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REVIEW

Hyperkalemia in Chronic Kidney Disease: Links, Risks and Management

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Abstract: Hyperkalemia is a common clinical problem with potentially fatal consequences. The prevalence of hyperkalemia is increasing, partially due to wide-scale utilization of prognostically beneficial medications that inhibit the renin-angiotensin-aldosterone -system (RAASi). Chronic kidney disease (CKD) is one of the multitude of risk factors for and associations with hyperkalemia. Reductions in urinary potassium excretion that occur in CKD can lead to an inability to maintain potassium homeostasis. In CKD patients, there are a variety of strategies to tackle acute and chronic hyperkalemia, including protecting myocardium from arrhythmias, shifting potassium into cells, increasing potassium excretion from the body, addressing dietary intake and treating associated conditions, which may exacerbate problems such as metabolic acidosis. The evidence base is variable but has recently been supplemented with the discovery of novel oral potassium binders, which have shown promise and efficacy in studies. Their use is likely to become widespread and offers another tool to the clinician treating hyperkalemia. Our review article provides an overview of hyperkalemia in CKD patients, including an exploration of relevant guidelines and nuances around management.

Keywords: CKD, electrolytes, hyperkalemia, potassium, RAAS

Introduction

Hyperkalemia is an elevation of the blood potassium level, usually defined as a serum concentration ≥5.5mmol/L. It is a frequently occurring biochemical abnormality, which can result in serious sequelae including arrhythmias and cardiac arrest. As such, its presence often causes alarm, and caution is taken to avoid it. Most of the body's potassium is stored intracellularly, and the extracellular potassium is maintained at a relatively constant level by a variety of homeostatic mechanisms.[1]

Serum potassium may increment via increased intake, reduced urinary excretion or from redistribution from cells/cell damage, eg tumour lysis syndrome or rhabdomyolysis/crush syndrome. Under normal circumstances, the body's (in particular the kidneys') ability to excrete potassium can be increased to avoid hyperkalemia. In certain disease states, such as chronic kidney disease (CKD), this compensation may not occur to the same degree.[1]

Medications that inhibit the renin-angiotensin-aldosterone system (RAAS) cause hyperkalemia; however, the evidence base for their use is compelling with prognostic benefits seen in heart failure with reduced ejection fraction, a reduction in progression of proteinuric CKD and a trend towards reduced hospitalisation in patients with heart failure and preserved ejection fraction.[2–4] It is a testament to the efficacy of these drugs that they have been used at supramaximal doses (for example, candesartan) in CKD with additive reductions in proteinuria (albeit with close potassium monitoring).[5] Research is ongoing as to how novel potassium binders can facilitate maximal dose RAAS inhibition, including studies on patients with CKD and heart failure.[6]

The new non-steroidal mineralocorticoid antagonist, finerenone, has been shown to improve cardiovascular outcomes in patients with type 2 diabetes mellitus and albuminuric CKD with lower rates of discontinuation due to hyperkalemia (in the FIGARO-DKD trial) than other drugs inhibiting the renin-angiotensin-aldosterone system.[7–9] The FIDELIO-DKD trial of finerenone in a similar patient population showed favourable outcomes for cardiovascular events and CKD

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progression. Discontinuation rates of finerenone due to hyperkalemia in FIDELIO-DKD were comparable to other established RAASi agents.[7,8,10,11] Finerenone *may* offer the benefit of RAAS inhibition with lower rates of hyperkalemia and so may have a role in patients at higher risk of hyperkalemia.

This article seeks to address hyperkalemia in the CKD cohort in more detail, including some nuances and content in clinical management.

Epidemiology, Links and Risk Factors

Hyperkalemia is a common problem, which appears to be increasing in incidence and prevalence. Reported rates of hyperkalemia in the literature vary greatly. A retrospective study from the US in 2014 estimated the annual prevalence of hyperkalemia to be 1.57% of all patients on a commercial claims database (which had increased since 2010).[12] Other sources suggest that hyperkalemia complicates at least 3.5% of hospital admissions, but this is likely to be an underestimate of the true figure.[13]

Patients with heart failure and/or chronic kidney disease in the aforementioned database study demonstrated an annual prevalence of hyperkalemia of 6.35%. Interestingly, of those patients found to have hyperkalemia, approximately half were noted to have CKD or heart failure. Older patients, men and those with more advanced CKD were more likely to be hyperkalemic.[12] One study of CKD patients with a mean estimated glomerular filtration rate (eGFR) of 14.6mL/min/1.73m^2 suggested a prevalence of 40% for serum potassium concentrations above 5.5mmol/L.

Another study estimating the prevalence of hyperkalemia prevalence showed that 4.3% of a control group without known cardiovascular disease, ischemic heart disease, hypertension, CKD or diabetes mellitus had a potassium value of ≥5.0mmol/L. This contrasts with rates of 9.1%. 11.5% and 8.3% in those with heart failure, CKD stages 3–5 and diabetes mellitus, respectively. All 3 of the aforementioned conditions had a prevalence of 13.1%.[14]

An additional prospective study of over 2000 patients with CKD in nephrology care demonstrated a hyperkalemia prevalence of 37%. In this study, hyperkalaemia predicted progression to end-stage kidney disease, independent of glomerular filtration rate. Interestingly, in this study, the presence of hyperkalemia did not predict mortality.[15]

Renin-angiotensin-aldosterone system inhibitors (RAASi) are known to increase the frequency and degree of hyperkalemia and their use is common in those with CKD or heart failure.[16]

Other drugs also contribute via numerous mechanisms (Table 1) as well as accepted links between hyperkalemia and diabetes mellitus, heart failure and renal impairment.[12,17]

Acute kidney injury, high dietary protein intake, white race, haemolysis, exercise, gout, mineral metabolic acidosis, cell breakdown (eg rhabdomyolysis), voltage dependent renal tubular acidosis, aldosterone deficiency/resistance and low serum bicarbonate have been identified as additional risk factors.[13,18]

Mortality is increased in those with hyperkalemia; with an increased risk when >5.0 mmol/L, more so between 5.5 and 6 mmol/L and highest when >6 mmol/L. This risk is magnified in those with comorbid conditions including diabetes mellitus, CKD and heart failure.[14]

Treatment of hyperkalemia has been shown to reduce in-hospital mortality when serum potassium is reduced to <5.5 mmol/L, whereas in-hospital mortality is strongly correlated with hyperkalaemic electrocardiographic (ECG) changes. Mortality from hyperkalemia was greatly increased in those with normal baseline renal function, which may support the existence of a chronic tolerance to hyperkalemia in those with CKD.[19]

A post-hoc analysis of the RENAAL trial demonstrated that losartan was associated with a high risk of hyperkalemia, which was associated with increased adverse renal outcomes. This has raised the question as to whether or not hyperkalemia may limit the utility and renoprotective effect of such agents in preventing CKD progression.[20]

Brief Overview of Potassium Physiology and Pathophysiology of Hyperkalemia

Potassium is the most abundant intracellular cation in the body.[21] Approximately, 98% of body potassium is stored within the cells.[1] On average, this would be 3–4 moles, the majority of which reside in skeletal muscle.[22] These intracellular stores serve as a reservoir for potassium which can be redistributed in times of need, as was elegantly demonstrated in a study of military personnel who were able to maintain serum potassium values close to normal levels in the face of significant potassium deficits accrued during physical activity.[23]

Table 1 Drugs Leading to hyperkalemia[84]

Mechanism for Hyperkalemia	Drug Class	Drug Name
Reduction of potassium excretion due to hypoaldosteronism	Aldosterone antagonist	Spironolactone, eplerenone, canrenoate potassium (neonatal medicine), drospirenone
	Angiotensin-converting enzyme inhibitors	Captopril, enalapril, lisinopril
	Angiotensin II receptor antagonists	Candesartan, losartan
	Non-steroidal anti-inflammatory drugs	Ibuprofen, naproxen, diclofenac, meloxicam
	Heparins	Enoxaparin sodium
	Immunosupressive drugs	Cyclosporin, tacrolimus
Reduction of passive renal excretion of potassium	Potassium-sparing diuretics other than aldosterone antagonists	Amiloride, triamterene
	Anti-infective drugs	Trimethoprim, pentamidine
Reduction of potassium cellular transport	Beta-blockers	Propranolol, atenolol, metoprolol, bisoprolol
	Cardiac glycosides	Digoxin
	Mood stabilisers	Lithium
Excess potassium supply	Potassium salts	Potassium chloride
Unknown mechanism	Epoetins	Epoetin alfa, epoetin beta

Notes: Adapted from Noize P, Bagheri H, Durrieu G, et al.Life-threatening drug-associated hyperkalemia: a retrospective study from laboratory signals. Pharmacoepidemiol Drug Saf. 2011;20(7):747–753. copyright 2011, John Wiley and Sons.[84]

Potassium movement into cells occurs at the same time as sodium efflux in a ratio of 2:3, driven by the Na-K-ATPase pump. This pump generates an electrical gradient which is critical to action potential generation, which, in turn, is needed for cell function, muscular contraction and nerve conduction.[1,21]

Dietary potassium intake is variable but is usually in the region of 40–200 mmol per day.[1] Ingested potassium undergoes absorption in the gastrointestinal tract and excretion is predominantly via the urinary route. The principal cells in the distal convoluted tubules are integral to this excretory process. The majority of the freely filtered potassium is absorbed in the proximal tubule; however, some paracellular and transcellular absorptions occur in the thick ascending limb of the loop of Henle.[21] The colon is responsible for approximately 10% of potassium excretion in those with normal kidneys; however, this route of excretion may be more significant in those with impaired renal excretion. It stands to reason that diarrhea and increased gastrointestinal losses as well as sweating could decrease serum potassium.[23]

Key factors in promoting potassium excretion include:

- Increased potassium intake or blood concentration
- Delivery of sodium to distal tubule (where it exchanges with potassium)
- Aldosterone secretion

Beta-2-adrenergic receptors and insulin serve to drive potassium into cells via increasing the activity of the Na-K-ATPase pump. This forms part of the rationale for their use in the management of acute hyperkalemia. Conversely, beta blockade and insulin deficiency will promote potassium efflux. Alpha-adrenergic receptor activation prevents cellular potassium entry.[24] Postprandial insulin secretion buffers potassium rises in a manner that is independent of its effect on blood glucose.[25]

Mineral metabolic acidosis, cell lysis and hyperosmolarity also promote extracellular shift of potassium.[1,21] Hyperosmolarity does so via water movement with solvent drag which also causes cell shrinkage, therefore increasing intracellular potassium concentration which in turn generates a concentration gradient upon which potassium can leave the cells. Cell lysis may be seen on a large scale in massive hemolysis, rhabdomyolysis/crush syndrome, burns, tissue necrosis and tumour lysis syndrome.[1,21]

Metabolic acidosis was historically thought to cause hyperkalemia via a direct exchange between hydrogen and potassium ions; subsequent work has highlighted that this direct coupling does not exist, at least to the extent that it was first thought to.[21,26] In states of mineral metabolic acidosis, the acidic extracellular pH affects cellular transporters, leading to a relative sequestration of potassium ions in the extracellular compartment. This contrasts with organic acids, which can enter cells and therefore do not exert the same effects. The net result of these processes in mineral metabolic acidosis is equivalent to the exchange between hydrogen and potassium.[21,26]

Potassium efflux in the cortical collecting duct is thought to occur via 2 main channels: the renal outer medullary potassium channel (ROMK) and the "BK" channel. The former is considered to be the major excretory pathway, while the latter is more active under conditions of increased luminal flow. Alpha-subunits of the BK channels are increased by aldosterone and beta subunits are increased in response to bicarbonate. The increase in BK channel components in the response to high urinary pH and decrease in response to low urinary pH further explains how metabolic acidosis can increase serum potassium levels and vice versa.[22]

The mineralocorticoid aldosterone serves a role in homeostasis by increasing in response to hyperkalemia in a negative feedback loop.[22] It binds to receptors and forms a complex which migrates to the nucleus and affects gene transcription with a resultant increase in activity of basolateral Na-K-ATPase pumps and the luminal epithelial sodium channel (ENAc). Distal tubular sodium uptake is therefore enhanced, which creates electronegativity within the tubular lumen, thus facilitating potassium excretion via an electrical gradient. Aldosterone drives a net efflux of hydrogen and potassium ions in tandem with sodium retention. This is the reason for the characteristic biochemical pattern of hypokalemia, metabolic alkalosis and relative hypernatremia seen with states of aldosterone excess.[21,27]

In addition, aldosterone directly increases the permeability of the luminal membrane to potassium, thus facilitating excretion.[28]

Aldosterone-independent pathways have been proposed, as evidenced by an increase in urinary potassium excretion in the context of potassium loading, which was not prevented by the mineralocorticoid receptor antagonist eplerenone. This putative pathway involves a hitherto unidentified gut-responsive kaliuretic factor. Rat models have demonstrated a greater kaliuretic response to enteral potassium loading compared to intravenous loading, emphasising the potency of this pathway. Renal potassium excretion is subject to a circadian rhythm, being lowest around midnight and highest around midday.[22,29–31]

Upstream reductions in renin secretion reduce aldosterone levels which can cause a so-called "hyporeninaemic hypoaldosteronism". Similar patterns may be seen where there is a resistance to the actions of aldosterone. These can be hereditary or acquired and may be seen in diabetes mellitus, amyloidosis, sickle cell anaemia, obstructive nephropathy, systemic lupus erythematosus or pseudohypoaldosteronism. The sequelae of reductions in amounts of or sensitivity to aldosterone (hyperchloremic metabolic acidosis with hyperkalemia) are often termed hyperkalemic (or type IV) renal tubular acidosis (RTA).[1,32–34] A reduction in steroid hormones, as seen in adrenal deficiency, causes hyperkalaemia by the same mechanism.

Under conditions where the renal excretory function is not severely impaired, ie a glomerular filtration rate of >20mL/min, hyperkalaemia may be caused by aldosterone deficiency or resistance. Measuring the ratio of renin to aldosterone may be diagnostically useful in this setting and may point towards diagnoses such as congenital adrenal hyperplasia. This and other rarer causes of hyperkalemia, such as hyperkalemic periodic paralysis, are beyond the scope of this review article.[34]

Diminished urinary flow impairs distal tubular sodium delivery, which reduces potassium excretion.[21] This explains why hyperkalemia is more common in advanced renal failure when the glomerular filtration rate (and therefore tubular flow) falls. Compensatory increases in potassium excretion can offset this to a certain degree, but less so as renal function declines further.[35]

Measurement of urinary electrolytes may add some diagnostic value, for instance calculation of the transtubular potassium gradient (TTKG). A TTKG of less than 6 indicates an inappropriate renal response to hyperkalaemia.[36] The administration of the mineralocorticoid fludrocortisone and subsequent repeat of the test may help distinguish between mineralocorticoid deficiency and resistance.[36,37] The TTKG has fallen out of favour, however, due to limitations by way of its assumptions regarding molecular transport in the distal nephron, which have now been disproved.[38]

Spot urinary potassium concentrations are limited as they do not take into account urinary water absorption, whereas urinary potassium-to-creatinine ratios do. A ratio of 10–15 mmol/mmol is an appropriate renal response to hyperkalemia. A 24-hour urinary potassium excretion of >150 mmol/day is appropriate in hyperkalemia. Values less than this in the context of raised serum potassium point towards inadequate renal excretion of potassium.[39]

Pseudohyperkalemia

Blood tests for potassium are not infallible and may result in unreliable results, such as spurious hyperkalemia, termed "pseudohyperkalemia". This is not uncommon and could lead to unnecessary aggressive treatments, which may result in patient harm, for instance, developing hypoglycemia because of insulin administration for hyperkalemia treatment.

Difficult venepuncture with turbulent blood flow may result in hemolysis of blood cells with a resultant increase in sample potassium concentration. To minimise the risk of pseudohyperkalemia, one should avoid forcibly expressing blood through the collection needle as this may hemolyse blood cells. Avoidance of shaking of samples and fist clenching is advisable and samples should not be shaken. A large vein with a wide bore needle may reduce the forced passage of blood and may reduce the chance of hemolysis.[40]

Potassium may extrude from cells after prolonged storage or when exposed to low temperatures. This is due to low temperatures disabling the Na-K-ATPase pump in stored samples. Conversely, warmer temperatures may result in falsely low potassium in both serum and plasma samples. Temperature-regulated storage vessels may mitigate this problem.

Pseudohyperkalemia may result from hematological abnormalities associated with leakage of potassium from inside cells in vitro. This is particularly apparent in thrombocytosis or significant leukocytosis. Anticoagulated plasma samples (eg lithium tubes) drawn at the same time may yield a more physiological result compared to serum samples. Extrusion of intracellular potassium is reduced in the presence of such anticoagulation.[40]

Dietary Potassium

The World Health Organization (WHO) recommends adults without renal disease should consume 3.9 g (100 mmol) a day of potassium through their diet.[41] For adults without impaired potassium excretion, the National Institutes of health (NIH) has suggested an adequate dietary intake of 60–85 mmol per day.[42] A daily potassium intake of 2–3 grams per day (51–77mmol) or <77 mmol/day are classed as low potassium diets and are recommended by the *Renal Association* for those with recurrent hyperkalemia ≥5.5 mmol/L.[43–45]

This normally requires a change in dietary intake as potassium is present in a variety of food groups, including certain fruits, vegetables, meat, cereals, and dairy. A strictly low potassium diet needs concessions to allow for the benefits of the foods that contain them, as many potassium-rich foods are sources of fibre and vitamins too.

Potassium is present intracellularly in animals to modulate cell membrane electric potentials, and therefore is abundant in animal-derived proteins. Potassium is involved in many processes required for plant growth, and plant-based foods are high in fibre.

Educating patients on the role that their diet plays in managing their health is vital. Principles such as boiling foods to reduce their potassium content by demineralisation, knowledge of foods that have a high potassium to fibre content, and awareness of additional sources of potassium such as salt substitutes are vital.

Variations in the preparation of potassium-rich foods can help to retain their benefits while reducing their potassium content.

Dietary potassium is absorbed in the duodenum and jejunum and is excreted with feces (approx. 10%) and urine (approx. 90%) under normal conditions.[1,21] Slowed fecal transit favours gastrointestinal potassium absorption and may be a major factor leading to hyperkalemia in end-stage renal disease.[46] Therefore, maintaining a high fibre content should be an important factor in managing dietary potassium.

Signs and Symptoms

Hyperkalemia is often clinically silent with no symptoms and is just apparent in biochemistry results. On occasions where patients do have symptoms, they are often vague and non-specific, including muscular weakness, nausea, muscle pain, lethargy and paresthesia.[34] Abnormalities may be detected on electrocardiogram (ECG) which can progress with increasing severity of hyperkalemia. Such changes include "tenting" of T waves, P wave loss/flattening, increased QRS duration and an eventual "sine wave pattern".[1]

Management

There are several steps which are widely adopted in the management of acute hyperkalemia. The *Renal Association* (RA) guidelines for the management of hyperkalemia were updated in 2020. The Kidney Disease Improving Global Outcomes (KDIGO) workgroup released similar guidelines for the management of hyperkalemia (also in 2020). These guidelines form our framework for discussion around management.[45,47] They suggest a pragmatic stepwise approach based on the severity of hyperkalemia and the presence of ECG changes We will first discuss the approach to acute hyperkalemia and follow this with a discussion of their approach to chronic hyperkalemia. Their recommendations for acute hyperkalemia are broken down into 5 key steps:

1. Protect the heart
2. Shift potassium into cells
3. Remove potassium from the body
4. Monitor potassium and glucose
5. Prevention of recurrence or further rise in potassium

The RA advocates the initial steps to ensure patient stability using the "ABCDE" approach (airway, breathing, circulation, disability, exposure), obtaining a 12 lead ECG (if serum potassium is greater than or equal to 6 mmol/L), excluding pseudohyperkalemia and empirically treating arrhythmia if hyperkalemia is suspected. The subsequent phase in their management is to stratify hyperkalemia to "mild", "moderate" or "severe" based on serum concentrations of 5.5–5.9 mmol/L, 6.0–6.4 mmol/L and ≥6.5 mmol/L, respectively. For those with "mild" hyperkalemia, it is suggested that one considers the cause and need for treatment. For those with "moderate" or "severe" hyperkalemia there is a recommendation for a 12 lead ECG. If ECG changes are present (ie peaked T waves, flat/absent P waves, broad QRS complex, sine wave pattern, bradycardia or ventricular tachycardia) then administration of intravenous calcium is recommended.

This could be 10 mL of 10% calcium chloride or 30 mL of 10% calcium gluconate, with repeat doses administered after 5 minutes if ECG changes persist. The role of the calcium is to stabilise the myocardium from the risk of dangerous arrhythmias. There are some concerns over the use of calcium in digoxin toxicity with a possible potentiation effect, however this is controversial.

The next step of the RA guideline focuses on shifting potassium into cells with the use of 10 units of soluble insulin with 25 grams of glucose (usually 50 mL of 50% glucose). There is a risk of hypoglycemia with this treatment and the guidelines have expressly stated that glucose should be monitored closely and for those with a pre-treatment glucose level of <7 mmol/L, an infusion of 10% glucose should be given at a rate of 50mL/hr for 5 hours (25 grams). A matched cohort study showed rates of hypoglycemia at 1 hour of 15.8% and 8.3% for patients who received 25 grams of glucose and 50 grams of glucose, respectively, with their insulin.[48] The RA guidelines mention a possible dose-dependent effect of insulin on potassium lowering, citing studies, which showed greater drops in serum potassium levels with 10 as opposed to 5 units of insulin. Rates of hypoglycemia may be less with low-dose insulin regimes. The KDIGO guidelines differ from the RA in that they recommend 5 units of insulin.

Adjunctive salbutamol nebulisers at a dose of 10–20 mg can be given to help shift potassium into cells. Novel oral potassium binders have been incorporated into the new guidelines for those with life-threatening hyperkalemia in the form of either sodium zirconium cyclosilicate (SZC) at a dose of 10 grams three times per day for 3 days, or patiromer at

a dose of 8.4 grams once a day. These are discussed in more detail in the section on novel potassium binders. Administration of insulin and glucose may need to be repeated, and in severe cases, kidney replacement therapy (KRT), for example hemodialysis, may need to be undertaken to remove potassium from the body. There may be a role for hemodialysis in hyperkalemic arrest and this should be considered in certain cases according to guidelines, although maintaining sufficient cardiopulmonary resuscitation to permit hemodialysis would inevitably be challenging.

There is conflicting evidence around the use of sodium bicarbonate in hyperkalemia. Case series have demonstrated variable response to administration of sodium bicarbonate, with some hyperkalemic patients having a less than 1 mmol/L reduction in serum potassium following administration, and others showing decreases in the region of 1.5–3 mmol/L. Patient selection may be relevant, with those patients with metabolic acidosis (pH <7.35), hyperkalemia (>6 mmol/) and bicarbonate <17 mmol/L appearing to respond in a more favourable manner. Hypertonic sodium bicarbonate has been used to treat hyperkalemia with success in severely acidotic patients, however some of its efficacy may be reversed due to its hypertonicity.[49]

The *Renal Association* guidelines support the use of oral sodium bicarbonate in CKD patients with or without hyperkalemia who have a serum bicarbonate level of <22 mmol/L. This recommendation is on the basis of studies they cite which demonstrate a chronic reduction in hyperkalemia with its use but not with acute use. As such, they do not advocate the use of sodium bicarbonate in the acute setting. The benefits of sodium bicarbonate in treating chronic metabolic acidosis associated with CKD are numerous and include a reduction in the progression of kidney impairment. The KDIGO guidelines support the use of intravenous sodium bicarbonate for those who are hyperkalemic with a metabolic acidosis if the patient is not at risk from an increased sodium load, however they too acknowledge the lack of robust evidence in this area.

Both sets of guidelines mention the possible role of loop diuretics, particularly in volume replete or hypervolemic patients who are non-oliguric. There is a paucity of evidence regarding their use, however based upon their pharmacology, it is predicted that they would help urinary potassium excretion. The KDIGO guidelines state that there may be a role for intravenous furosemide in acute hyperkalemia, however the RA guidelines only advocate for their use as an adjunct for the management of chronic hyperkalemia.

The *Renal Association* guidelines for hyperkalemia also address management of outpatients; this section generally focusses on modification of diet and medications to mitigate risk of harm from mild-to-moderate hyperkalemia.

Commencement of a low potassium diet is recommended for all patients with persistent serum potassium values greater than 5.5 mmol/L in the guidelines from the *Renal Association*. It is noted, however, that the evidence for dietary modification is not particularly strong.[45,47]

It is recommended by the *Renal Association* that patients with severe hyperkalemia (serum concentration ≥6.5 mmol/L) are referred to hospital for immediate emergency management, this is slightly more liberal than the threshold of >6 mmol/L in the KDIGO guidelines.

RA guidance states that those in hospital with moderate hyperkalemia or in the community with mild-to-moderate hyperkalemia may benefit from oral cation exchange resins until the serum potassium is ≤5 mmol/L, which may enhance gastrointestinal excretion of potassium. Care must be taken to avoid constipation and co-prescription of laxatives, such as lactulose is sensible. Laxatives such as *Movicol* should be avoided as these contain potassium. There are some concerns over gastrointestinal perforation and necrosis with these medications, but with judicious patient selection they may be useful tools.[49]

Patients with heart failure who are taking mineralocorticoid antagonists (MRA, eg spironolactone) can be maintained on their medication until their potassium is ≥6.5 mmol/L in the absence of acute illness (RA guidelines). Temporary cessation is advised in the event of acute illness such as sepsis or acute kidney injury.

The RA states that if patients are well (ie not acutely ill) and their potassium is >6 mmol/L-6.4 mmol/L, then the use of sodium zirconium cyclosilicate or patiromer is advocated to keep them on their MRA with close monitoring of renal function and electrolytes. In patients without heart failure, MRA cessation is advised if serum potassium is ≥6 mmol/L. Initiation of sodium zirconium cyclosilicate and patiromer should be restricted to secondary care, should exclude patients on dialysis and should be discontinued if RAAS inhibition is halted.

Although this is not addressed in the guidelines, patients with acute kidney injury who have volume depletion and hyperkalemia may benefit from intravenous fluids. Crystalloids such as saline, Plasmalyte or Hartmann's contain sodium which may exchange with potassium in the distal tubule and therefore aid potassium excretion.[47,50] Balanced crystalloids such as Hartmann's and Plasmalyte contain potassium, but this is at a low concentration. Some may be reluctant to use such fluids for fear of inducing hyperkalemia, however this is a fallacy. The potassium concentration of such fluids is not high enough to increase the serum potassium (and is lower than the serum concentration in a hyperkalemic patient) and high-quality studies have consistently demonstrated higher rates of hyperkalemia in those given saline rather than balanced crystalloids, likely due to an extracellular shift of potassium in the context of a mineral metabolic acidosis.[50–53]

Fludrocortisone is a mineralocorticoid agonist that has shown some promise in small case series of hyperkalemic patients.[54–56] This is alluded to in the KDIGO guidelines but without any firm recommendations for use. Aldosterone has fibrotic effects on the cardiovascular system and kidneys and antagonism has led to an improvement in cardiovascular renal outcomes in the FIDELIO-DKD and FIGARO-DKD studies.[9,10,57] In light of this, mineralocorticoid receptor activation may theoretically be associated with deleterious consequences.

Hyperkalemia on Peritoneal Dialysis and Hemodialysis

Dyskalemias are more common in patients receiving dialysis than in the general population.[58] At a population level, those patients on peritoneal dialysis have potassium levels distributed toward the lower end of the normal range with the reverse being true for those on hemodialysis. The risk of death increases at both ends of the spectrum.[59,60] Particularly with hemodialysis, for the individual patient potassium levels can fluctuate significantly and it can be a challenge to maintain normokalemia throughout the week.

Potassium removal for a typical four-hour session is 70 to 100mmol.[61] For adults without impaired potassium excretion, the National Institutes of health (NIH) has suggested an adequate dietary intake of 60–85 mmol per day.[42] Even at the most favourably discordant ends of these spectra it is clear that, without any residual urinary function, even with enhanced GI secretion, hyperkalemia is inevitable without dietary modification. Herein the focus will be on the acute management of hyperkalemia.

For stable patients on maintenance hemodialysis, the definitive treatment for hyperkalemia is dialysis.[62] Treatment with insulin or beta-2-agonists is generally discouraged as they substantially reduce the potassium clearance in a dialysis session, which is dependent on potassium exchange between the dialysed blood compartment and the intracellular space.[63] This may be appropriate if there is likely to be a delay to treatment, but it is important to recognise this reduction in the risk of complications acutely as it may increase the risk of rebound hyperkalemia after dialysis.

Practically, the choice of renal replacement usually depends on the availability of access and equipment. Hemodialysis is very effective at reducing potassium concentrations in serum. It would be expected to reduce potassium by an average of one millimole in the first hour and then at an exponentially decreasing rate as the session continues and the gradient for diffusion diminishes.[64] Serum potassium concentration generally follows two compartment kinetics. Practically, this means that equilibrated post-dialysis potassium is directly proportional to the pre-dialysis concentration.[65]

Clearance of potassium by dialysis is most dependent on the serum to dialysate potassium concentration. Data on the optimum dialysate potassium concentration are conflicting. Using lower dialysate potassium concentrations, particularly below 2mmol/L, results in greater potassium clearance and lower post-equilibrium potassium levels.[61] However, this may be at the expense of greater risk of arrhythmia due to more rapid changes in serum levels and transmembrane potentials. It is not clear how much benefit faster clearance confers to the patient. This has caused some to advocate for dialysate potassium profiling, reducing potassium concentration in line with serum level to maintain a steady gradient, theoretically optimising clearance and reducing arrhythmia risk. Pragmatically, the difference in outcomes between high, 2–3 mmol/L potassium dialysate, and low, 0–1 mmol/L, when performing dialysis for acute hyperkalemia is small enough that the optimal approach is yet to be definitively proven and instead relies on secondary outcome measures.[49,66,67] If there is a facility to monitor potassium levels and provide further dialysis, if required, then a 2 mmol/L dialysate or profiling probably represents the safest strategy.

Bicarbonate concentration in the dialysate also affects potassium concentrations. Higher bicarbonate concentrations, up to 38 mmol/L, cause more rapid reductions in serum potassium compared to lower bicarbonate levels. This occurs early in the session and is felt to be predominantly due to intracellular shift as the higher bicarbonate level results in lower potassium removal. This is borne out by the fact that, although the final serum concentrations of potassium tend to be lower in higher bicarbonate dialysis, they tend to rebound more.[68] The role of manipulating the dialysate bicarbonate concentration in the management of hyperkalemia is also not yet completely clear.

Hemofiltration in general has a significantly lower clearance for potassium due to its reliance on clearance by convection and lower flow rates.[69] This is compensated for by longer treatment duration and accordingly much less rebound.

Peritoneal dialysis can be very effective in the management of hyperkalemia. Although there has been renewed interest in peritoneal dialysis for the management of acute kidney injury, most centres would struggle to provide peritoneal access to facilitate emergent management of hyperkalemia. Hereon, the focus will be on those with established peritoneal access.

As mentioned earlier, it is unusual for patients on peritoneal dialysis to be hyperkalemic. Therefore, if they are hyperkalemic, this may be due to dialysis failure which precludes its use as an emergent treatment. Peritoneal dialysis can be very effective at clearing potassium and there are a number of case series demonstrating its efficacy in the management of hyperkalemic acute kidney injury.[70–72] However, it is worth noting that potassium clearance with peritoneal dialysis is not as efficient as hemodialysis, as it may remove around half as much as a standard four-hour session in 24 hours.[73] Most clinicians faced with truly life-threatening hyperkalemia would consider hemodialysis as the definitive treatment.

For patients in whom the risk is lower, high volume daily peritoneal dialysis is an option; this can be done manually or more usually with an automated cycler. Different groups have used different protocols where draining to dryness or tidal settings can be used effectively. The principle behind both is similar: large volumes of fluid, adjusted for patient size, are used to maximise the surface area for exchange. Regular exchanges occur to ensure large potassium gradients are maintained between the serum and peritoneal dialysis fluid; most commercial dialysis fluids contain no potassium at all. Reasonable volumes of ultrafiltrate should also be targeted as the patient's haemodynamic state allows. A standard prescription might be 2 litres of a 1.5% glucose solution instilled for 30 to 120 minutes, drained and repeated throughout a twenty-four-hour period aiming for around two litres ultrafiltrate. It may be possible to improve clearance by adjusting the dwell time according to the patient's transport status. Practically, this involves weighing the time lost without dialysis, which occurs when more exchanges are carried out against diminishing potassium clearance as the dwell time increases.

Initially, there may be a drop in potassium above that which might be expected as a result of clearance alone. This is thought to be due to the intracellular shift of potassium as glucose from the dialysis fluid is absorbed.[61] As peritoneal dialysis is a continuous therapy, it also prevents rebound which can be troublesome in hemodialysis. Other benefits that have been suggested include increased haemodynamic stability, better tolerability in those with heart failure, lack of need for vascular access and patient familiarity.

Emergence of Novel Potassium Binders

As previously discussed, chronic hyperkalemia is common in patients with advanced CKD, heart failure, resistant hypertension, diabetes mellitus and may be further precipitated by medications. Unfortunately, some of these medications, such as ACE (angiotensin-converting enzyme) inhibitors, beta-blockers and potassium-sparing diuretics have prognostic benefits in these conditions, yet all can contribute to the underlying hyperkalemia.

Chronic outpatient treatment for hyperkalemia, aside from the reduction or discontinuation of RAASi medications and recommending a low potassium diet (although the evidence for this remains limited), was previously limited to loop diuretics and/or sodium polystyrene sulfonate (SPS), a resin that exchanges potassium for sodium in the colon. However, this is poorly tolerated and has substantial gastrointestinal adverse effects (eg GI necrosis) which can result in poor adherence.[74]

Recently, the emergence of novel potassium binders acting primarily in the gastrointestinal tract facilitate the removal of potassium ions bound to faeces, which have provided new tools for tackling chronic hyperkalemia. Patiromer (Veltassa) and sodium zirconium cyclosilicate (SZC; Lokelma) are both well tolerated in comparison to

SPS and are now approved by NICE for use in the UK. The current NICE guidelines advise using both agents for people with persistent hyperkalemia with CKD stages 3b to 5 (not including dialysis patients) or heart failure, with serum potassium of at least 6.0 mmol/L, whilst on RAASi therapy. Furthermore, it can be used to treat acute life-threatening hyperkalemia alongside standard care.[74]

Trials with patiromer, a polymer that exchanges potassium cations for calcium ions primarily in the distal colon, have shown a dose-dependent reduction in serum potassium concentrations.[75] The onset of the action occurs after approximately 7 hours, with a mean potassium reduction of 0.21 mEq/L.[76] Normokalaemia was maintained at 12- and 52-week follow-ups in a separate study in 77.4%–95.1% of patients[77] (although the 52-week period was open-label and not placebo controlled). Similar to SPS, patiromer is nonselective for potassium ions and also binds magnesium and sodium.[78] Furthermore, patiromer should be given approximately 3 hours apart from other oral medications as they may bind to it, thus affecting their efficacy. Common side effects include gastrointestinal discomfort (including constipation, diarrhoea and nausea), and electrolyte abnormalities (hypokalaemia or hypomagnesaemia).[75]

In patients with diabetes and CKD, including those on RAASi therapies, normokalaemia was maintained with patiromer for up to 12 months.[77] Furthermore, for patients with CKD and resistant hypertension, significantly more patients were maintained on spironolactone (25–50 mg once daily) and patiromer compared to placebo over 12-weeks,[79] allowing continuation or up-titration of prognostically useful medications.

SZC is a non-polymer compound that exchanges potassium for sodium and hydrogen ions. Given the specificity of the potassium ion and the inorganic structure of this molecule, it is less likely to possess significant interactions.[80] It is the most recently approved potassium binder with efficacy and safety established in Phase 2 and 3 clinical trials for patients with hyperkalemia and CKD, heart failure and/or diabetes mellitus. There are no serious associated adverse effects; however, milder side effects include gastrointestinal upset (nausea, constipation or diarrhoea), dose-dependent oedema and hypokalaemia. The onset of action occurs after 1 hour, with a reduction in potassium of 0.17 mEq/L,[81] and a maximal reduction after 48 hours (0.67 mEq/L, Meaney et al; 1.1 mmol/L, HARMONIZE).[82] With acute hyperkalemia, ENERGIZE trial compared SZC with standard care to standard care alone (insulin and dextrose). No significant difference was seen at 1 hour; however, a greater reduction was seen after 2 hours,[83] suggesting an additional role for SZC in emergency settings as well.

Both patiromer and SZC represent significant advances in the treatment of hyperkalemia and given their mild adverse effects, they are both likely to be better tolerated than SPS. However, given the more rapid onset of action, SZC is more likely to play a role as an adjunctive acute treatment. Either drug may play a role in allowing continuation of RAASi therapies for patients with advanced CKD with heart failure and/or diabetes mellitus, who may otherwise be limited by hyperkalemia. Further trial data is still required to assess whether these drugs would be beneficial to other at-risk groups, such as those with end-stage kidney disease. See Table 2 for the properties of patiromer and SZC and Table 3 for a summary of some key trials involving these medications.

Table 2 Pharmacological Characteristics of Novel Potassium Binders

	Patiromer (Veltassa)	**SZC (Lokelma)**
Mechanism of action	Some selectively binds K^+ (also Mg^{2+}) in the GI tract and facilitates excretion in the faeces.	Highly selective to bind K^+ in the GI tract and facilitates excretion in the faeces.
Onset of action	7 hours	1 hour
Duration of action	12–24 hours	12 hours
Dose	8.4 g once daily	10 g three times a day Maintenance 5–10g once daily

Abbreviations: GI, gastrointestinal; K^+, potassium; Mg^{2+}, magnesium; SZC, sodium zirconium cyclosilicate.

Table 3 Summary of Trials Involving Patiromer and Sodium Zirconium Cyclosilicate (SZC)

Trial Name	Study Design	Patient Population	Primary Aims	Study Treatment	Major Findings
PATIROMER (Veltassa)					
PEARL-HF 2011[85]	Randomised, double-blind, placebo-controlled	105 HF patients with CKD (eGFR <60 mL/min/ 1.73 m^2)	To evaluate safety and efficacy on serum K+ levels in patients with chronic HF receiving standard therapy and spironolactone	30 g vs placebo	Treatment group had significantly lower serum K+ (−0.45 mEq/L; P<0.001)
AMETHYST-DN 2015[77]	Phase 2 multicentre, open-label, dose-ranging, randomised controlled trial	306 patients with T2DM and CKD (eGFR 15–60 mL/ min/1.73 m^2) on RAASi	Mean change in serum K+ from baseline to week 4 through to week 52	Mild hyperkalemia: 8.4 g or 12.6g BD Moderate hyperkalemia: 12.6 g or 16.8 g BD	Mean change in serum K+ at from week 4 through to week 52 (P<0.001)
AMBER 2019[86]	Randomised, open-label, placebo-controlled	295 patients with CKD (eGFR 25–45 mL/min/ 1.73m^2)	Proportion of patients remaining on spironolactone	Patiromer 8.4 g vs placebo	84% (Patiromer) vs 68% (placebo)
SODIUM ZIRCONIUM CYCLOSILICATE (SZC; Lokelma)					
HARMONIZE 2014[82]	Phase 3, multicentre, randomised, double-blind, placebo-controlled (initial 48 h were open-label)	258 patients with serum $K^+ \geq 5.1$ mEq/L	To evaluate the efficacy and safety of zirconium cyclosilicate for 28 days in patients with hyperkalemia. Mean serum K+ change versus placebo in each group	10 g tds for 48 h (correction phase) Normokalaemic (3.5–5.0 mEq/L) patients randomised to 5 g, 10 g, 15 g od (maintenance phase)	Open label (first 48 h): Serum K+ dropped from 5.6 mEq/L to 4.5 mEq/L. 84% (95% CI 79%-88% achieved normokalaemia (3.5–5.0 mEq/L). Randomised phase. Serum K+ significantly lower at each dose (P<0.001)
DIALIZE 2019[87]	Phase 3b, multicentre, randomised, double-blind, placebo-controlled	97 patients with ESKD and HD (x3/ week), pre-dialysis serum $K^+ \geq 5.4$ mmol/L	Proportion of patients who maintained pre-dialysis serum K+ between 4.0–5.0 mmol/L	SZC 5 g, 10 g and 15 g vs placebo	41.2% (treatment) vs 1.0% (placebo); P<0.001
ENERGIZE 2020[83]	Exploratory, Phase 2, multicentre, randomised, double-blind, placebo-controlled	70 patients (in A&E) with serum $K^+ \geq 5.8$ mmol/L	Mean change in serum K+ from baseline until 4 h after initial dose.	SZC 10 g vs placebo	Mean serum K+ change of -0.41 mmol/L (±0.11 mmol/L)

Abbreviations: CKD, chronic kidney disease; ESKD, end-stage kidney disease; HD, hemodialysis; HF, heart failure; K^+, potassium ions; RAASi, renin angiotensin aldosterone system inhibitors; SZC, sodium zirconium cyclosilicate; T2DM, type 2 diabetes mellitus.

Conclusion

Hyperkalemia is a common problem in CKD patients, aggravated by concomitant risk factors, such as drug therapy, diabetes and heart failure, and is associated with increased mortality. Inhibition of the RAAS is therapeutically desirable because of the plethora of prognostic benefits that it brings, such as slowing progression of kidney disease; but this is in association with an increased risk of hyperkalemia. A multitude of risk factors for the development of hyperkalemia must be considered when initiating or altering medications. The newer mineralocorticoid receptor antagonist, finerenone,

offers clinicians a new tool which may have a lower risk of hyperkalemia. Multiple medications and strategies are available to manage acute and chronic hyperkalemia with a strong physiologic rationale but a variable evidence base. There are a number of unanswered questions regarding the efficacy and tolerability of treatments. Dialysis may be required in refractory cases to facilitate potassium removal from the body. Novel potassium binders have shown promise and are being investigated in a broader patient cohort, with hopes that they will become a mainstay of management and will allow maximal dose RAAS inhibition in those who may benefit.

Disclosure

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