CONSENSUS DOCUMENT

Recommendations for the management of hyperkalemia in the emergency department

Esther Álvarez-Rodríguez[1,2], Alberto Olaizola Mendibil[1,3], María de los Ángeles San Martín Díez[1,4], Ainhoa Burzako Sánchez[1,4], Alberto Esteban-Fernández[2,5], Emilio Sánchez Álvarez[6]

Hyperkalemia, a common electrolyte disorder, is seen often in emergency departments. Patient outcomes are impacted by proper management, which requires consideration of both clinical and laboratory findings in relation to kidney function, hydration, the acid–base balance, and heart involvement. Delicate decisions about the timing of potassium level correction must be tailored in each case. For these reasons the Spanish Society of Emergency Medicine (SEMES), the Spanish Society of Cardiology (SEC), and the Spanish Society of Nephrology (SEN) joined forces to come to a consensus on defining the problem and recommending treatments that improve hospital emergency department management of hyperkalemia. Intravenous calcium, insulin and glucose, and salbutamol continue to be used to treat acute hyperkalemia. Either loop or thiazide diuretics can help patients if volume is not depleted, and dialysis may be necessary if there is kidney failure. Ion-exchange resins are falling into disuse because of adverse effects and poor tolerance, whereas novel gastrointestinal cation-exchange resins are gaining ground and may even be of some use in managing acute cases. It is essential to adjust treatment rather than discontinue medications that, even if they favor the development of hyperkalemia, will improve a patient's long-term prognosis. Valid alternative treatment approaches must therefore be sought for each patient group, and close follow-up is imperative.

Keywords: Emergency department. Elevated potassium concentration. Hyperkalemia. Renal insufficiency. Heart failure.

Recomendaciones para el manejo de la hiperpotasemia en urgencias

La hiperpotasemia es un trastorno electrolítico frecuente en los servicios de urgencias y un manejo adecuado impacta en el pronóstico de los pacientes. Este requiere de la integración de datos clínicos y analíticos sobre el estado de la función renal, la hidratación, el equilibrio ácido-base y la afectación cardiaca. Además, es necesaria una precisa toma de decisiones sobre la corrección de la concentración de potasio en el tiempo indicado para cada caso. Por estos motivos la SEMES (Sociedad Española de Medicina de Urgencias y Emergencias), la SEC (Sociedad Española de Cardiología) y la SEN (Sociedad Española de Nefrología) unen esfuerzos en consensuar definiciones y tratamientos que podrían mejorar el abordaje de estos pacientes en los servicios de urgencias hospitalarios. El calcio intravenoso, la insulina con glucosa y el salbutamol siguen siendo los tratamientos que se emplean en la hiperpotasemia aguda. Los diuréticos de asa y tiazídicos también pueden ayudar en pacientes no depleccionados, y la hemodiálisis puede ser necesaria en hiperpotasemias graves en el contexto de insuficiencia renal. Los efectos secundarios y la baja tolerabilidad de las resinas de intercambio iónico están haciendo que caigan en desuso mientras que los nuevos intercambiadores catiónicos gastrointestinales van ganando su espacio e incluso podrían tener algún valor en el tratamiento agudo. Es fundamental el ajuste del tratamiento evitando retirar fármacos que, a pesar de favorecer la hiperpotasemia, mejoren el pronóstico a largo plazo, por lo que es imperativo buscar alternativas válidas para cada grupo de pacientes, asegurando después un estrecho seguimiento.

Palabras clave: Servicio de Urgencias. Hiperpotasemia. Hiperkalemia. Insuficiencia renal. Insuficiencia cardiaca.

Author Affiliations:
[1]SEMES Working Group-Diabetes, Endocrinology and Metabolism.
[2]Severo Ochoa University Ochoa University Hospital, Leganés, Madrid, Spain.
[3]Cruces University Hospital, Barakaldo, Bizkaia, Spain.
[4]Hospital de Basurto, Bilbao, Spain.
[5]Spanish Society of Cardiology.
[6]Hospital Universitario de Cabueñes, Asturias, Spain.
Spanish Society of Nephrology.

Author Contributions:
All authors have confirmed their authorship in the document of author responsibilities, publication agreement and assignment of rights to EMERGENCIAS.

Corresponding Author:
Esther Álvarez-Rodríguez
Emergency Department
Hospital Universitario Severo Ochoa
Av. de Orellana, s/n
28911 Leganés, Madrid, Spain

Email:
diabetes@gruposemes.org

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Introduction

Hyperkalemia is a relatively frequent ionic disorder in hospital emergency departments (ED). Depending on the series, it can be identified in between 3% and 13% of patients seen in the ED.[1-3] It is mainly related to chronic diseases such as renal failure (its frequency is estimated at 28% and can reach up to 50% if renal failure is advanced), heart failure (HF), probably related to the use of certain drugs, and in patients with diabetes mellitus (DM).[4-6] In a recently published series which included episodes of hyperkalemia diagnosed in a Spanish ED, 71% of patients had some degree of renal failure, 35% had a history of HF and 57% suffered from diabetes.[7] It should be emphasized that one of the important settings in which these patients are attended is the ED and its dependent units, and that the development of multidisciplinary consensus improves the quality of care. Apart from the importance of its correction in the acute phase due to its eventual lethality, the appearance of hyperkalemia can potentially restrict the use of certain drugs, such as renin-angiotensin-aldosterone system inhibitors (RAASi), depriving the patient of their medium and long-term benefits. In fact, most patients who have already had an episode of hyperkalemia discontinue or are on suboptimal doses of these drugs,[8]

which is associated with an increased risk of mortality and the occurrence of major adverse cardiovascular events (MACE)[9].

The emergence of new drugs in the prevention of hyperkalemia in patients with chronic diseases that favor it, or who benefit from taking RAASi, could be beneficial, since it would help to maintain and titrate these without the need for their suspension. It is necessary for the ED physician to be aware of these strategies and for them to be proactive in this regard, including the prevention of the development of hyperkalemia, especially in patients who have already had an episode. Recurrence of hyperkalemia has in fact been associated with an increased risk of mortality.[7]

For all these reasons, an ED plan is needed to clarify both the acute treatment of hyperkalemia and the role of new drugs and the attitude towards discharge that completes the transition and reconciliation of treatment.

Methods

This document is the result of the work of a group of experts representing three scientific societies involved in the management of hyperkalemia: the Spanish Society of Emergency Medicine (spanish acronym SEMES), the Spanish Society of Cardiology (Spanish acronym SEC) and the Spanish Society of Nephrology (Spanish acronym SEN). It has been written with the aim of clarifying and establishing a series of recommendations based on the available scientific evidence and related to the therapeutic management of hyperkalemia, with the objective of establishing and facilitating guidelines for integrated multidisciplinary management. This consensus reflects the opinion of the authors who have been chosen as experts by each of the scientific societies involved in its drafting, and the complete text has been developed after discussion and approval by all of them.

Pathophysiology of hyperkalemia

Potassium (K) is the most important intracellular cation in the body. Ninety-eight percent of total body K (about 3,000 mEq) is found inside the cells and only 2% is found in the extracellular fluid. Therefore, the intracellular K concentration is 140 mEq/l and the extracellular K concentration (which is the one measured in clinical practice) is 4-5 mEq/l. The difference in the distribution of the two cations is maintained by the Na/K-ATPase pump of the cell membrane, which pumps sodium (Na) and K into the cell in a 3:2 ratio. This concentration difference on both sides of the cell membrane is the major determinant of the resting membrane potential, which is essential for cardiac and neuromuscular excitability, as well as the maintenance of cellular functions. There is evidence to suggest that increased K intake can lower blood pressure and reduce the risk of stroke.[10,11]

Regulation of potassium homeostasis

Plasma K concentration is determined by the relationship between ingested K, its distribution between the extracellular and intracellular space, and its elimination.

Daily requirements

The minimum daily requirement of K is 1600 to 2000 mg (40-50 mEq). Such an intake is achieved with a varied diet, including fruits and vegetables. It is not uncommon to find elderly people living alone or with limitations, with an insufficient K intake to cover daily needs.[12] On the other hand, certain chronic medications and diseases can alter the K balance.

Transcellular distribution of potassium

The difference in K concentration between the extracellular and intracellular space is maintained by the Na/K-ATPase pump that catalyzes the entry of 2 moles of K into the cell for every 3 moles of Na leaving, generating an intracellular electronegative gradient. Insulin and β_2-adrenergic stimulation are the main stimuli of the Na/K-ATPase pump promoting K entry into the cell. Changes in pH and plasma osmolarity also regulate transcellular K movement.[13]

Insulin mobilizes K into the cells, whereby high concentrations of insulin decrease blood K concentration. Low insulin concentrations, such as those seen in diabetic ketoacidosis, drive K movement out of cells, leading to hyperkalemia, sometimes despite total body K deficiency. b-adrenergic agonists bring K into cells, whereas a-adrenergic agonists inhibit K entry into the cellular interior. Acute metabolic acidosis stimulates the outflow of K out of the cells, whereas acute metabolic alkalosis stimulates its inflow. However, changes in serum bicarbonate concentration may be more important than changes in pH, since acidosis caused by mineral acids (hyperchloremic acidosis without anion gap) is more likely to increase potassemia. In contrast, metabolic acidosis secondary to accumulation of organic acids (acidosis with increased anion gap) does not cause hyperkalemia. Therefore, the hyperkalemia often associated with diabetic ketoacidosis is more often due to insulin deficiency rather than acidosis. Respiratory acidosis and alkalosis affect serum K concentrations to a lesser extent than metabolic acidosis and alkalosis. However, serum K concentration should always be interpreted in the context of serum pH and bicarbonate concentration.

Elimination of potassium

The main route of K elimination is renal. Eighty percent of ingested K is excreted by the kidney, 15% by the gastrointestinal tract through the feces and the remaining 5% through sweat. Extrarenal K losses are of little importance, except in special situations such as patients with extensive burns or after intense exercise. In patients with advanced chronic renal failure (CRF), K losses through the intestine can reach 25% of the daily losses.[14] 90% of filtered K is reabsorbed in the proximal tubule. It

is in the principal cells of the distal convoluted tubule and collecting duct that final K excretion is regulated according to physiological needs. Aldosterone-dependent and aldosterone-independent mechanisms are involved. The kidneys respond to acute or chronic changes in K intake with corresponding changes in excretion. Excess K is excreted rapidly, whereas the renal response to K depletion is slower, requiring 7-14 days to reduce K excretion to minimal values.[15]

Definition of hyperkalemia

Hyperkalemia is defined as a serum K concentration greater than 5.5 mEq/L. It is the most serious electrolyte disorder, as it can lead to lethal ventricular arrhythmias and cardiac arrest. It is classified into mild (K 5.5-5.9 mEq/L), moderate (K 6.0-6.4 mEq/L) or severe (K equal to or greater than 6.5 mEq/L) hyperkalemia. A serum K concentration above 10 mEq/L is usually lethal. Hyperkalemia is present in 10% of admitted patients. Its incidence is increasing especially in the elderly population treated with RAASi drugs. It is not uncommon for some of these drugs to be used simultaneously in the same patient, and it is often an iatrogenic disorder.[16]

Etiology of hyperkalemia

The mechanisms leading to hyperkalemia are: insufficient renal excretion of K, transcellular shift, excessive and rapid K supply or pseudohyperkalemia due to measurement errors.[17] In clinical practice, renal failure is almost always in the causal background of hyperkalemia, followed by drug use and hemolysis.[18,19]

– Pseudohyperkalemia: hemolyzed sample, extreme leue kocytosis or thrombocytosis.
– Transcellular redistribution: metabolic acidosis, hypep rosmolarity in hyperglycemia with insulin deficiency or mannitol use, familial periodic paralysis, beta-blockers, digoxin, succinylcholine, non-depolarizing muscle relaxants, somatostatin.
– Tissue destruction: hemolysis, tumor lysis, rhabdome yolysis, extensive trauma, burns, intestinal ischemia.
– Defect in renal excretion: acute renal failure or CRF (when glomerular filtration rate is less than 10-15 ml/min); primary (Addison's) or secondary hypoaldosteronism (hyporeninemic associated with interstitial nephritis, lupus, sickle cell disease, diabetic nephropathy); pseudohypoaldosteronism, due to drugs that block the synthesis or action of aldosterone or that increase tubular reabsorption of K:
  • RAASi, angiotensin-converting enzyme inhibitors (ACE inhibitors), angiotensin II receptor antagonists (ARA-II), direct renin inhibitors.
  • Dual neprilysin and angiotensin receptor inhibitor (ARNI): sacubitrile/valsartan.
  • Mineralocorticoid receptor antagonists (MRAs): eplee renone or spironolactone.
  • K-sparing diuretics: amiloride or triamterene.
  • Nonsteroidal anti-inflammatory drugs.
  • Anticalcineurinics: cyclosporine and tacrolimus.
  • Some anti-infectives: cotrimoxazole, pentamidine.
  • Heparin.

Clinical manifestations of hyperkalemia

Hyperkalemia results in depolarization of the membrane of excitable the membrane of excitable tissues such as heart, muscle and nervous system.[20]

This generates varied clinical manifestations, ranging from a laboratory finding in asymptomatic patients, to nonspecific clinical manifestations such as fatigue or malaise, to severe cardiac conduction disturbances. The rapidity of change in extracellular K is more important than the absolute value of K, so that clinical manifestations generally appear when serum K is greater than 7 mEq/L in chronic hyperkalemia and at slightly lower values when hyperkalemia is acute.[20]

Neuromuscular manifestations

Cramps, paresthesias and weakness are frequent and may progress to an ascending flaccid paralysis starting in the lower limbs and progressing to the trunk and arms (mimicking Guillain-Barré syndrome). Osteotendinous reflexes are abolished or diminished with preservation of cranial nerves and sphincter tone. Respiratory muscles are rarely affected. There is an autosomal dominant genetic disorder, hyperkalemic periodic paralysis, which presents with episodes of myopathy triggered by K release after intense exercise or ingestion of small amounts of K.[20]

Cardiac manifestations

Hyperkalemia depolarizes the cell membrane, slowing ventricular conduction and decreasing the duration of the action potential.[20] Bradycardia, asystole, ventricular tachycardia, ventricular fibrillation (VF), pulseless electrical activity and, in patients with pacemakers, an alteration in capture when the stimulation threshold is raised[21]. Although the sensitivity of the electrocardiogram (ECG) for detecting changes in K levels is low,[22] sequential alterations have been classically described: with K concentrations around 6.5 mEq/L, sharp T waves appear, with levels around 6.5-7.5 mEq/L the PR interval is prolonged and the P wave flattens or disappears. The QRS complex widens with K levels around 7-8 mEq/L. At higher levels, the QRS complex converges with the T wave to form a sinus wave followed by VF and asystole. It is important to emphasize that this is an academic classification and that ECG changes can be affected by the pH of the extracellular fluid, the concentration of calcium and sodium and the rapidity of potassium elevation, so that at any degree of hyperkalemia ventricular arrhythmias can appear as the first manifestation or present a normal ECG.[20]

Recommended management of hyperkalemia in the ED

Continuous cardiac monitoring is necessary in patients with hyperkalemia requiring fast-acting therapies.

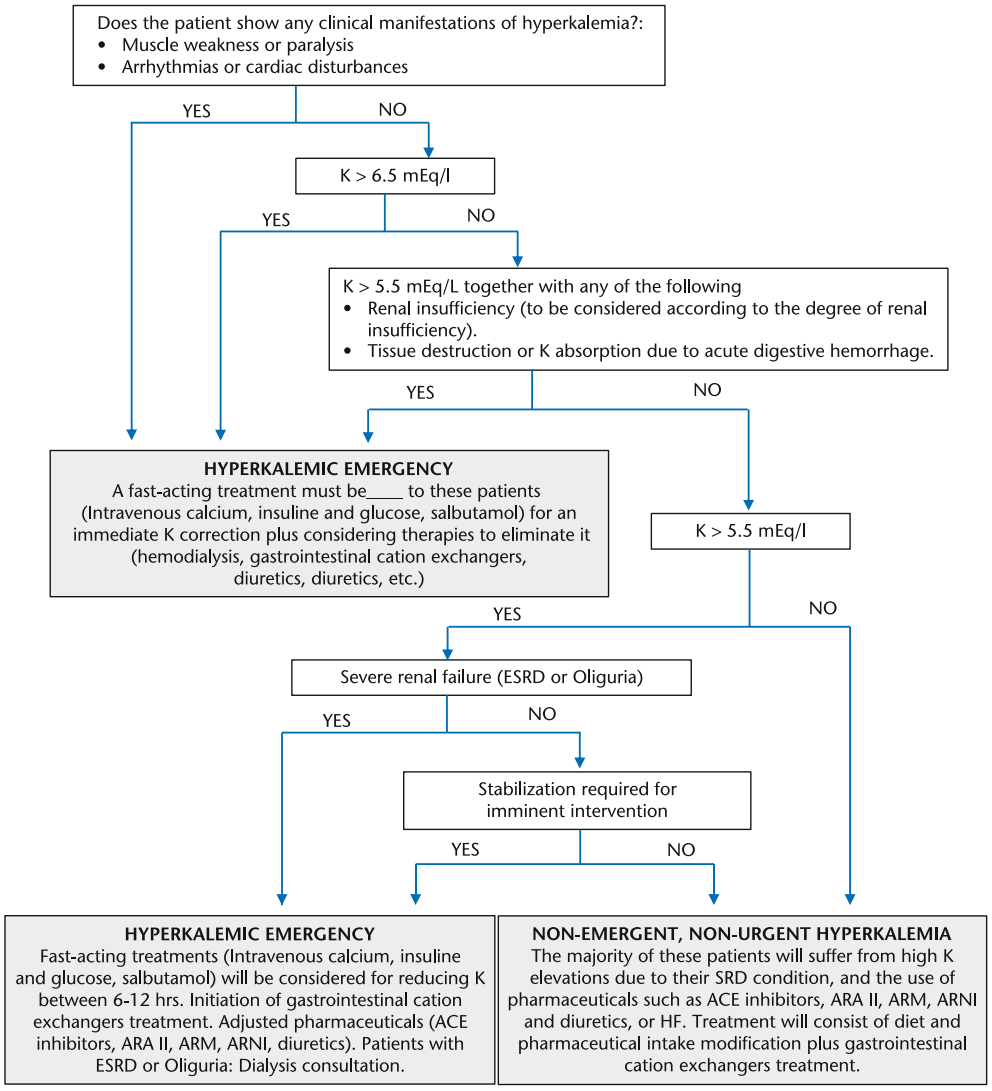

Figura 1. Recommended management of hyperkalemia in the emergency department.
K: potassium; ACE: angiotensin-converting enzyme; ARA II: angiotensin II receptor antagonists; ARNI: angiotensin-neprilysin receptor inhibitor; CRF: chronic renal failure; ESRD: End-stage renal disease SRD: Severe renal disease.

Serum K should generally be measured at 1 to 2 hours, at 6 hours and at 12 hours. The urgency of treatment of hyperkalemia depends on the presence or absence of symptoms, electrocardiographic disturbances, the severity of K elevation, and the cause of hyperkalemia. It should be determined whether emergent, urgent or neither treatment is required as shown in Figure 1.

Hyperkalemic emergency

In general, the following patients should be considered to have a hyperkalemic emergency and should therefore be treated with fast-acting therapies (intravenous calcium, insulin and glucose, salbutamol) in addition to K-eliminating therapies (gastrointestinal cation exchange or diuretics, hemodialysis):

– Patients presenting with clinical signs or symptoms of hyperkalemia, especially muscle weakness or paralysis and ECG alterations.[23]
– Patients with severe hyperkalemia (K greater than 6.5 mEq/L), especially if there is tissue destruction or gastrointestinal bleeding, even if there are no clinical signs or symptoms.
– Some patients with moderate hyperkalemia (greater than 5.5 mEq/L) who have renal insufficiency (to consider the degree of renal insufficiency) and tissue destruction (rhabdomyolysis or crush injury, tumor lysis syndrome), continued K absorption due to gastrointestinal bleeding or a metabolic acidosis or respiratory acidosis.

Hyperkalemic emergency

Patients without a hyperkalemic emergency, but who must reduce their K within 6 to 12 hours.[24]

Non-emergent and non-urgent hyperkalemia (slow treatment)

Some patients have a K between 5.5 mEq/L and 6.5 mEq/L, without clinical manifestations or electrocardiographic alterations, in a context in which CRF, HF and the use of ACE inhibitors, ARBs and ARMs are usually added. These patients do not require urgent or emergent K reduction and can often be treated with dietary modifications, adjustment of diuretics (if appropriate) or adjustment of medications that may cause hyperkalemia. In some cases, RAASi are reduced or even discontinued in the interest of lowering K levels. However, it should be taken into account that this practice will deprive the patient of treatments needed for the good evolution of his or her underlying disease. For this reason, the prescription during the ED stay and at discharge of drugs that eliminate K by gastrointestinal cation exchange is essential, because it guarantees a rapid and sustained reduction in K concentrations with good tolerance, avoiding the reduction or suspension of these necessary chronic treatments.[24-26]

Therapeutic options in hyperkalemia

Antagonizing membrane effects

Calcium directly antagonizes the membrane actions of hyperkalemia,[27] whereas hypocalcemia increases the cardiotoxicity of hyperkalemia.[28] Hyperkalemia-induced depolarization of the resting membrane potential leads to inactivation of Na channels and decreases membrane excitability. The effect of intravenous calcium administration begins within minutes, but is of relatively short duration (30 to 60 minutes), so calcium should not be given as monotherapy for hyperkalemia, but should be combined with therapies that drive extracellular K into cells. Calcium administration can be repeated every 30 to 60 minutes if the hyperkalemic emergency persists and serum calcium does not rise. Calcium can be administered as calcium gluconate or calcium chloride. Calcium chloride contains three times the concentration of elemental calcium compared to calcium gluconate (13.6 vs. 4.6 mEq in 10 ml of a 10% solution). However, calcium gluconate is generally preferred because calcium chloride can cause local irritation at the injection site. The usual dose of calcium gluconate is 1000 mg (10 ml of a 10% solution) infused over 2 to 3 minutes, with constant cardiac monitoring. The usual dose of calcium chloride is 500 to 1000 mg (5 to 10 ml of a 10% solution), also infused over 2 to 3 minutes, with constant cardiac monitoring. The dose of any formulation may be repeated after 5 minutes if ECG changes persist or recur. Concentrated calcium infusions (particularly calcium chloride) are irritating to veins and extravasation may cause tissue necrosis. For this reason, a central or deep vein is preferred for calcium chloride administration.

Calcium can potentiate the cardiotoxicity of digitalis, so in patients with hyperkalemia and who are taking digoxin it should be given diluted and within 20-30 minutes. If hyperkalemia is secondary to digitalis toxicity, anti-digoxin antibodies should be administered.[29]

Introducing potassium into cells

Insulin and β_2-adrenergic agonists

Insulin administration reduces serum K concentration by introducing it into cells, mainly by enhancing Na/K-ATPase pump activity in skeletal muscle.[29,30] Glucose is usually administered with insulin to prevent the development of hypoglycemia. However, insulin should be administered alone if blood glucose is greater than 250 mg/dL (13.9 mmol/L).[31] The commonly used regimen for administering insulin and glucose is 10 units of regular insulin in 500 ml of 10% glucosate, administered intravenously over 60 minutes, but other concentrations are also valid.[32-35] Another regimen consists of a bolus injection of 10 units of regular insulin, followed immediately by 50 ml of 50% glucosate (25 g of glucose). This regimen may provide a greater early reduction in serum K, as the K-lowering effect is greater at higher insulin concentrations achieved with bolus therapy. However, hypoglycemia occurs in approximately 20%.[36]

The effect of insulin begins in 10-20 minutes, reaches its peak between 30 and 60 minutes and lasts from 4 to 6 hours, so blood glucose should be measured for 6 hours after insulin administration.[37,38] In general, serum K concentration falls between 0.5 and 1.2 mEq/l.[38,39] Although patients with renal failure are resistant to the hypoglycemic effect of insulin, they are not resistant to the hypokalemic effect, because the Na/K-ATPase pump is still activated.[40-41]

β_2-adrenergic agonists act similarly to insulin by driving K into the cellular interior through the Na/K-ATPase pump in skeletal muscle.[20,29,42-44] The drug usually used is intravenous salbutamol 0.5 mg in 100 ml of 5% glucose in 15 minutes or inhaled in doses of 10-20 mg in 10 minutes (which is 4 to 8 times the dose used for bronchodilation). Its onset of action is 6-8 minutes and its effect lasts 3 hours. The maximum effect is observed within 30 minutes with intravenous infusion and at 90 minutes with nebulization.[43] As a side effect it can produce tachycardia, and should be used with caution in ischemic heart disease. Adrenaline is not indicated for the treatment of hyperkalemia.

Insulin is just as effective as the administration of β_2-adrenergic agonists and their combination is much more effective than either treatment used alone, as they have an additive effect, reducing serum K concentration by approximately 1.2 to 1.5 mEq/L.[37,38,44,45]

Elimination of excess potassium from the body

Diuretics, gastrointestinal cation exchangers and dialysis

Hemodialysis should always be considered as therapy in patients with a hyperkalemic emergency, especially in patients with severe renal failure or end-stage renal

disease (ESRD). The use of dialysis does not exclude the use of the above measures. It is indicated in hyperkalemic patients with severe renal failure.[46] Hemodialysis is preferable to peritoneal dialysis, since the rate of K elimination is much faster.[47] Hemodialysis can remove 25 to 50 mEq of K per hour, with variability based on the initial serum K.

Loop and thiazide diuretics increase urinary K loss in patients with normal renal function or mild to moderate renal insufficiency. However, patients with persistent hyperkalemia usually have impaired renal K secretion and there are no data demonstrating a clinically important short-term kaliuretic response to diuretic therapy.

Although data are limited, treatment with chronic diuretics is probably effective in the long term in increasing K excretion, particularly in patients with mild to moderate CRF.[47]

Patiromer, sodium zirconium cyclosilicate (SZC) and ion exchange resins such as sodium or calcium polystyrene sulfonate are available as gastrointestinal cation exchangers.

Patiromer is a non-absorbable spherical organic polymer, formulated as a powder for suspension, which binds K in the colon in exchange for calcium.[48,49] It is effective in the sustained reduction of K concentration in patients with renal failure or HF, even if they are on RAASi therapy.

In the phase II, open-label, dose-finding trial (AMETHYST-DN), 306 diabetic patients on ACEI or ARB-II therapy with a glomerular filtration rate (GFR) less than 60 mL/min and mild or moderate hyperkalemia were randomized to different patiromer dose ranges. At 52 weeks, serum K concentrations remained in the normal range and discontinuation of patiromer resulted in an increase in serum K within 3 days.[49] There were no treatment-related serious adverse events. The most common included constipation (6.3% of patients) and hypomagnesemia (8.6%) especially at higher doses.

The phase III OPAL-HK trial included 243 patients on treatment with ACEI or ARA-II with GFR less than 60 mL/min and mild or moderate hyperkalemia and compared it with placebo. The mean decrease in serum K at 4 weeks was 1.0 mEq/L (greater decrease at higher doses). Approximately 75% of the patients reached the serum K target of 3.8 to 5.0 mEq/L, and the decrease was more pronounced during the first 3 days, with this effect disappearing when the drug was discontinued.

In addition to binding to cations, patiromer can bind to other drugs in the gastrointestinal tract. Interactions have been identified with ciprofloxacin, thyroxine and metformin. These three drugs should be administered at least 3 hours apart before or after patiromer[51].

SZC is effective in urgent hyperkalemia and also in slow correction,[52,53] and appears to be promising in emergent hyperkalemia. It is a non-absorbable inorganic crystalline compound that exchanges Na and hydrogen ions for K along its intestinal transit[54]. The efficacy of SZC in hyperkalemic ambulatory patients, most of whom were also being treated with RAASi, was evaluated in two randomized placebo-controlled phase III trials.

In the HARMONIZE study of 258 patients with hyperkalemia, the most pronounced decrease in serum K with SZC occurred during the first 4 hours of therapy.[52,55] This suggests an acute effect on intestinal K secretion, rather than simply a reduction in K absorption.

The long-term efficacy of SZC was examined in an open trial of 751 patients with hyperkalemia, mean eGFR of 47 mL/min and 12-month follow-up, most of whom were receiving an ACEI or an ARM.[56,57] During the maintenance phase, 88% had a mean serum K of 5.0 mEq/L or less, 87% of those taking an RAASi did not have to modify this treatment, and 14% of those not taking it at the start of the study could be started.

SZC is also effective for the treatment of hyperkalemia in patients receiving hemodialysis. In the DIALYZE study, 196 patients with pre-dialysis hyperkalemia were randomized to treatment with SZC or placebo for 8 weeks. Normal K concentrations were achieved in 41% in the SZC line versus 1% in the placebo line.[58]

Pending further trials in the ED setting, the ENERGIZE pilot study (phase II, multicenter, randomized, double-blind, placebo-controlled), included patients with hyperkalemia treated with insulin and glucose together with SZC or placebo. There was a significant reduction in serum K from baseline with SZC compared to placebo at 2 and 4 hours. Fewer patients in the SZC group required additional therapy to reduce K. Comparable proportions of patients experienced adverse events in both treatment groups from 0 to 24 hours. This pilot study suggested that SZC with insulin and glucose may provide incremental benefit in the emergency treatment of hyperkalemia over insulin and glucose alone.[25]

The dispensation in Spain of both patiromer and SZC requires a visa requested by specialists in nephrology, cardiology and internal medicine, and is limited to patients with advanced CRF and grade III-IV HF, with mild to moderate hyperkalemia (5.5-6.4 mE-q/L), in treatment with RAASi, in whom its continuation is considered essential and with failure or intolerance to ion exchange resins.

Sodium or calcium polystyrene sulfonate was, until recently, the only resin for intestinal elimination of K available. Their digestive tolerance and the constipation they produce tend to lead to low therapeutic adherence. Their use is limited in emergencies, since the onset of action of intestinal elimination of K is slow for emergent and urgent needs. On the other hand, there are reported cases of intestinal necrosis, especially when combined with sorbitol[59-61] and, furthermore, there are no specific studies available in patients with HF.

What about after potassium correction in the ED?

In patients who require admission due to hyperkalemia or for any other reason, K levels should be

monitored during admission and their stay should be used to adjust their chronic treatment. In patients discharged from the ED, a specific follow-up with analytical control should be programmed, preferably within 24 hours.

Both for hospital admission and for discharge home, gastrointestinal cation exchangers, such as SZC and patiromer, could make it possible not to suspend or reduce basic treatments that promote hyperkalemia and thus not deprive the patient of their beneficial effects in the medium and long term.

Particularities of the cardiological patient

Hyperkalemia is frequent in cardiac patients, especially in those with HF due to the coexistence of cardiorenal syndrome, DM and treatment with RAASi. Its presence can be associated with the development of malignant arrhythmias and increased mortality, especially when hyperkalemia is relevant or significant fluctuations in K levels occur.[62] Hyperkalemia is more frequent in episodes of HF decompensation, due to the use of high doses of diuretics, activation of the neurohormonal system and alterations in renal function.[63]

In patients with HF and reduced ejection fraction, treatment with RAASi reduces mortality, readmissions, and improves quality of life, and it has been shown that high doses of these drugs have a greater benefit than low doses.[64] The use of RAASi, especially at high doses and in nephropathic patients, increases the risk of hyperkalemia, and this is responsible for the discontinuation of these drugs in 4% of cases, which is associated with higher mortality.[65,66]

Therefore, it is essential to establish lines of communication with the HF units and primary care after an episode of hyperkalemia resolved in the emergency department, in order to avoid the definitive suspension or reduction of these drugs, which has an impact on the prognosis of these patients.

The management of cardiac patients treated with RAASi is shown in Table 1.[67,68] It should always be individualized and, on occasions, completed at discharge in the early outpatient visit. The coexistence of renal disease or previous acute renal failure should always be investigated, as well as previous episodes of hyperkalemia.

The discharge report will include treatment modifications aimed at resolving the acute episode, but continuity of care must be guaranteed to avoid new episodes of hyperkalemia and the reduction or withdrawal of drugs with prognostic benefit. In the follow-up, an attempt will be made to reintroduce, maintain and even titrate the doses of the RAASi. Due to the high risk of recurrence, it is important to identify patients who have presented an episode of hyperkalemia, to carry out periodic analytical follow-up and to opt for a slower reintroduction or titration, considering the association of K chelators. Some recommendations to facilitate this task are given in Table 2.[68]

Features of the nephrological patient

The kidney is the main organ regulating serum K levels. It is able to modify urinary elimination according to the K load absorbed from the diet in order to keep the total body K content constant. Under normal conditions, urinary K loss is equal to intake. Elimination through the feces is small, although it may increase in situations of K overload, especially if associated with a decrease in renal function.[71,72]

Hyperkalemia is a common electrolyte disturbance in CRF, especially in its more advanced stages. It has been found that around 10% of patients with glomerular filtration rates below 60 ml/min have some degree of hyperkalemia. This percentage increases as renal function decreases or when the patient uses hemodialysis as replacement treatment for renal function.[73] The percentage of patients on peritoneal dialysis with hyperkalemia is significantly lower.

In general, it can be said that a situation of hyperkalemia occurs when K intake and absorption exceeds renal excretion capacity. This capacity is clearly influenced by the degree of renal insufficiency and by the concentration and/or action of aldosterone in the distal tubule.[74] Furthermore, it should not be forgotten that the role of K redistribution between the intra- and extracellular compartments is clearly influenced by the acid-base balance.[75]

The organism is capable of inducing adaptive mechanisms with the aim of normalizing the concentration of K. In the kidney, an increase in tubular K secretion is produced.[76,77] On the other hand, an increase in intestinal K excretion can also develop.[78] Both mechanisms are established gradually. It should not be forgotten that, in the situation of renal failure, a state of metabolic acidosis is produced that favors the outflow of K from the intracellular space to the extracellular space.

Bases for the management of acute hyperkalemia in the renal patient

The management of this situation should be based on a comprehensive assessment of the patient, which should include several sections:

Baseline renal status

As previously mentioned, the kidney is capable of maintaining K homeostasis until advanced stages of the disease. Hyperkalemia is more frequent in cases of impaired renal function.[73]

Knowing the renal status of the patient helps to decide how to act to correct hyperkalemia. In the case of partially preserved renal function, measures can be implemented to favor renal elimination of K. However, in very advanced stages of renal function deterioration, the strategy should be different, and it will probably be necessary to establish some extrarenal clearance technique.

Table 1. Management of hyperkalemia in patients with HF treated with RAASi

K figure	Recommendation
Any	Decrease K intake (food, supplements, etc.). Avoid certain drugs (NSAIDs). Optimize diuretics (minimum dose that guarantees euvolemia). Monitor renal function.
4.0-5.0 mEq/L	Maintain RAASi
5.1-5.5 mEq/L	Initiate measures for the management of hyperkalemia[a] and maintain doses of iSRAA.[b]
5.5-6 mEq/L	Reduce RAASi dose. Evaluate the association of K chelators (patiromer or sodium zirconium cyclosilicate).[c]
> 6 mEq/L	Consider reducing or suspending some of the iSRAA and monitor.

[a]Review diet, supplements and diuretics, and rule out deterioration of renal function. The association of K chelators can be evaluated.
[b]Within the RAASi, those that produce the most hyperkalemia are the aldosterone receptor antagonists, 69 which is why they would be the first to modify. Neprilysin and angiotensin II receptor inhibitors produce less hyperkalemia than ACE inhibitors.[70]
[c]The use of sodium or calcium polystyrene should be avoided due to the lack of evidence in HF and the side effects it produces. In the case of patiromer, it can be started with a dose of 8.4 g per day, with follow-up monitoring of Mg. In the case of sodium zirconium cyclosilicate, it can be started with a dose of 5 g per day and monitoring for the appearance of peripheral edema or hypokalemia.
ACE: angiotensin-converting enzyme inhibitors; HF: heart failure; NSAIDs: nonsteroidal anti-inflammatory drugs; RAASi: renin-angiotensin-aldosterone system inhibitors; K: potassium.

Hydration status

In a situation of overhydration there may be a certain degree of K dilution that may increase when attempting to correct this excess water. On the other hand, the use of loop diuretics favors K elimination through urine. However, their use in a situation of dehydration can have deleterious effects.

Acid-base balance

In renal disease, both acute and chronic, a situation of metabolic acidosis is usually associated. K and bicarbonate concentrations should be viewed as the two plates of a balance; if one goes up, the other goes down and vice versa.

Cardiac repercussions of hyperkalemia

When hyperkalemia is associated with ECG alterations, urgent action should be taken given the seriousness of the situation and the possible fatal effects it may have, although there may also be cardiac repercussions with a normal ECG.

General measures for hyperkalemia and renal insufficiency

Avoid outflow of K from the intracellular space to the extracellular space

In renal failure there is usually a certain degree of metabolic acidosis that favors the outflow of intracellular K.[79] Serum K concentration should always be assessed together with acid-base balance. The blood sample for blood gas analysis can be venous. Sodium bicarbonate should be administered, generally 1/6 molar.

Other situations that favor the outflow of K to the extracellular space and that should be evaluated are hyperglycemia and digitalis intoxication. If they exist, they should be corrected.

Table 2. Recommended actions upon discharge of the patient attended in the emergency department for an episode of hyperkalemia (adapted from Almenar et al.[68])

Actions	Recommendations
Determine type, severity, reversibility and cause of hyperkalemia.	Review medical history (including renal function) and previous blood tests. Review diet, diuretics, RAASi and supplements.
Record in the clinical history the therapeutic measures for the correction of hyperkalemia and the clinical repercussion.	Acute phase treatment and discharge measures. Symptoms and ECG alterations.
Record pharmacological adjustments in iSRAA and diuretics.	Pre-treatment. Treatment after discharge.
Record in the discharge report the analytical figures at admission and discharge.	Renal function (Cr, eTFG, urea). Ions (K, Na, Cl and Mg).
Provide at discharge an appointment with the primary care physician or HF unit in less than 1 week.	Review of symptoms. Blood tests with renal function and function and ions. Review of iSRAA and doses. Review diet, diuretics and supplements.

Cr: creatinine; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; HF: heart failure; RAASi: renin-angiotensin-aldosterone system inhibitors; K: potassium; Mg: magnesium; Na: sodium.

Assess the causes of an exogenous increase in K

It should be ruled out that the patient, especially patients with advanced stages of CRF, is eating a diet very rich in vegetables or fruits or has not implemented measures to reduce the K in these foods (for example, simple measures such as soaking before cooking and double cooking).[80] It is also important to rule out the use of salt substitutes, since these provide a considerable amount of K, or nutritional supplements that provide K.

Resolving a urological disease

One cause of a poor response to universal treatment measures for hyperkalemia is the existence of a urological disease that causes urinary tract obstruction. If this situation arises, an imaging test should be performed to assess the urinary tract and the urinary tract should be resolved.[79]

Assessing drugs that can cause hyperkalemia

Some drugs indicated for different diseases can cause hyperkalemia, especially by increasing tubular reabsorption of K.[81] The most implicated drugs are: RAASi, ARNI or ARM.

Use of drugs that increase renal elimination of K

The most effective drugs in increasing renal elimination are the loop diuretics (furosemide, torasemide and

bumetanide).[82] The efficacy of these drugs decreases as renal failure progresses, but they usually achieve some decrease in K concentration. It is important to assess the patient's hydration status, since their use, especially in hypoperfused or dehydrated individuals, can lead to deterioration of renal function that can further worsen the situation.[83]

Use drugs that increase K elimination via the digestive tract

Cation exchange resin enemas (calcium polystyrene sulfonate) have shown some efficacy in decreasing serum K concentration.[84] Sodium resins with sorbitol should be avoided because of the risk of ulcers and colonic necrosis. Given the efficacy of other measures used in the control of hyperkalemia, their use is not frequent at present, but perhaps in other socio-healthcare settings that are more disadvantaged than in Spain they may have some usefulness.

Use drugs that decrease the intestinal absorption of K

a. Classical agents

During the last half century, only cation exchange resins were available, so they were the only drugs used. Their usefulness was compromised by gastrointestinal intolerance and persistent constipation, which led to a large number of drug discontinuations. In addition, a significant number of cases of ulcers and colon necrosis were described when they were administered together with sorbitol as a laxative, so that currently only cation exchange resins (calcium polystyrene sulfonate)[85] are used.

b. New agents

Both patiromer and SZC are nonabsorbable polymers that exchange K for calcium and K for Na, respectively, in the intestine. Both have shown very interesting results[86,87] and although they allow maintenance and titration of RAASi, their impact on prognosis has not yet been demonstrated.

Indication for dialysis

If hyperkalemia occurs in patients included in dialysis programs, the most efficient and rapid way to correct hyperkalemia is to perform the technique.

In the case of hemodialysis patients, they will be connected to the monitor as soon as possible; in general, complications associated with hyperkalemia toxicity are resolved within the first hour, although it depends on the basal serum K concentration.

In the case of peritoneal dialysis, it is important to know that hyperkalemia is quite infrequent since it is a continuous technique and to the significant diffusion of K from the peritoneal capillaries to the peritoneal cavity when using dialysis solutions without K in their composition. If necessary, the peritoneal dialysis regimen should be intensified by frequent exchanges of short duration (2 hours).

In case of very severe hyperkalemia with significant repercussions on the ECG, central vascular access cannulation and urgent hemodialysis is necessary.[88,89]

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