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ORIGINAL RESEARCH

Management of hyperkalemia: Expert consensus from Kuwait – a Modified Delphi Approach

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Introduction: Hyperkalemia is common in heart failure (HF) patients on renin angiotensin aldosterone inhibitors (RAASi), in chronic kidney disease (CKD), and in hemodialysis, and it negatively impacts their management. New potassium binders, such as sodium zirconium cyclosilicate (SZC), are effective in management of acute and chronic hyperkalemia. However, guidelines inconsistencies and lack of standardized treatment protocols are hindering proper and wider use of such agents. Therefore, an expert panel from Kuwait developed a consensus statement to address hyperkalemia management in acute settings, in HF, in CKD, and in hemodialysis.

Methods: A three-step modified Delphi method was adopted to develop the present consensus, which consisted of two rounds of voting and in-between a virtual meeting. Twelve experts from Kuwait participated in this consensus. Statements were developed and shared with experts for voting. A meeting was held to discuss statements that did not reach consensus at the first round and then the remaining statements were shared for final voting.

Results: The consensus consists of 44 statements involving an introduction to and the management of hyperkalemia in acute settings, HF, CKD, and hemodialysis. Thirty-six statements approved unanimously in the first vote. In the second vote, four statements were removed and four were approved after editing.

Conclusion: Hyperkalemia management lacks standardized definitions, treatment thresholds and consistent guidelines and laboratory practices. This consensus is in response to lack of standardized treatment in the Arabian Gulf, and it aims to establish guidance on hyperkalemia management for healthcare practitioners in Kuwait and highlight future needs.

Keywords: chronic kidney disease, heart failure, hemodialysis, hyperkalemia, potassium binders

Introduction

Hyperkalemia is a common electrolyte disorder in chronic kidney disease (CKD),[1] which can have negative consequences for cardio-renal management in the medium and long term.[1,2] The European Resuscitation Council defines hyperkalemia as a plasma K^+ level greater than 5.5 mmol/L and severe hyperkalemia as a level greater than 6.5 mmol/L.[3]

Factors that can predispose to hyperkalemia include kidney-related factors such as low glomerular filtration rate (GFR), reduced tubular flow, reduced distal sodium delivery, and/or reduced aldosterone activity/production[1,2,4–6], Also, one of the contributing factors to hyperkalemia in patients with CKD is metabolic acidosis, especially diabetics, which causes a shift of K^+ from the intracellular to the extracellular space[1,4], further exacerbating hyperkalemia and limiting the use of renin-angiotensin-aldosterone inhibitors (RAASi) for the treatment and prevention of cardiovascular diseases (CVD),[1,7] and the management of CKD. Other major risk factors for hyperkalemia include diabetes mellitus, adrenal disease, and heart failure (HF).

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Management of hyperkalemia is challenging at the level of thresholds and type of intervention.[8] Another challenge is the inconsistencies reported between diagnostic laboratories as of when and how specialists are notified of hyperkalemia results and the suggested thresholds for urgent intervention.[8]

In acute cases of hyperkalemia, immediate interventions may be necessary to lower K^+ levels and stabilize the patient.[9] These interventions may include the administration of medications such as calcium gluconate to protect the heart from the effects of high K^+ levels, insulin, and glucose to promote cellular uptake of K^+ and medications that enhance K^+ excretion, such as loop diuretics or sodium polystyrene sulfonate.[3] Additionally, long-term management strategies to return to normokalemia in chronic hyperkalemia should involve the use of medications such as potassium-binders, which help remove excess K^+ from the body, or the initiation of kidney replacement therapy (KRT) in severe cases.[1]

In recent years, there have been developments in the use of novel potassium-binders, such as sodium zirconium cyclosilicate (SZC) and patiromer, which have been found to effectively lower K^+ levels and have been well tolerated by patients, and hence, are used to treat chronic hyperkalemia in patients with CKD.[10–12] These binders aim to reduce dietary K^+ absorption and may have implications for long-term cardiovascular and renal outcomes.[11]

With the lack of standardized treatments and evidence-based guidelines for outpatient hyperkalemia management,[8,9] this consensus aims to gather experts' insights and consensus regarding guidance for hyperkalemia management for healthcare practitioners in Kuwait. This consensus is based on identifying and critically appraising research evidence and generating recommendations based on the available evidence and expert opinion.

Materials and Methods

Study Design and Panel Recruitment

This consensus is based on a three-step modified Delphi method, which has proven its reliability for building consensus in a variety of clinical settings through repeated voting rounds on a specific set of statements; these statements were developed via a series of systematic literature searches and experts' feedback. A modified version of the Delphi method, known as the modified Delphi process or Estimate-Talk-Estimate process, was then introduced to incorporate a face-to-face meeting in the Delphi process, and aims to gain more insights from the experts on statements with no consensus agreement in the first round of voting. The modified Delphi method provides more effective interaction and agreement than the original version of the Delphi process. This study utilized two rounds of voting and in-between virtual meetings to develop consensus statements.

A total of 12 experts from Kuwait were invited to participate in the Delphi study and were asked to participate in the process's three steps. All experts were required to have an active research profile in the field of nephrology and cardiology.

Literature Review and Statements Development

A systematic literature search was conducted on Medline via PubMed from its inception to April 2023 to collect relevant information. The following search terms were used in combination with the term "hyperkalemia": "management", "treatment", "diagnosis", "acute hyperkalemia", "heart failure", "hemodialysis", "Kuwait", "guidelines", "KDIGO", "monitoring", "chronic kidney disease", "CKD", "K^+ binders", and "potassium". Initially, the titles and abstracts of the retrieved records were screened. Then, full texts of the publications that address the consensus objectives were reviewed. A manual search of the references of retrieved publications was also conducted.

Statements were developed and questionnaire was sent via Email to experts for revision and voting. The questionnaire consisted of binary statements, in which the experts were asked to choose between "agree", "disagree", and "abstain" options. Each expert was able to comment on each statement and provide suggestions. A descriptive statistic quantified experts' responses to each statement. Each statement was considered to achieve consensus if it achieved an agreement level of ≥75%. The statements that did not achieve the agreement level were persevered for step 2 to be modified or omitted by the experts.

A virtual advisory board meeting was conducted in the second step and engaged all experts. Whether they reached the agreement level or not, all statements were presented during this meeting to gain the experts' feedback and

recommendations. The meeting was divided into two parts. In the first part, the statements that achieved ≥75% agreement were presented for full consensus by the panel, while the remaining statements were presented for modification or omission. The second part of the meeting aimed to develop the final guideline form for hyperkalemia management.

In the final step, the list of modified statements and the final form of the guidelines were emailed to experts for voting and followed the same voting process as step 1. The final consensus statements and manuscript were reviewed and approved by all experts.

Results and Discussion

A total of 44 statements were developed. At first voting round 36 received consensus and did not require a second voting round; eight statements were edited and proceeded to a second vote where four were removed and four achieved consensuses after editing. Finally, 40 statements are included in this consensus.

Hyperkalemia introduction and Management

Introductory statements to hyperkalemia and its management are outlined in Table 1. The panel agrees that hyperkalemia is defined by blood K^+ level >5 mmol/L, as suggested by guidelines and medical societies.[2,13–15] However, others define hyperkalemia as blood K^+ level >5.5 mmol/L.[16,17] The panel also agrees that blood K^+ level >6.5 mEq/L is life-threatening increasing the risk of arrhythmia and cardiac arrest, in agreement with published literature.[18,19] However, some suggests that a blood K^+ level >6.0 mEq/L is where hyperkalemia starts to be life-threatening and increases the risk of arrhythmia and cardiac arrest.[14,15,20]

The panel also acknowledges the fact that hyperkalemia is a common electrolyte disorder and that its clinical manifestations may be non-specific, in agreement with published literature.[9,26] Similarly, the panel agrees that hyperkalemia is a predictable, and manageable condition in high-risk patients such as HF and CKD.[27–30] Also, studies declare that kidney function plays a significant role in K^+ regulation, and impaired kidney function can increase the risk of hyperkalemia.[31]

The panel agrees that the mortality rate is particularly high in hyperkalemic patients with severe underlying diseases and coexisting illnesses independent of kidney function and sickness severity. As studies also show the mortality rate was higher in hyperkalemic patients with CKD than the non-hyperkalemic patients with CKD.[32,33]

The panel agrees with published literature that hyperkalemia is associated with significant long-term economic burdens due to an increase in emergency department (ED) visits, and associated with frequent hospitalizations and mortality, since studies show that hyperkalemia can have toxic effects on the cardiac conduction system, potentially

Table 1 Introductory Statements

Statements	Reference No	Final voting %
1. Hyperkalemia is generally defined by an abnormal high level of potassium in the blood (>5 mmol/L) where levels >6.5 mEq/L increase the risk of arrhythmia and cardiac arrest.	[6,14]	100%
1. Hyperkalemia is a common electrolyte abnormality, and its clinical manifestations may be non-specific.	[21]	88%
1. Hyperkalemia should be considered as a predictable, treatable, and manageable side effect of patients with heart failure and chronic kidney disease; and a history or high risk of hyperkalemia.	[22]	100%
1. Independent of kidney function and sickness severity, the mortality rate is particularly high in hyperkalemic patients with severe underlying diseases and coexisting illnesses.	[23]	100%
1. Hyperkalemia is associated with significant long-term economic burden and frequent hospitalizations, indicating the importance of hyperkalemia treatment to reduce these burdens and clinical complications.	[24,25]	100%
1. Assessment of cardiac and kidney function as well as volume status are required in the management of hyperkalemia.	[24]	75%

leading to lethal outcomes.[34] Thus, indicating the importance of hyperkalemia prevention and management to reduce these burdens and clinical complications.[24,35,36]

Regarding the management of hyperkalemia, the panel agrees that it requires assessment of cardiac and kidney function as well as volume status. The panel also agrees that assessment of cardiac function, kidney function, and volume status are crucial for hyperkalemia management, as recommended by published literature.[3,37] Monitoring serum K^+ levels and assessing kidney function help identify patients at risk of hyperkalemia especially in patients with CKD or patients taking RAASi, and help managing hyperkalemia by guiding medication adjustments.[31,38]

Managing Hyperkalemia in the Acute Setting

This section discussed all aspects of acute hyperkalemia and its management and statements discussed are in Table 2. The majority of the panel's members (88%) agree that acute hyperkalemia, defined as 5.5 mmol/L or more, may be under-recognized in ED due to normal electrocardiogram (ECG) and absence of clear clinical signs and symptoms that lead to treatment. There are only a few recent studies on acute hyperkalemia and the most recent studies confirm that elevated serum K^+ levels of 5.5 mmol/L or more is frequently asymptomatic with a normal ECG which mislead healthcare professionals causing hyperkalemia under-recognition.[3,15,34,39–41]

On the other hand, the panel agrees with the fact that hyperkalemia of sudden onset and severe hyperkalemia can cause lethal cardiac arrhythmias in most cases if not rapidly treated. This is supported by several studies displaying that severe hyperkalemia is life-threatening and can lead to sudden death from cardiac arrhythmias and asystole if not corrected promptly with a rapid point-of-care.[14,45–47]

The majority of the panel's members (75%) agree that there is no standard management protocol applicable to any case of acute hyperkalemia widely practiced or used in the ED. On the contrary, studies claim that no universally accepted standard of care protocol has been established for the treatment of patients presenting with acute hyperkalemia, whether in the ambulatory or ED setting.[48–50]

Regarding acute hyperkalemia management, the majority of the panel's members (88%) agree that it is recommended to focus on stabilizing the myocardium, redistributing K^+, and eliminating K^+ with potassium-binders, dialysis, and loop diuretics. This is consistent with published literature that list these three methods for treating acute hyperkalemia.[15,34,51] The panel also agrees that the potassium-binder patiromer can be used to treat hyperkalemia; however, it may not be effective as an add-on therapy to standard of care for management of life-threatening acute hyperkalemia when prompt reduction in blood K^+ is required, due to its slow onset of action (~7 h).[30,52] On the other hand, the panel agrees that the potassium binder SZC can be used for the management of acute hyperkalemia as an add-on therapy to standard of care in

Table 2 Managing Hyperkalemia in Acute Setting

Statements	Reference No	Final voting %
1. Acute hyperkalemia (serum potassium ≥5.5 mEq/L) may be under-recognized in emergency department due to normal ECG and absence of clinical signs and symptoms that lead to treatment delay.	[42]	88%
1. The sudden onset of hyperkalemia and extreme hyperkalemia can cause lethal cardiac arrhythmias in the majority of cases if not rapidly treated.	[14]	100%
1. The standard protocol applicable to any case of acute hyperkalemia is not widely practiced or used in the emergency department.	[39]	75%
1. For acute hyperkalemia management, it is recommended to focus on the integrity of the cardiac membranes, potassium redistribution, and potassium elimination by using potassium binders, dialysis, and loop diuretics.	[34,39]	88%
1. Patiromer is used to treat hyperkalemia; however, it is not approved as a sole agent for the management of life-threatening acute hyperkalemia due to its slow onset of action (~7 h).	[43]	100%
1. Sodium zirconium cyclosilicate (SZC) is used for the management of acute hyperkalemia (on top of SOC) as well as chronic maintenance therapy due to its rapid onset of action.	[43,44]	100%

the emergency setting for K+ removal from the body due to its more rapid onset of action, as studies showed that patients who received SZC had a decrease in serum K^+ levels within one hour of therapy,[53,54] and due to its effectiveness throughout the whole digestive system.[10,55] Patients managed for life-threatening hyperkalemia require frequent monitoring of serum K^+ to ensure reduction to a safe level in response to medical therapy. Otherwise, urgent hemodialysis is indicated.

Management of Hyperkalemia in Patients with Heart Failure

This section includes statements on the recommendations and guidelines for managing hyperkalemia in patients with HF, outlined in Table 3. The panel agrees that both hypo- and hyperkalemia are associated with increased mortality in patients with HF, as reported in recent studies.[56–60] Cooper et al conducted a cohort study using data from the Swedish Heart Failure Registry and found an association between K^+ levels and mortality, with the lowest risk of mortality observed at a K^+ level of 4.2 mmol/L.[58] Additionally, Linde et al reported that serum K^+ >4.6 mmol/L is associated with an increased risk of 90-day mortality, while serum K^+ >4.8 mmol/L in chronic HF patients increases all-cause mortality risk.[60] K^+ is vital in maintaining the electrical activity of the heart, and imbalances in K^+ levels can disrupt normal cardiac rhythm and function.[59,60] Therefore, hypokalemia can lead to arrhythmias and impaired contractility, while hyperkalemia can cause cardiac conduction abnormalities and potentially fatal arrhythmias.

The panel agrees that in HF patients, it is recommended to assess the medical history of hyperkalemia, determine its etiology and degree of reversibility, and determine levels of K^+ and estimated glomerular filtration rate (eGFR), as advised by published literature.[61,64,65]

Also, the majority of the panel's members (88%) agree that the management of hyperkalemia in patients with HF is based on serum K^+ levels. This statement advises different treatment strategies for four K^+ thresholds suggested by studies on hyperkalemic individuals with HF.[61,66,67] The panel recommends prescribing or up tittering RAASi if K^+-level is between 4 and 5.5mEq/L, adding potassium-binder when considering up titrating RAASi if K-level is between 5.1 and

Table 3 Managing Hyperkalemia in Patients with Heart Failure

Statements	Reference No	Final voting %
1. In heart failure (HF), hypo and hyperkalemia are associated with increased mortality.	[60]	100%
1. For all HF patients, it is recommended to assess the medical history of hyperkalemia, determine its etiology and degree of reversibility, and determine levels of K and estimated glomerular filtration rate (eGFR).	[61,62]	100%
1. Treatment of hyperkalemia in HF patients is based on serum K- levels: • Prescribe or titer Renin–angiotensin–aldosterone system inhibitors (RAASi) if K-level is between 4 and 5 mEq/L. • Consider adding potassium binder along with increasing RAASi if K-level is between 5.1 and 5.5 mEq/L. • Introduce K-reducing drug with RAASi if K-level is between 5.5 and 6.0 mEq/L. • Suspend the RAASi and reassess if K-level >6.0 mEq/L.	[61]	88%
1. Frequent monitoring for hyperkalemia in HF patients undergoing RAASI treatment is recommended as follows: • Initial follow-up: 1− 2 weeks. • Transitional follow-up: 8–12 weeks. • Maintenance follow-up: every four months after stabilization.	[61]	75%
1. In patients with HF, the use of sodium zirconium cyclosilicate (SZC) to reduce serum potassium levels can enable the start-up, restart, and up-titration of RAASi therapy, enabling the achievement of optimal medical therapy.	[63]	100%
1. Previous hyperkalemia treatment regimens should be used with caution in HF patients with special conditions, including: • Calcium gluconate or calcium chloride in hypotensive patients, • Short-acting insulin in combination with dextrose in hyperglycemic patients, • Salbutamol in patients with cardiac arrythmias, • Sodium bicarbonate in non-acidotic patients.	[43]	100%

5.5mEq/L, adding K-reducing drug to RAASi if K-level is between 5.5 and 6.0mEq/L, and finally withholding RAASi and reassess if K-level >6.0mEq/L. However, this approach differs from what is recommended in a multidisciplinary study that suggests the up titration of RAASi should not be restricted if serum K^+ levels between 5.1 and 5.5 mEq/L, introducing novel potassium-binders with RAASi up titration when serum K^+ levels >5.5 mEq/L, and discontinuing or reducing RAASi and introducing potassium-binders when serum K^+ >6.0mEq/L.[66]

The majority of the panel's members (75%) agree that HF patients receiving RAASi should be monitored for hyperkalemia frequently. The phrase implies that the first follow-up should occur 1–4 weeks after the initiation of RAASi; however, experts recommend reducing the time range to 1–2 weeks. Therefore, the panel agrees that the initial assessment after RAASi initiation should be at 1–2 weeks, followed by further evaluations at 8–12 weeks, and thereafter every four months once stability is achieved.[66] Furthermore, the panel recommends to closely observe the serum potassium levels during a period of 7 to 10 days after initiating RAASi treatment and while adjusting the dosage.[68] Although published literature agrees with the importance of frequent monitoring for hyperkalemia in HF patients receiving RAASi, some suggest that serum K^+ levels should be checked first 48–72 hours after RAASi introduction and again a week later, then a month later, then every 3–6 months after.[66,68–70]

The panel agrees that SZC by lowering serum K^+ levels facilitates the initiation, the reintroduction, and the up-titration of RAASi, allowing the optimization of medical therapy in HF patients, as shown in published studies.[71–75]

Finally, the panel agrees that current treatment regimens for acute hyperkalemia should be used with caution in certain groups of HF patients. This statement is divided into four sections. The first one discusses the cautious use of calcium gluconate or calcium chloride in hypotensive patients for the treatment of hyperkalemia. This is supported by a few studies showing that the administration of calcium gluconate or calcium chloride is not without risks. Since, extravasation of intravenous calcium preparations, such as calcium gluconate, can lead to complications such as calcinosis cutis, skin necrosis, and bullous reactions.[76] Therefore, studies recommend that caution should be exercised when using these treatments, and healthcare professionals should be aware of the potential risks and monitor patients closely. However, other studies oppose this statement demonstrating that the administration of calcium gluconate or calcium chloride for hyperkalemia in hypotensive patients counteract the effects of elevated K^+ levels on the heart.[39,77,78]

The second section deals with the use of short-acting intravenous insulin in combination with dextrose to shift K^+ intracellularly, that must be used with caution in hyperglycemic patients for the treatment of hyperkalemia, and consider the risk of hypoglycemia.[79–81] Hence, it is advised to supply enough glucose to prevent hypoglycemia, and careful glucose monitoring is essential while treating hyperkalemia with insulin and dextrose.[81,82] The third part discusses the use of salbutamol for the treatment of hyperkalemia in patients with cardiac arrhythmias. Several studies highlighted the possible risks of cardiac arrhythmias like atrial fibrillation, supraventricular tachycardia, complete heart block, and ventricular tachycardia associated with salbutamol use.[83] Another study linked salbutamol use to side effects including lactic acidosis, hyperglycemia, ketosis, diastolic hypotension, myocardial damage, and cardiac arrhythmias.[84] Furthermore, in a study conducted on healthy individuals participating in intense rowing exercise, salbutamol administration attenuated exercise-induced hyperkalemia but exacerbated post-exercise hypokalemia. Additionally, impaired cardiac repolarization (QT hysteresis) associated with hypokalemia was observed suggesting that salbutamol may have an impact on cardiac electrical activity.[85] Overall, these studies indicate that salbutamol use should be approached with caution in hyperkalemic patients with cardiac arrhythmias.

The fourth section advises on the cautious use of sodium bicarbonate in non-acidotic patients to treat hyperkalemia. Sodium bicarbonate is commonly used in the management of hyperkalemia, particularly in patients with metabolic acidosis; however, the use of sodium bicarbonate in non-acidotic hyperkalemic patients can lead to metabolic alkalosis, and/or hypernatremia.[3,86] Hypocalcemia can also occur as a side effect of sodium bicarbonate administration due to the pH-dependent binding of calcium by bicarbonate. In addition, fluid overload, bloating, nausea, vomiting, and abdominal pain are common side effects reported after the use of sodium bicarbonate.[3,87] Hence, sodium bicarbonate should be used with caution in non-acidotic hyperkalemic patients, and alternative treatments such as sodium polystyrene sulfonate may be considered.[88]

Management of Hyperkalemia in Patients with CKD

Statements related to the causes and the management of hyperkalemia in patients with CKD are outlined in Table 4. The majority of the panel (88%) agree that diabetic patients with CKD are more prone to hyperkalemia due to several factors. Firstly, CKD progression in itself can lead to hyperkalemia, especially in diabetics, since it leads to reduction in the urinary excretion of K^+, causing K^+ accumulation in the body.[89] Furthermore, diabetic patients with CKD may develop renal tubular acidosis type 4 or hyporeninemic hypoaldosteronism, which is characterized by decreased ammonium excretion and impaired urinary acidification and impaired renal K^+ excretion due to decreased mineralocorticoid activity.[90] Other factors include the use of K^+-sparing diuretics, such as spironolactone, which can increase serum K^+ levels by inhibiting aldosterone activity.[91]

The panel also states that patients with CKD not treated by kidney replacement therapy with hyperkalemia experience a significant health and economic burden, that varies based on patient's condition, such as CKD stage, hyporeninemic hypoaldosteronism in diabetic patients, renal transplantation, and RAASi use, in agreement with published literature.[1,2,98]

The panel also agrees that hyperkalemia in patients with CKD is present when serum K^+ is 5.0 mEq/L or higher, with therapeutic intervention required at a level of 5.5 mEq/L or higher due to its association with increased risk of death, cardiovascular disease, hospitalization, and CKD progression, as supported by published literature.[94,99,100] They also advised on the co-administration of mineralocorticoid receptor antagonists with RAASi in patients with CKD cautiously due to the increased incidence of hyperkalemia, in line with published literature.[57,99,101,102]

Furthermore, the majority of the panel (88%) agree that serum K^+ levels should be regularly monitored in patients with CKD within 7–14 days of initiating or increasing the dose of RAASi. Published literature provides varying monitoring window duration.[66,69,100] Chapman et al reported that repeated laboratory testing between 10 and 14 days

Table 4 Managing Hyperkalemia in Patients with CKD

Statements	Reference No	Final voting %
1. CKD patients with diabetes are more prone to present potassium disorders, in particular hyperkalemia due to kidney disease progression, use of renin-angiotensin-aldosterone blockers, renal tubular acidosis type 4, or hyporeninemic hypoaldosteronism.	[92]	88%
1. Hyperkalemia in patients with non-dialysis CKD exerts a remarkable burden with various frequencies among different conditions, including advanced CKD stages, hyporeninemic hypoaldosteronic diabetic patients, renal transplantation, and patients receiving RAAS inhibition.	[93]	100%
1. In chronic kidney disease (CKD) patients, hyperkalemia is diagnosed when serum potassium is 5.0 mEq/L or higher and therapeutic intervention is required at 5.5 mEq/L or more.	[94]	100%
1. Mineralocorticoid receptor antagonist should be co-administered with caution with angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB) in patients with CKD due to the much higher incidence of hyperkalemia.	[92]	100%
1. Serum K^+ levels should be regularly monitored in patients with CKD within 7–14 days of beginning or increasing the dose of RAASi.	[68]	88%
1. Potassium binding SPS could be used in the absence of other alternatives or potassium binders in chronic hyperkalemia in the hospital setting. It is less frequently used in the outpatient setting due to low tolerability and unknown long-term efficacy.	[95]	75%
1. Potassium binders can help in controlling hyperkalemia in patients on RAASi.	[96]	75%
1. In CKD patients with hyperkalemia, SZC is used for hyperkalemia treatment as well as might help in the treatment of metabolic acidosis by increasing the excretion of ammonium from the intestinal tract.	[97]	75%
1. Patiromer could be used in managing chronic hyperkalemia in CKD patients. However, its delayed onset of action (7 hours) and potential drug interactions should be taken in consideration in the acute setting.	[95]	100%

after delaying, initiating, or adjusting RAASi dose is crucial, and close monitoring is essential once a stable RAASi dose is achieved.[69] Blood K^+ levels should be also checked at 48–72 hours and again after one week after initiating or increasing the dosage of a new potassium-binder.[66]

The majority of the panel (75%) agree that the potassium-binder sodium polystyrene sulfonate could be used in the absence of other potassium-binders for hyperkalemia in the hospital setting but not in the outpatient setting due to poor tolerability, uncertain onset of action, and unexpected K-lowering magnitude.[103] Proper history and physical examination should be conducted before the initiation of SPS in any patient, and all interprofessional healthcare team members must be cautious when considering using SPS for the treatment of hyperkalemia if there is no available alternative medication. According to the recent international cardiorenal guidelines, the two-novel potassium-binders are safe and well tolerated for the management of chronic hyperkalemia, enabling RAASi utilization.[104,105] Therefore, clinicians should now attempt to use the new potassium-binders to treat hyperkalemia.

The majority of the panel members (75%) agree that potassium-binders can help control hyperkalemia in patients on RAASi, as shown by several studies,[68,106] and that the new potassium-binders can facilitate the continuation and optimization of RAASi, allowing the maintenance or up-titration of RAASi to maximum target doses.[1,66] Additionally, potassium-binders utilization can increase primary care physicians and internists confidence in managing hyperkalemia.[68]

Studies have shown that SZC effectively reduces serum K^+ levels in patients with hyperkalemia, leading to normokalemia within a few hours of the first dose.[107] SZC exhibits non-pH-dependent binding of K^+ throughout the gastrointestinal tract, including the small intestine,[108] In addition, the majority of the panel members agree that SZC used for hyperkalemia may also have potential benefits of correcting CKD-associated metabolic acidosis by increasing ammonium excretion from the intestinal tract.[109]

The panel agree that patiromer could be used in managing chronic hyperkalemia in patients with CKD, while considering patient comorbidities, practical limitations due to drug-to-drug interactions and delayed onset of action particularly when rapid potassium control is needed.[110–113]

Table 5 addresses hyperkalemia management in hemodialysis patients. The majority of the panel members agree on the definition of hyperkalemia in hemodialysis patients as a serum K^+ level of ≥5.5 mmol/L and that it is a common electrolyte disorder in this population. This statement is consistent with published literature.[114,115] However, other groups characterize hyperkalemia in hemodialysis as serum K^+ concentrations greater than 5.0 mmol/l.[108,116]

Table 5 Managing Hyperkalemia in Patients on Hemodialysis

Statements	Reference No	Final voting %
1. In hemodialysis patients, hyperkalemia is defined as a serum potassium level of ≥5.5 mmol/L and is a frequent electrolyte disorder.	[117]	75%
1. In severely elevated (>6.0 mmol/L) serum K^+ concentrations, or if hyperkalemia is accompanied by electrocardiogram changes, pharmacological treatment should be immediately initiated if dialysis was not available.	[118]	100%
1. For chronic hemodialysis, missed treatments and 2-day interdialytic intervals may have a negative impact on outcomes.	[119]	100%
1. K^+ binders are highly cost-effective compared to usual care (hemodialysis) by decreasing hospitalization and the need for dialysis in acute hyperkalemia or non-dialysis dependent CKD patients.	[120]	100%
1. SZC is an effective addition to maintenance hemodialysis in lowering pre-dialysis K^+ concentration in patients with end-stage kidney disease and severe hyperkalemia.	[12,121]	100%
1. When needed, SZC should be given once a day on non-dialysis days to effectively maintain pre-dialysis serum potassium levels in dialysis patients who experience frequent hyperkalemia.	[1]	100%
1. In the acute setting, Parotimer should not be used alone without concomitant use of immediate acting emergency treatments for acute hyperkalemia in patients with end-stage kidney diseases.	[119]	88%

The panel agrees that in severely elevated serum K^+ concentrations (>6.0 mmol/L), or if hyperkalemia is accompanied by ECG changes, pharmacological treatment should be initiated immediately if dialysis is not available.[3,14]

Chronic hemodialysis is a crucial treatment for patients with kidney failure, and the panel agreed that missed dialysis sessions and prolonged (>2-day) interdialytic intervals may have a negative impact on chronic hemodialysis outcomes,[122] and treatment can be challenging.[113]

The panel also agrees that K^+ binders are highly cost-effective compared to usual care (hemodialysis), since the use of this medication is reported to decrease hospitalization and the need for dialysis in acute hyperkalemia or patients with CKD not treated by kidney replacement therapy, and hyperkalemic events.[120,123]

The panel advises that SZC should be given once a day on non-dialysis days to effectively maintain pre-dialysis serum K^+ levels in hemodialysis patients who experience frequent hyperkalemia. As per the DIALIZE trial, the only double-blind randomized control trial on hemodialysis patients, SZC can be administered on non-dialysis days at 5 g once daily, with the option of gradually up-titrating the dose if needed depending on patients' response and on pre-dialysis serum K^+ value after the long interdialytic interval.[52,121,124]

Closure Statements with Future Steps

Finally, the experts discussed future steps and recommendations for hyperkalemia treatment and improved outcomes, as outlined in Table 6.

The panel agrees that the management of hyperkalemic patients with cardiorenal disease requires a multidisciplinary approach involving healthcare professionals from various specialties, including primary care physicians, cardiologists, nephrologists, and endocrinologists, and that collaborative care teams can provide holistic, coordinated, and specialized care, leading to improved patient outcomes and optimized healthcare resources.[127]

The majority of the panel members (75%) suggest that more research is needed to determine the long-term prognostic impact of RAASi down-titration or discontinuation in patients with HFrEF. This statement is supported by calls for more research in published literature since guidelines recommend maximal RAASi dosing to improve clinical outcomes; however, this is often limited by the development of hyperkalemia.[66] In addition, some evidence suggests that RAASi submaximal dosing and discontinuation may increase risks of adverse outcomes in patients with cardiorenal disorders such as faster progression to kidney failure, hospitalizations due to cardiovascular causes, and cardiovascular mortality at mid-to-long-term, and RAASi discontinuation may increase healthcare costs associated with such poor outcomes.[123]

The panel agrees that further clinical studies are also needed to address knowledge gaps and provide much-needed patient outcomes data for the treatment of hyperkalemia, as studies have indicated that there are significant unmet needs

Table 6 Closure Statements with Future Steps

Statements	Reference No	Final voting %
1. Cross-specialty collaboration would improve outcomes for people with cardiorenal disease. Clinical teams should be supported and encouraged to find effective ways to accomplish this in their care environment.	[8]	100%
1. More research is needed to determine the long-term prognostic impact of RAASi down-titration or discontinuation in Heart Failure with Reduced Ejection Fraction (HFrEF) patients.	[125]	75%
1. Further clinical studies are needed to address knowledge gaps and to provide much needed patient outcomes data for the treatment of hyperkalemia in the acute setting.	[39]	100%
1. Standardizing the definitions for hyperkalemia categories is recommended to allow proper standardized treatment plan and data gathering.	[39]	100%
1. Standardized care is needed for acute and chronic hyperkalemia in order to evaluate its efficacy and safety.	[39]	100%
1. Edema, with a low percentage, is the most typical adverse reaction to SZC, and its frequency increases as the drug's daily dosage increase.	[126]	100%

for managing hyperkalemia effectively, particularly in acute setting.[39,68] The panel also suggests to develop a comprehensive review paper that outlines the knowledge gaps in management of acute and severe hyperkalemia in outpatients, guides best practices in the development of care and reporting recommendations and issues a call to action on the research needs.[8]

The panel also highlights the need for standardized definitions for hyperkalemia categories to allow proper standardized treatment plans and data gathering, since published literature lacks a clear definition for grading hyperkalemia severity as mild, moderate, or severe, to allow proper treatment and data gathering standardization.[34,68,128]

The panel reiterates the importance of establishing a standardized approach in acute and chronic hyperkalemia and evaluate its effectiveness among patients in Kuwait based on clinical presentation, K+ levels and comorbidities. The efficacy and safety of the different treatments for acute and chronic hyperkalemia in published literature are poorly explored.[3,39,100,129]

The panel also agrees that peripheral edema was the most common adverse event of 15 g SZC. It is observed at a low rate of 5.7% in clinical trials, with 53% of the edema resolving on its own without any intervention and 47% resolved after adjustment of diuretic dose.[130] However, it is important to note that the 15 g dose is not approved nor available in GCC countries and hence, the risk is minimal. In addition, no gastrointestinal side effects were observed even when given on empty stomach and there are no significant drug–drug interactions reported with oral medications except for a limited list of PH-dependent drugs, including azole antifungals, anti-HIV drugs, tyrosine kinase inhibitors and tacrolimus. However, they should be administered at least ±2 hours before or after SZC intake to avoid any interaction.[55,107,131]

Conclusion

The management of hyperkalemia lacks standardized definitions and treatment threshold and lacks consistent guidelines and laboratory practices. This local consensus provides guidance and recommendations for healthcare practitioners in Kuwait for hyperkalemia management in acute settings, in HF, in CKD not treated by kidney replacement therapy, and in hemodialysis. It encourages the utilization of the new odorless and tasteless potassium-binder, SZC, due to its rapid onset of action (which is particularly helpful in acute settings) as well as its efficacy, tolerability and safety for patients with multiple comorbidities and on multiple oral medications. Moreover, this consensus highlights the need for future cross-specialty collaboration, standardized definitions and treatment protocols, and more research to address knowledge gaps related to hyperkalemia management.

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Ethical Approval

Not Applicable.

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Author Contributions

All authors made a significant contribution to the work reported including conception, design, execution, acquisition of data, analysis and interpretation; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no competing interests.

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