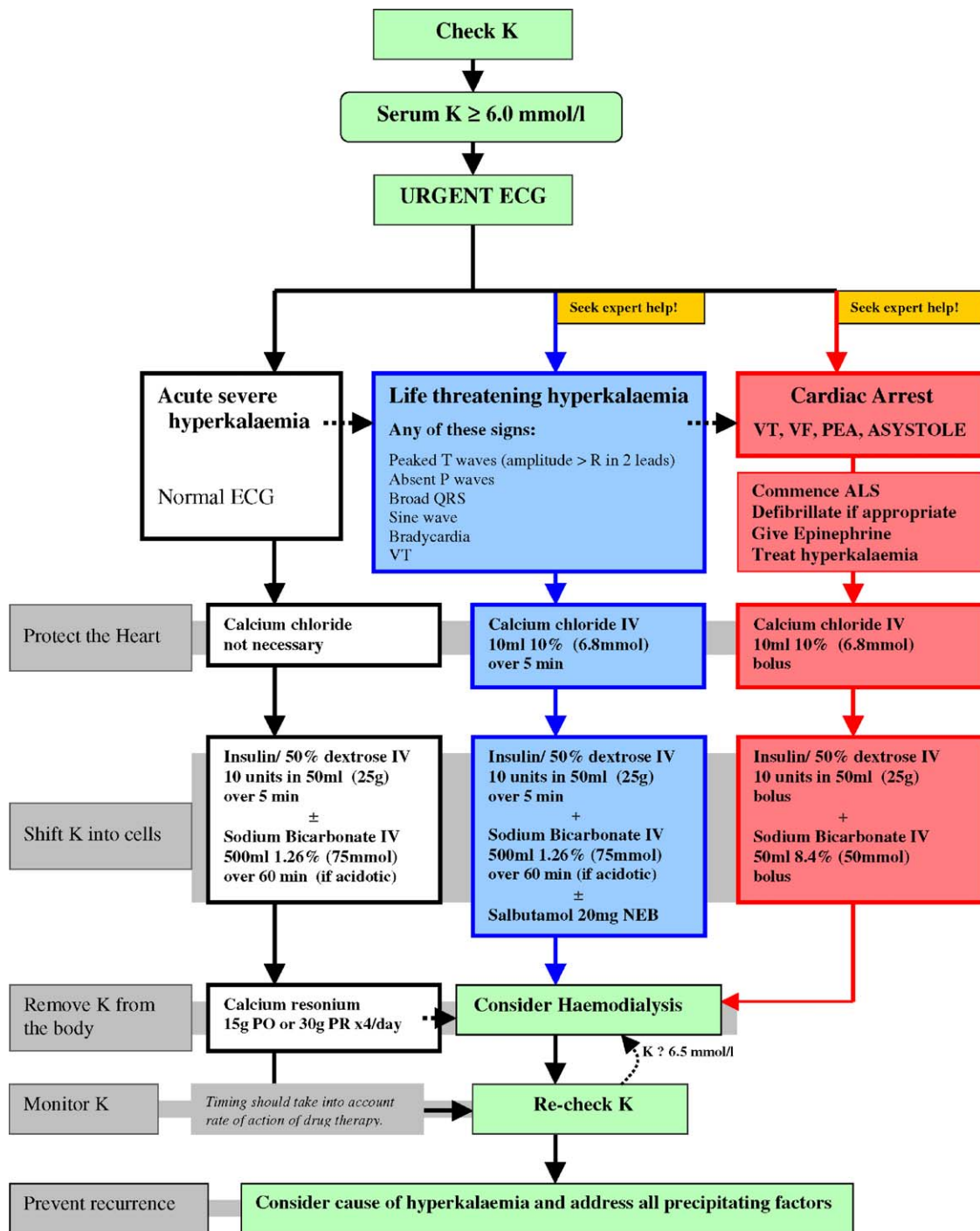
Figure 2 Emergency treatment algorithm for hyperkalaemia in adults.

Development of an emergency treatment algorithm

It has been previously noted that there is great variability in treatment of hyperkalaemia from patient to patient even within the same centre, without a clear rationale.[63] This is not an isolated phe-nomenon and suggests a need for a consistent protocol. The main objectives in designing such a protocol are to provide a level of serum potassium at which action should be initiated, to prompt early recording of an ECG to guide management and to outline a structured approach depending on the clinical setting. Emergency treatment is likely to

be required for patients with moderate to severe hyperkalaemia, therefore the recommended treatment threshold of serum potassium has been set at 6.0 mmol/l (Figure 2). The ECG features and clinical condition of the patient then guide immediate clinical decisions. Analogous to acute asthma, we have defined similar treatment categories which incorporate the severity of hyperkalaemia, as reflected by level of serum potassium, ECG features and the clinical setting.

Acute severe hyperkalaemia
Acute severe hyperkalaemia is defined as a raised serum potassium in the presence of a normal ECG. As these patients do not show evidence of cardiac toxicity, calcium chloride is not indicated. In these patients, the intensity of treatment is guided by the level and rate of rise of serum potassium and the likelihood or re-establishing good urine output.

Life-threatening hyperkalaemia
Life-threatening hyperkalaemia is defined as hyperkalaemia which is sufficiently severe to cause ECG abnormalities ranging from tented T waves to arrhythmias. The level of serum potassium causing these abnormalities is highly variable, but is likely to exceed 6.5 mmol/l. Life-saving treatment should be initiated immediately, even before laboratory results are available, in the presence of the ECG changes outlined in Figure 2.

Cardiac arrest
Patients may suffer cardiac arrest as the initial presentation or following life-threatening hyperkalaemia. Standard ALS should be initiated, followed by the administration of calcium chloride and shifting agents (Figure 2). Haemodialysis should be considered if hyperkalaemia is resistant to initial medical therapy.

Principles of treatment algorithm
The treatment of hyperkalaemia in all of the above settings is based on five key principles:

1. Cardiac protection by antagonising the effects of hyperkalaemia.
2. Shifting K^+ into cells.
3. Removing K^+ from the body.
4. Monitoring serum K^+ for rebound hyperkalaemia.
5. Prevention of recurrence of hyperkalaemia.

These steps follow a logical sequence and successful treatment is also dependent on seeking expert advice as early as possible. It is important to re-assess the effects of initial treatment by monitoring the serum potassium. Rebound is a well-recognised phenomenon, even after haemodialysis, with 70% of potassium reduction being abolished at 6 h after dialysis.[3]

Prevention of hyperkalaemia

A treatment strategy is incomplete unless preventative measures are taken to avoid development or recurrence of hyperkalaemia. Patients with advanced renal failure are most susceptible to hyperkalaemia and care should be taken with drug prescribing and diet in this patient group. Patients with other chronic illnesses including proteinuric kidney diseases, cardiac failure, diabetes mellitus and portal hypertension are also susceptible to hyperkalaemia. This risk may be compounded by the presence of even mild renal failure in association with other co-morbidity. However, medicines which may increase serum potassium levels such as ACE inhibitors, angiotensin II antagonists, NSAIDs, and potassium sparing diuretics, especially if combined, are the most common preventable cause of hyperkalaemia. Severe hyperkalaemia was reported in 2% of patients in the RALES study despite multiple exclusion criteria.[64] Hyperkalaemia may also occur in the setting of acute illness in patients taking these agents, especially if there is a degree of volume depletion.

For primary prevention, patients at risk of hyperkalaemia should have close monitoring of serum biochemistry and should discontinue drugs known to potentiate serum potassium during acute illness. Patients with severe renal failure, acute or chronic, should receive specialist attention as early as possible. For secondary prevention after initial treatment of hyperkalaemia, it is important to monitor electrolyte levels and to prevent recurrence of the abnormality by removing any precipitating factors (e.g. drugs).

Hypokalaemia

Low serum potassium is reported to be the most common electrolyte abnormality in hospitalised patients.[1] There are many causes of hypokalaemia as shown in Table 4, but drugs and gastrointestinal disease account for a significant proportion. Potassium concentration in the blood is also affected by the metabolic status of the patient. In the presence of a metabolic alkalosis, potassium shifts into cells. Hypokalaemia can also contribute to the maintenance of a metabolic alkalosis by enhancing bicarbonate absorption and increasing chloride excretion in the kidney.[1] Hypokalaemia is defined as a serum potassium ≤ 3.5 mmol/l.[1,2,65,66] It may

Table 4	Causes of hypokalaemia

Increase potassium loss
   Drugs—diuretics, laxative abuse, liquorice, steroids
   GI losses—diarrhoea, vomiting, ileostomy, intestinal fistula, villous adenoma
   Renal—renal tubular disorders, Bartter's syndrome, Liddle's syndrome, Gitelman's syndrome, nephrogenic
     diabetes insipidous
   Endocrine—hyperaldosteronism, Cushing's syndrome, Conn's syndrome
   Dialysis——haemodialysis on low potassium dialysate, peritoneal dialysis

Transcellular shift
   Insulin/glucose therapy
   Beta-adrenergic stimulation—e.g. salbutamol
   Alkalosis
   Hypokalaemic periodic paralysis

Decreased potassium intake
   Poor dietary intake (less than 1 g/day)

Magnesium depletion (increases renal potassium loss)
   Poor dietary intake
   Increased magnesium loss

be classified as mild (K 3.0—3.5 mmol/l), moderate (K 2.5—3.0 mmol/l) or severe (K < 2.5 mmol/l) and symptoms are more likely with increasing severity.

Clinical spectrum of hypokalaemia

Symptoms
Patients with mild hypokalaemia usually have no symptoms. As serum potassium level falls further, the nerves and muscles are predominantly affected causing fatigue, weakness, leg cramps, and constipation. In severe cases, rhabdomyolysis, ascending paralysis and respiratory difficulties may occur. The probability of symptoms appears to correlate with the presence of pre-existing heart disease (ischaemia, heart failure, left ventricular hypertrophy), and the rapidity of the onset of hypokalaemia.[65—67]

ECG abnormalities
There are usually no ECG changes in patients with mild hypokalaemia, but these may become evident in moderate to severe hypokalaemia including the presence of U waves, T wave flattening, or ST segment changes.[2]

Arrhythmias associated with hypokalaemia
Severe hypokalaemia predisposes to arrhythmias and cardiac arrest. In patients treated with digoxin, hypokalaemia of any severity can increase the incidence of arrhythmias.[65] Patients with established digoxin toxicity are particularly at risk. The following is a review of the common arrhythmias associated with hypokalaemia and the effect of hypokalaemia in patients maintained on anti-arrhythmic agents.

Ventricular tachycardia/fibrillation. Hypokalaemia can predispose to ventricular tachycardia or ventricular fibrillation.[11] This risk is particularly high following acute myocardial infarction and maintaining the serum potassium above 3.9 mmol/l may reduce the risk of early VF.[66] The arrhythmia may not respond to electrical or chemical cardioversion until the serum potassium is corrected.

Long QT syndrome and torsade de pointes. The long QT syndrome, which may be inherited or acquired, is caused by malfunction of the ion channels responsible for ventricular repolarisation.[68] Potassium and/or magnesium depletion are the main metabolic disorders associated with channel malfunction and hence predispose to arrhythmias. The characteristic arrhythmia seen is torsade de pointes which may present as syncope or cardiac arrest. This is recognised as a variant of ventricular tachycardia in which the QRS complexes change amplitude around the isoelectric line and is frequently preceded by pauses.[68] The mainstay of treatment is the correction of hypokalaemia and administration of magnesium sulphate.

Patients taking anti-arrhythmic drugs. Hypokalaemia may also interfere with the beneficial effects of anti-arrhythmic drugs rendering the patients susceptible to a recurrence of the underlying arrhythmia.[66] In addition, hypokalaemia can compound the effects of Class III anti-arrhythmic agents such as sotalol predisposing to arrhythmias.[66,68] Indeed, torsade de pointes has been reported in 2—4% of patients treated with

sotalol and this risk is increased in older patients and in the presence of renal impairment.[68] Although this risk is also dose-dependent, there are reported cases of torsade de pointes induced by low doses of sotalol.[69]

Treatment of hypokalaemia

The treatment approach depends on the severity of hypokalaemia and the presence of symptoms and ECG abnormalities. As a guide to the deficit in total body potassium, serum potassium decreases by 0.3 mmol/l on average for every 100 mmol reduction in total body potassium stores, but this is variable depending on body mass.[1,65] Hence, the deficit can be considerable in moderate—severe hypokalaemia and care should be taken during replacement. The administration of potassium, particularly by the intravenous route is not without risk. Gradual replacement of potassium is safer and avoids excessive replacement.

Many patients who are potassium deficient are also deficient in magnesium. Magnesium is important for potassium uptake and for the maintenance of intracellular potassium levels, particularly in the myocardium. Combined deficiency may potentiate the risk of cardiac arrhythmias. Repletion of magnesium stores will facilitate more rapid correction of hypokalaemia and is recommended in severe cases of hypokalaemia.[66,70]

Developing a treatment algorithm for hypokalaemia

A recent report has highlighted the inadequacy of treating this common medical problem.[71] This report assessing treatment adequacy showed that hypokalaemia was found in 2.6% of hospitalisations over a one year period with inadequate management of hypokalaemia in 24% of these cases. These inadequacies included failure to measure serum potassium subsequently in 6.4% of patients and failure to correct hypokalaemia in 30% of patients prior to discharge. The mortality of the hypokalaemic population was 10-fold higher than the general hospitalised population. Hence, it is important to detect, monitor and treat hypokalaemia appropriately.

The main considerations in designing an emergency treatment algorithm for hypokalaemia are to establish the level of serum potassium where intravenous replacement is indicated, the rate of potassium replacement according to the clinical setting and the need for co-administration of magnesium. Stable patients with mild hypokalaemia (K

3.0—3.5 mmol/l) are not included in the treatment algorithm as oral potassium replacement is usually sufficient. Expert help should be considered for patients with hypokalaemia of any severity which is associated with arrhythmias or cardiac arrest. Continuous ECG monitoring is essential during IV administration and the dose should be titrated after repeated sampling of serum potassium levels. The emergency management of hypokalaemia is summarised in Figure 3. Treatment is guided by the degree of hypokalaemia and the clinical setting.

Patients with no symptoms
In the absence of digoxin toxicity or severe heart disease, potassium should be gradually replaced at a rate of 10 mmol/h in asymptomatic patients. Magnesium replacement is required only if found to be magnesium deficient.

Life-threatening arrhythmias
In an emergency such as an arrhythmia, intravenous potassium is required, but the rate of correction of serum potassium causes uncertainty. The maximum recommended intravenous dose of potassium is 20 mmol/h, but more rapid administration (initial infusion of 2 mmol/min for 10 min, followed by 10 mmol over 5—10 min) is indicated for unstable arrhythmias when cardiac arrest is imminent.[2] Rapid bolus injection of potassium should be avoided in all circumstances as this may precipitate cardiac arrest. Magnesium should be administrated early after initiating potassium replacement, even before the serum magnesium level is known.

Cardiac arrest
Cardiac arrest may occur in patients known to be hypokalaemic. Alternatively, hypokalaemia may only be discovered after resuscitation is underway. Although the metabolic status after cardiac arrest usually favours an increase in serum potassium, total body potassium remains low. Prompt correction of hypokalaemia may not only render defibrillation more successful, but may reduce the incidence of further arrhythmias in the post-arrest period as the metabolic status of the patient improves and potassium shifts back into cells.

Prevention of hypokalaemia

Hypokalaemia is frequently iatrogenic and hence potentially avoidable. For primary prevention, electrolytes should be monitored in patients at risk. In the general population, this includes patients treated with diuretics and those with high gastrointestinal losses. For secondary prevention, it
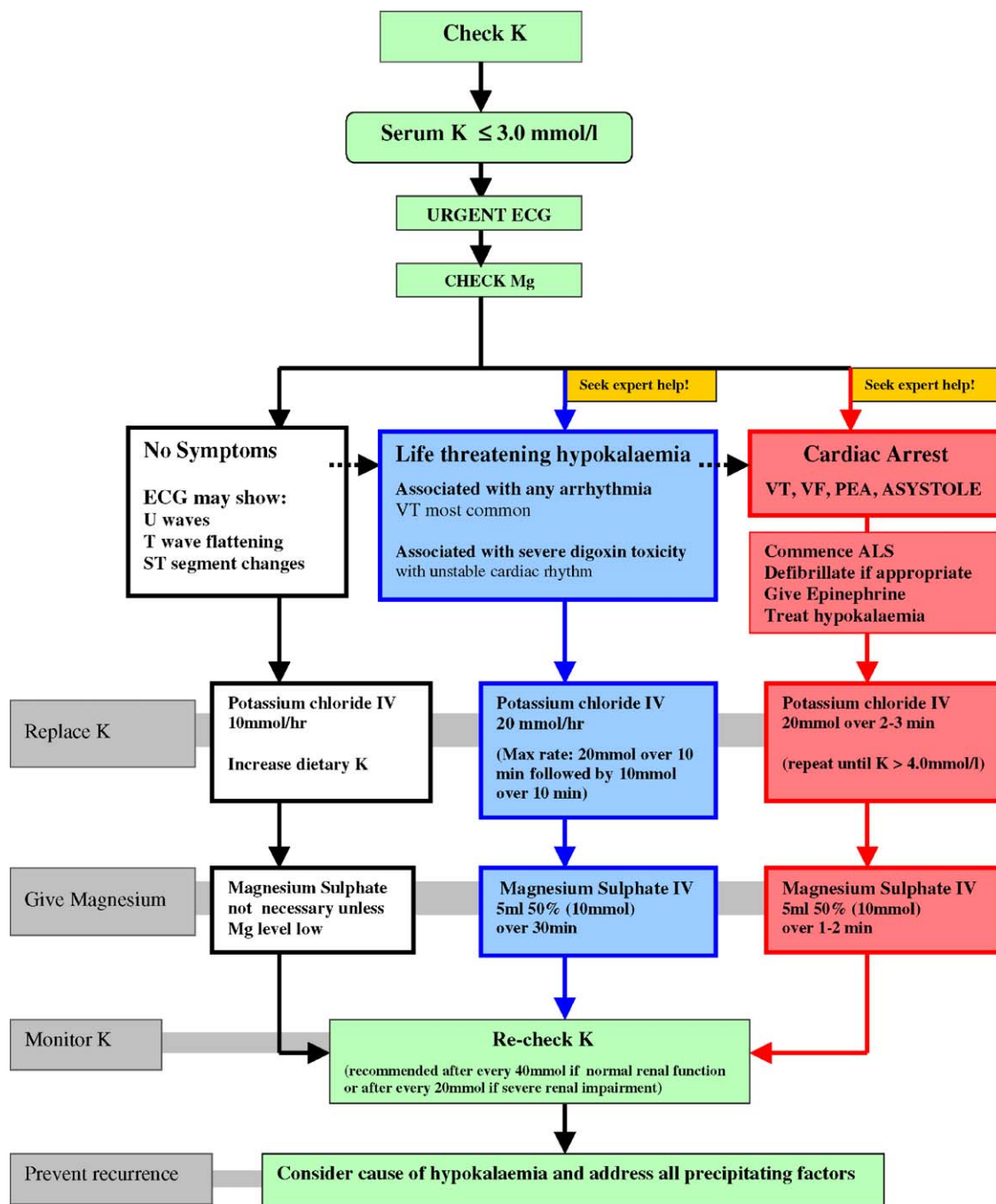
Figure 3 Emergency treatment algorithm for hypokalaemia in adults.

is important to monitor serum potassium after initial treatment and to prevent recurrence of hypokalaemia by removing any precipitating factors.

Hypokalaemia may also occur in patients with renal failure requiring renal replacement therapy. Non-renal specialists may be unaware of the degree of potassium flux which occurs with different dialysis modalities. Hypokalaemia is a frequent occurrence in patients receiving peritoneal dialysis and potassium supplements are often required. In those receiving haemodialysis, hypokalaemia is most likely toward the end or immediately after a session. Patients most at risk are those with a low serum potassium before beginning a dialysis session, particularly if dialysed against an inappropri-

ately low potassium dialysate. Therefore, patients with advanced renal failure are also potentially susceptible to hypokalaemia and it is important to consider measures to prevent hypokalaemia in patients at all levels of renal function.

Summary

Potassium disorders may have life-threatening consequences. It is important to recognise that both hyperkalaemia and hypokalaemia are potentially avoidable complications of commonly prescribed drugs. The clinician should be aware that both may present with a range of ECG changes, virtually any arrhythmia or cardiac arrest. Treatment algorithms provide a stratified approach based on biochemical, clinical and pharmacokinetic criteria and may assist clinicians in the immediate care of these common medical emergencies.

Conflict of interest

The authors have no conflict of interest in relation to this paper.

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