REVIEW ARTICLES

Hypokalemia and hyperkalemia: Two Sides of the Same Coin

Hipocalémia e Hipercalémia: Dois Lados da Mesma Moeda

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ABSTRACT

Introduction: Potassium (K^+) is the main intracellular cation and is crucial for normal cellular function, especially during children's development and growth course. Changes in the homeostatic mechanisms of potassium regulation can lead to hypokalemia or hyperkalemia.

Objective: This study aimed to provide a narrative review of this common, yet complex, condition of the clinical practice.

Development/Conclusion: A comprehensive knowledge of the physiology of potassium metabolism is required to diagnose and treat its disturbances. Nearly 98% of potassium is intracellular, with the concentration gradient maintained by the sodium (Na^+)/K^+ ATPase pump located in the plasma membrane of cells. Several mechanisms, as β-adrenergic tone, insulin, and acid-base status, interfere with potassium intracellular distribution, but it is the kidney that has the key role in determining the total body potassium content, as it is responsible for approximately 80% of its excretion. The causes of hypokalemia are a mirror of hyperkalemia. Although these are two different entities, both require prompt intervention. The rate of correction depends on the severity of symptoms, presence of changes in electrocardiogram, and time of development of the disorder.

Keywords: dyskalemia, hyperkalemia, hypokalemia, potassium disturbance, potassium homeostasis, renal physiology

RESUMO

Introdução: O potássio (K^+) é o principal catião intracelular, sendo um elemento essencial para o normal funcionamento das células, especialmente em crianças, que se encontram numa fase de desenvolvimento e crescimento. Alterações nos mecanismos fisiológicos que regulam a homeostasia do potássio podem levar a hipocalémia ou hipercalémia.

Objetivo: Este estudo pretendeu efetuar uma revisão narrativa deste tema tão comum mas complexo da prática clínica.

Desenvolvimento/Conclusão: O reconhecimento da fisiopatologia subjacente ao metabolismo do potássio é essencial para estabelecer o diagnóstico e tratar os seus distúrbios. A enzima sódio (Na^+)/K^+-ATPase, localizada na membrana celular, é a principal responsável pela manutenção do potássio dentro das células. Vários mecanismos interferem com a distribuição intracelular de potássio, nomeadamente a atividade β-adrenérgica, a insulina e o equilíbrio ácido-base, mas é o rim que tem o principal papel na determinação da quantidade corporal total de potássio, sendo responsável por aproximadamente 80% da sua excreção. As causas de hipocalémia são um espelho das causas de hipercalémia e, embora sejam entidades opostas, ambas requerem intervenção imediata. A rapidez da correção depende da gravidade dos sintomas, das alterações eletrocardiográficas e do tempo de instalação do distúrbio.

Palavras-chave: discalémia, distúrbio do potássio, fisiologia renal, hipercalémia, hipocalémia, homeostasia do potássio

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INTRODUCTION

Potassium is the main intracellular cation and its concentration across the cell membrane is determinant for maintaining the cellular membrane potential and normal cellular function. The kidney is essential for potassium regulation, but other homeostatic pathways contribute for potassium distribution, such as acid-base disorders, hormones as catecholamines, insulin and aldosterone, plasma osmolality, and exercise.[1,2] Despite these regulatory mechanisms, potassium disorders remain one of the most common electrolyte disturbances found in the clinical practice.

Normal potassium values are similar in children and adolescences and in adults. However, children younger than one year old have greater gastrointestinal absorption and reduced urinary excretion of this ion due to low glomerular filtration rate, and thus tend to present a higher range of values.[3]

OBJECTIVES

The present study aimed to provide a narrative review of potassium disturbances in children, summarize the homeostatic pathways of potassium regulation, and review the diagnostic methodology and treatment of each disorder. Dyskalemias can be life-threatening, and all clinicians should have a systematized approach to these conditions.

NORMAL PHYSIOLOGY OF POTASSIUM METABOLISM

The kidney is the main regulator of the total body potassium content, with the remaining potassium being secreted by the gastrointestinal system. However, to avoid transient increases in potassium levels that can potentially affect the cellular membrane potential, several mechanisms that interfere in the cellular distribution of this ion are in place (**Figure 1**).

Insulin, as β2-adrenergic agonists, stimulates the Na^+/K^+ pump, inducing potassium uptake and hypokalemia, whereas activation of the α1-adrenoreceptor tends to increase potassium levels. Aldosterone also enhances potassium uptake through Na^+/K^+ pump stimulation, independently of its effects on renal potassium excretion.[2,4]

Plasma tonicity affects potassium distribution because effective osmoles cause a water shift from the intracellular to the extracellular space. This increases the intracellular potassium concentration and favors potassium efflux through K^+-permeable channels.[5] Of note, glucose and urea are ineffective osmoles, as they cross the membrane but do not alter the cell volume or potassium concentration.[6]

Acid-base disorders, especially if metabolic, also interfere with internal potassium balance.[5] Compared to high anion gap acidosis – as diabetic ketoacidosis and lactic acid acidosis –, hyperchloremic metabolic acidosis causes a greater potassium shift out of cells. A low bicarbonate (anion) serum concentration causes an influx of chloride (anion) that will additionally contribute to the efflux of potassium through the K^+/Cl^- cotransporter.[7]
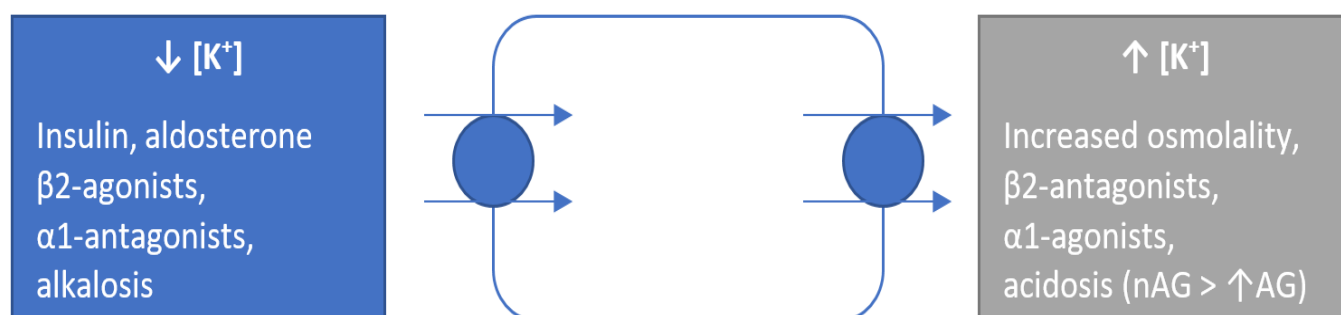
Figure 1 - Mechanisms interfering in potassium cellular shift

↑AG, high anion gap; K, potassium; nAG, normal anion gap

THE ROLE OF THE KIDNEY

The kidney regulates the total potassium content in the body . As potassium is ionized, it does not bound to plasma proteins, being freely filtered in the glomerulus. Potassium is almost completely reabsorbed in the proximal tubule, along with water and sodium, and in the ascending limb of Henle, through the $Na^+/K^+/2Cl^-$ cotransporter. Most potassium reabsorbed by this cotransporter seems to be recycled back to the lumen by the renal outer medulla potassium channel (ROMK).

The main regulatory site of potassium renal excretion is the collecting duct. In the cortical collecting duct, the main cells secrete potassium through the Na^+/K^+-ATPase, stimulated by sodium entry through the epithelial sodium channel (ENaC). This channel is highly sensitive to aldosterone, which is responsible for increasing potassium secretion by enhancing the expression of ENaC but also Na^+/K^+-ATPase and apical potassium channels.

A second potassium channel designated Big Potassium (BK) or Maxi-K ion channel responds to distal tubule flow and leads to potassium secretion. Increasing the distal flow and sodium delivery (either with loop or thiazide diuretics) contributes to potassium secretion and hypokalemia. Additionally, metabolic acidosis decreases potassium secretion through direct effects on potassium channels and ammonia production stimulation. The exact mechanism underlying the relationship between potassium and ammonia metabolism is not fully understood.[8]

In contrast, intercalated cells in the collecting duct are responsible for actively reabsorbing potassium in exchange for a hydrogen ion through the apical H^+/K^+-ATPase. In this case, the major contributors for potassium balance are potassium levels, aldosterone, and serum pH. Hypokalemia and aldosterone increase H^+/K^+-ATPase expression, on the one hand, and metabolic acidosis induces potassium reabsorption, on the other.[5-7]

In patients with chronic kidney disease (CKD), potassium secretion is preserved until late stages (stage 4) or may be compromised earlier in the presence of distal tubule dysfunction, as occurs in diabetes mellitus or tubulointerstitial disease.[7]

The fractional excretion of potassium (FEK) can be a simple and useful diagnostic tool, as it establishes an association between the amounts of potassium excreted and filtered. The increase of FEK normal values may be a sign of decreased glomerular filtration rate (GFR), even prior to a rise in serum creatinine. FEK (%) can be estimated through the formula 100*[(urinary K^+ x serum creatinine)/(serum K^+ x urinary creatinine)].[9]

Additional diagnostic information about urinary potassium loss can be retrieved through the transtubular potassium gradient (TTKG). TTKG reflects the preservation of potassium in the collecting duct and estimates the ratio of potassium in the lumen of cortical collecting ducts and peritubular capillaries, which may be relevant to distinguish the causes of hyperkalemia or hypokalemia. The formula to calculate TTKG is [(urinary K^+/serum K^+)/(urinary osm/serum osm)]. TTKG <6

points suggest a renal cause of hyperkalemia, while TTKG >6 points indicates an extrarenal cause. For example, low TTKG levels with hyperkalemia may indicate mineralocorticoid deficiency.[10]

HYPOKALEMIA

Case report nr. 1 - Hypokalemic patient under furosemide treatment
A three-month-old boy with interventricular communication and under furosemide 2 mg/kg per day presented to the Emergency Room (ER) with vomiting and diarrhea with two days of evolution. He was hypotensive and dehydrated. Laboratory tests revealed the following serum values: sodium 138 mmol/L, potassium 2.2 mmol/L, bicarbonate 18 mmol/L, creatinine 0.4 mg/dL, and urea 45 mg/dL.

Question 1.1. Which of the following best explains the development of hypokalemia? (More than one answer can be correct)
    a) *Reduced intake*
    b) *Gastrointestinal loss*
    c) *Renal loss*
    d) *Metabolic acidosis*
    e) *Hypovolemia*
The answer will be provided ahead.

Causes of hypokalemia

Hypokalemia may frequently occur in hospitalized children, especially if critically ill.[11] It can occur due to decreased intake, increased intracellular movement, or excessive loss of potassium.

In healthy children, decreased intake alone is not sufficient to cause hypokalemia, but may contribute to the condition if another potassium depletion mechanism is present.

Answer to Question 1.1. *– Given this, the option a) alone does not justify the potassium value observed in the present case report.*

As previously mentioned, increased intracellular potassium uptake can occur in cases of alkalosis, increased insulin activity, and beta-adrenergic stimulation, as these stimulate the Na^+/K^+-ATPase pump. Attention should be paid to iatrogenic hypokalemia in cases of diabetic ketoacidosis treatment and of refeeding syndrome after prolonged starvation in cases of eating disorders.[12]

Other factors potentially responsible for increase intracellular potassium uptake include hypokalemic periodic paralysis and some drugs besides insulin and beta 2-agonists, such as barium, antipsychotic drugs (risperidone/quetiapine), and chloroquine .

Hypokalemic periodic paralysis is a rare condition resulting from a defect in muscle ion channels of calcium or sodium and is associated with periods of severe muscular weakness and flaccid paralysis. When occurring in late childhood/adolescence, a familiar cause with

autosomal dominant transmission can be suspected. Less commonly, it can be acquired due to hyperthyroidism in pediatric age.[13,14]

Excessive potassium loss can be divided in extrarenal and renal, and FEK can be useful to distinguish between both (in hypokalemic patients, FEK >9% suggests an underlying renal cause, while FEK <6.5% suggests an extrarenal origin).[9]

In extreme cases, cutaneous potassium loss can occur through sweating, with some reports also describing hypokalemia in cystic fibrosis.[15,16] More commonly, hypokalemia is associated with gastrointestinal (GI) loss. In cases of upper GI loss, renal mechanisms secondary to metabolic alkalosis are responsible for potassium loss.[6]

Answer to Question 1.1. – *In the present case report, hypokalemia could be explained by GI potassium loss due to diarrhea (Option b) was correct). Vomiting did not contribute to hypokalemia, since the patient did not have metabolic alkalosis.*

The most common causes of hypokalemia are usually secondary to renal loss. Renal loss etiologies can be subdivided in increased distal flow, renal tubular acidosis, increased mineralocorticoid activity, and other causes.

As previously mentioned, increased distal sodium and water delivery directly leads to potassium secretion, with an increase in mineralocorticoid activity secondary to hypovolemia additionally present.[5] Possible causes of increased distal flow include:[17]

- Diuretics (thiazides to a greater extent than loop diuretics)
- Osmotic diuresis (most common in diabetic ketoacidosis)
- Nonabsorbable ions: bicarbonate (excessive vomiting), beta-hydroxybutyrate (diabetic ketoacidosis), hippurate (toluene exposure)
- Genetic disorders: Bartter and Gitelman syndromes, resulting from mutations in genes encoding for transporters involved in sodium reabsorption (diuretic-like syndrome). Urinary calcium is helpful in distinguishing these two entities, as it is increased in Bartter syndrome.
- Tubular injury: due to decreased tubular capacity of sodium reabsorption. It can occur in tubulointerstitial diseases and with cisplatin.

Answer to Question 1.1. - *T*he use of loop diuretics can also contribute to the development of hypokalemia (Option c) is also correct).*

Renal tubular acidosis (RTA):

Type 1 RTA (distal): Dysfunction in any of the transporters involved in the overall process of maximally acidifying the urine, namely lesion of intercalated cells due to genetic mutations in the distal tubule,leading to proton secretion inability and increasing potassium secretion.[18]

Type 2 RTA (proximal): Reduced bicarbonate reabsorption (acetazolamide or Fanconi syndrome).

Answer to Question 1.1. - *Acid-base disturbances can affect the cellular distribution of potassium. However, it is alkalosis that is associated with hypokalemia. Still, some conditions that result in acidosis can be associated with hypokalemia. These conditions do not seem to be present in the considered case report, so option d) is incorrect.*

Increased mineralocorticoid activity increases potassium urinary excretion. Hypovolemia is one of the most frequent causes.[17]

Answer to Question 1.1. - *Hypovolemia could have also contributed to the development of hypokalemia in the present case, due to an increase in aldosterone secondary to volume depletion (Option e) is also correct).*

Other factors can justify increased mineralocorticoid activity, such as independent secretion of renin, aldosterone, or other mineralocorticoids, or persistent mineralocorticoid-like secretion.[5]

Diagnostic workup of hypokalemia

Since hypokalemia can be a life-threatening condition, initial treatment should precede any diagnostic assessment.

Algorithm 1 summarizes the diagnostic workup of hypokalemia in children.

Algorithm 1 - Hypokalemia diagnostic workup
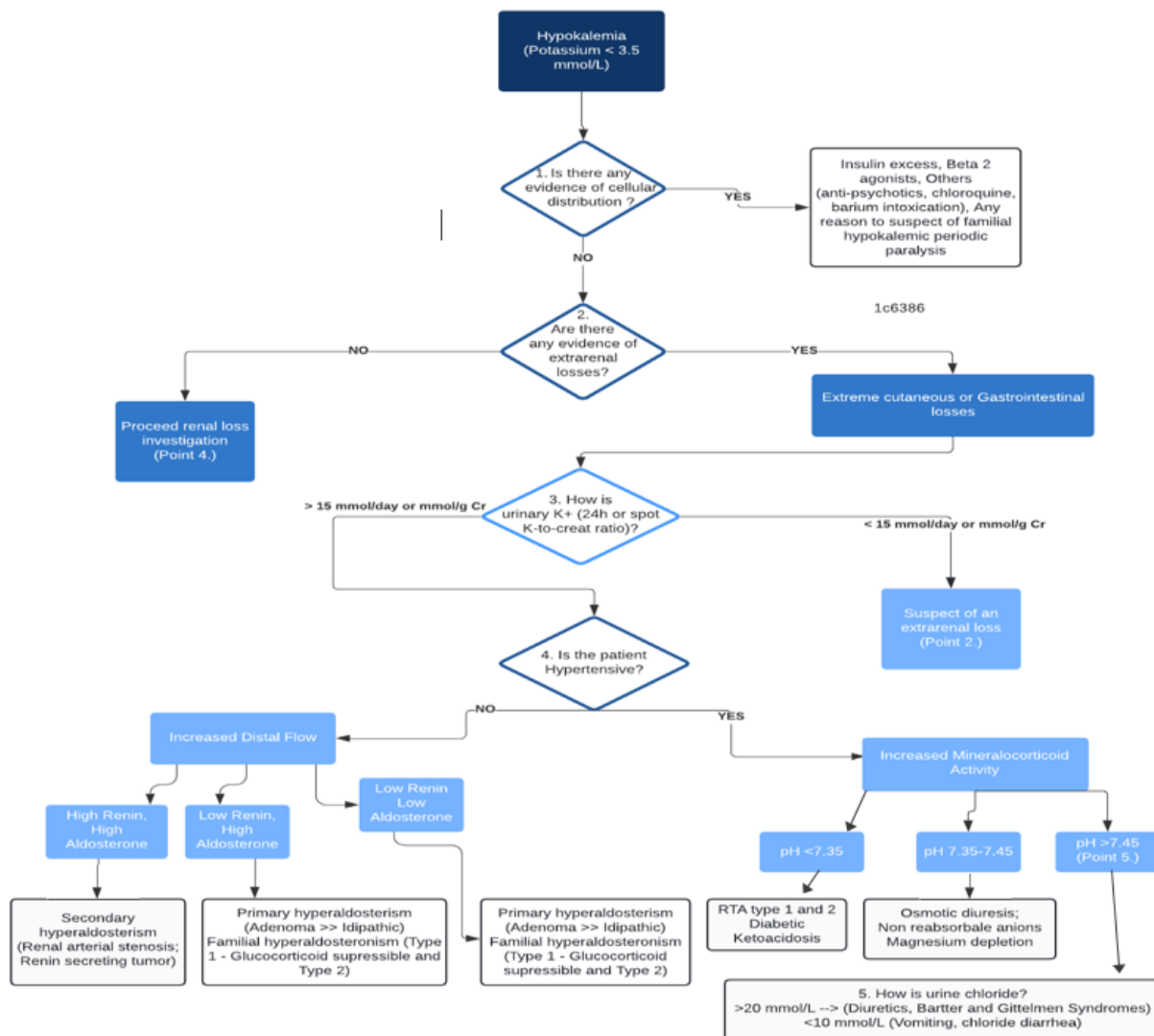
Cr, creatinine; ENaC, epithelial sodium channel; GI, gastrointestinal; RTA, renal tubular acidosis

Clinical manifestations of hypokalemia

Signs and symptoms of hypokalemia depend on its severity and time of development of the disorder. Mild hypokalemia (K+ 3-3.5 mmol/L) may not cause symptoms, especially in children. Clinical manifestations are mainly related to the muscle tissue, skeletal muscle, cardiac muscle, and intestinal smooth muscle.

Skeletal muscle weakness usually progresses from the proximal end of lower extremities to the trunk and upper extremities. In severe cases, it can affect the respiratory muscles. It can lead to muscle cramps and fasciculation, resulting in rhabdomyolysis and myoglobinuria. In the smoot muscle, it can cause an ileus that may present with abdominal distension, nausea, or vomiting.

Characteristic electrocardiogram (ECG) changes are related to cardiac repolarization and include flattening of the T wave and ST segment, prolonged QRS complex, and prominent U wave. Other arrythmias can occur, as premature atrial and ventricular complex beat, sinus bradycardia, paroxysmal atrial or junctional tachycardia, atrioventricular block, ventricular tachycardia, or even ventricular fibrillation.

Persistent hypokalemia can also have renal implications, through decreased ability of urinary concentration, decreased sodium excretion, and increased renal ammoniagenesis.[5,6]

Treatment of hypokalemia

Question 1.2. What is the best approach for this patient? [Patient weight: 4.5 kg]

The answer will be provided ahead.

The main goal of hypokalemia management is to prevent and treat life-threatening conditions, as arrythmias, paralysis, rhabdomyolysis, and diaphragmatic weakness. Acute and severe hypokalemia require prompt observation and careful follow-up through ECG monitoring.[17]

The therapeutic approach and drug dosages are summarized in **Table 1**. If the patient is symptomatic and/or has ECG changes, rapid supplementation should be provided through intravenous (IV) infusion. IV potassium administration is associated with pain and phlebitis. Limiting the concentration to less than 20 mEq/L when using a peripheral vein for potassium infusion and placing a central venous line for concentrations above 40 mEq/L help reducing the referred side effects. If the patient is asymptomatic, ECG is normal, and potassium levels are under 3 mmol/L, supplementation is still required, but oral administration should be preferred.[19]

Less severe potassium deficits can be corrected by controlling the underlying condition and implementing dietary changes.[17]

Other conditions, as hypovolemia, should be corrected. Glucose-free saline fluids should be preferred, as glucose stimulates insulin release and exacerbates hypokalemia.[20]

Magnesium deficiency also contributes to hypokalemia and should be simultaneously corrected (IV 25-50 mg/kg/dose). This deficit inhibits the muscle Na^+/K^+-ATPase, decreasing potassium entry into cells and increasing its distal secretion, and inhibiting potassium reabsorption in the loop of Henle.[21]

Contrary to what happens in acute hypokalemia, in chronic hypokalemia (like in tubulopathies) potassium concentration can be gradually corrected, as patients with chronic hypokalemia usually have lower potassium levels.

Table 1 - Hypokalemia treatment

Hypokalemia (K^+ <3.5 mmol/L)	
Is the patient symptomatic and/or has ECG changes?	
YES	**NO**
Note: K^+ deficit: 0.3 (mL) x body weight (Kg) x ($K_{normal\ lower\ limit} - K_{measured}$) Ideally **<20 mEq/L** for peripheral veins Use central venous line if concentration **>40 mEq/L**	
7.5% KCl bolus 0.2-1 mEq/kg/h *Max 40 mEq/L*	**Oral administration 1-5 mEq/kg/day** *Max 40 mEq 6/6 hours* [Preferred administration] **IV administration 2-4 mEq/kg/day**
If hypovolemia is present	
Give **glucose-free** saline fluids	
If hypomagnesemia is present	
Give **magnesium sulfate IV** 25-50 mg/kg/dose	

ECG, electrocardiogram; IV, intravenous; K, potassium; KCl, potassium chloride.

Answer to Question 1.2.

- *ECG monitoring should be initially performed*
- *K^+ deficit should then be estimated: 0.3 (mL) x body weight (Kg) x ($K^+_{normal\ lower\ limit} − K^+_{measured}$) = 0.3 x 4.5 x (3.5-2.2) = 1.8 mmol*
  Assuming the patient is symptomatic (i.e., vomiting), a 7.5% KCl bolus (0.2-1 mEq/kg/h) could be started.
  E.g.: 0.4 x 4.5/h = 1.8 mEq/h for a maximum of 40 mEq/L
  If 40 mEq of K⁺ is present in 1000 mL of solution, a 45 mL solution is required for 1,8 mEq of K⁺
  (Rule of three)
  Administer a mixture of 1.8 mL of KCl plus 43.2 mL of saline solution (total solution of 45 mL) over a period of 1 to 2 hours.
- *Stopping the diuretic to prevent renal loss and administering fluids to inhibit aldosterone secretion help increase potassium levels.*
- *if present, magnesium deficiency should be corrected.*

HYPERKALEMIA

Case report nr. 2 – Shock and hyperkalemia in a two-month-old patient

A two-month-old boy with no relevant history presented to the ER with anorexia and diarrhea with two days of evolution. He had trouble breathing and cyanosis and was non-reactive. The boy was hypotensive, tachycardic, and had bad peripheral perfusion. Laboratory tests revealed glucose 94 mg/dL, sodium 163 mmol/L, potassium 8.6 mmol/L, bicarbonate 10 mmol/L, creatinine 5.9 mg/dL, urea 317 mg/dL, C-reactive protein 6.2 mg/dL, and myoglobin 26 ng/mL.

Question 2.1. Which of the following best explains the development of hyperkalemia? (More than one answer can be correct)

   a)   *Increased potassium intake*
   b)   *Metabolic acidosis*
   c)   *Rhabdomyolysis*
   d)   *Acute kidney injury*
   e)   *Hypovolemia*
         The answer will be provided ahead.

Causes of hyperkalemia

Opposite mechanisms are implicated in the development of hyperkalemia, including excessive potassium intake, shift of intracellular potassium into the extracellular space, and decreased renal excretion.
Increased potassium intake alone is not enough to explain hyperkalemia. However, when combined with impaired kidney function and/or diminished mineralocorticoid activity, hyperkalemia can occur.[6]

Answer to Question 2.1. - *In a two-month-old boy with breast milk- or formula-exclusive diet, this option should not be considered. Therefore, option a) is incorrect.*

An outwards transcellular shift can occur in cases of acidosis, hyperglycemia, and insulin deficiency, as in diabetic ketoacidosis. Drugs like β2-blockers, renin-angiotensin-aldosterone inhibitors, and digoxin (in toxic levels) can also result in potassium flow out of cells.
In cases of hypertonicity (e.g.: after mannitol infusion), water moves to the extracellular space, increasing potassium cellular concentration, favoring a flow out of cells, and leading to hyperkalemia.
Cellular injury is another cause of extracellular potassium flow. Rhabdomyolysis, extreme physical exercise, tumor lysis syndrome, and severe hemolytic conditions are examples of cellular injury.[22]

Answer to Question 2.1. - *In the present case, the presence of metabolic acidosis, particularly if hyperchloremic, could have contributed to the high serum potassium observed (review Figure 1). Rhabdomyolysis could also explain hyperkalemia. However, myoglobin levels were normal, so option b) is correct (in contrast with option c)).*

As in hypokalemia, familial hyperkalemic periodic paralysis consists of episodes of extreme muscle weakness and paralysis. Compared to hypokalemic patients, these patients tend to be younger and present with more frequent but shorter attacks. Symptoms usually occur during the morning rather than at nighttime.[5]
Impaired renal function (acute or chronic) is a common underlying cause of hyperkalemia. Acute kidney injury, with distal tubule injury, impairs potassium excretion. If oligoanuria is present, salt and water are decreased, and potassium secretion is further reduced. In cases of CKD, adaptive mechanisms are developed, and hyperkalemia is usually rare until 15 to 20 ml/min/1,73m² of estimated GFR (eGFR). Gastrointestinal potassium secretion seems to be augmented in these patients. But there are exceptions, with some patients developing hyperkalemia in earlier CKD stages. Some conditions, like amyloidosis, chronic tubulointerstitial nephritis, lupus nephritis, urinary obstruction, and sickle cell disease, as well as renal transplant can cause early tubular injury in the distal nephron, leading to hyperkalemia with mild eGFR decrease.[5]

Answer to Question 2.1. - *Both acute kidney injury and hypovolemia (with consequent reduction of distal salt and water delivery) can cause potassium increase. Therefore, options d) and e) are correct.*

Decreased renin-angiotensin-aldosterone system activity is also a hypothesis to consider in presence of normal renal function.
Hypoaldosteronism can be primary or secondary, leading to hyperkalemia, urinary salt wasting, and hypotension. Renin levels are normal to elevated in the first case and low in the second. A similar

case occurs in patients with diabetes or obstructive uropathy, who also present RTA type 4. Drugs like non-steroid anti-inflammatory drugs and cyclosporine/tacrolimus can cause hyperkalemia by the same mechanism.[23]

Other conditions can mimic hypoaldosteronism but present normal aldosterone levels. This is the case of drugs that antagonize the mineralocorticoid receptors, such as spironolactone, or that block sodium channels of the luminal membrane of principal cells, such as trimethoprim, amiloride, and triamterene. Pseudo-hypoaldosteronism (PHA) is a rare condition that causes hyperkalemia. Type 1 PHA is associated with metabolic acidosis and renal salt wasting and occurs due to mutations in the ENaC channel or mineralocorticoid receptors. Type 2 PHA, or Gordon syndrome, is associated with hypertension due to mutations in WNK1 and WNK4 genes that interfere with sodium and potassium transport into and

out of cells. This syndrome is the opposite of Gitelman syndrome.[5,24]

Diagnostic workup of hyperkalemia

Like hypokalemia, hyperkalemia can be a life-threatening condition, thus requiring prompt treatment. The investigation of underlying causes should come in a second moment, when the patient is stabilized.

Before starting treatment, it is important to exclude pseudo-hyperkalemia, which can occur in cases of difficult phlebotomy procedures due to hemolysis, or in cases of severe leukocytosis or thrombocytosis due to potassium release from other cells.[6]

A five-step diagnostic hyperkalemia workup is illustrated in **Algorithm 2**.

Algorithm 2 - Hyperkalemia diagnostic workup

eGFR, estimated glomerular filtration rate; ENaC, epithelial sodium channel; HIV, human immunodeficiency virus; K, potassium; MR, mineralocorticoid receptor

Clinical manifestations of hyperkalemia

Most children with mild-to-moderate hyperkalemia are asymptomatic, but ECG changes can be identified when monitoring patients. ECG changes initially include non-specific repolarization abnormalities, peaked T-waves and QT interval narrowing, prolonged PR interval, decreased P wave, QRS-complex widening, and amplified R wave.

Patients with potassium levels above 7 mmol/L are usually symptomatic. They can complain of palpitations, nausea, muscle weakness or paralysis, and paresthesia. In cases of severe hyperkalemia, syncope can be present, secondary to ECG changes as bundle branch block, progressive QRS-complex widening and sinusoidal pattern, and cardiac arrest due to ventricular fibrillation or asystole.[22,23]

Treatment of hyperkalemia

Question 2.2. How should the hydroelectrolyte disorders of this patient be treated? [Patient weight: 3.5 kg]
The answer will be provided ahead.

The urgency of hyperkalemia treatment depends on its speed of development, absolute serum potassium concentration, and presence of symptoms. In cases of severe hyperkalemia (K+ >7 mmol/L), cardiac arrhythmia represents the biggest concern. Therefore, the first approach when treating hyperkalemia consists in stabilizing the cardiac membrane with IV calcium infusion and implement measures to increase the intracellular potassium uptake via insulin and glucose infusion and administration of inhaled-β2-agonists. Of note, the dose of β2-agonists required for potassium cellular shift must be two to eight times higher than the one required for bronchodilation.

The increase of serum pH with sodium bicarbonate is also associated with an increase of potassium uptake. However, controversies remain on whether isolated hyperkalemia should be treated with bicarbonate, and current recommendations advise not to use sodium bicarbonate unless the patient is acidotic (pH <7.2) or has marked renal impairment. In addition, the risk of hypernatremia should be considered, since it may represent further volume overload in oliguric, hypervolemic patients.[6]

The increase of potassium cellular uptake may be effective but transient, with evidence suggesting a limited duration of action before rebounding. Potassium removal is required, either by the kidneys or GI tract. Potassium renal loss can be achieved with diuretics, but these are ineffective in presence of renal failure, as the diuretic action depends on renal function. Cation exchange resins, such as calcium polystyrene sulfonate, exchange calcium for potassium in the GI tract and promote its elimination. However, their onset of action can be quite slow, plus they can be dependent on GI transit time.[23]

Renal replacement therapy (RRT) can be considered when medical measures fail. Intermittent hemodialysis is much more effective in potassium removal than continuous types of RRT, as peritoneal dialysis and continuous venovenous hemofiltration. The choice of the technique will depend on the patient's clinical condition and on the experience of the center.[25]

Answer to Question 2.2.

- *ECG monitoring should be initially performed*
- *Calcium gluconate 10% 0.5-1 mL/kg should be administered*

(1 x 3.5 = 3.5 mL ⇔ 350 mg) + 3.5 NaCl 0.9% (= 7 mL » 350 mg/7 mL ⇔ 50 mg/mL). Administer over 5-10 minutes. *Suspend if bradycardia is observed.*

- *Administration of 10% glucose 2-5 mL/kg (2 x 3.5 = 7 mL) + insulin 0.1 U/kg (0.1 x 3.5 = 0.35 U) in 30 minutes*
- *Administration of inhaled β2-agonists 0.3-0.5 mg/kg/dose (0.3 X 3.5 = 1 mg/dose)*
[Sodium bicarbonate could improve acidosis, but would worsen hypernatremia]

The critical medical conditions of hypovolemic shock, oliguric acute kidney injury, severe acidemia, and hyperkalemia plus severe hypernatremia require further care: vasopressor support, invasive mechanical ventilation, and continuous renal replacement therapy.

The therapeutic approach is summarized in **Table 2**.

Table 2 - Hyperkalemia treatment

Hyperkalemia (K$^+$ >5.5 mmol/L; >6.5 mmol/L if preterm/small infants)	
Does the patient have any of following?	
Symptoms, ECG changes, [K$^+$] >7 mmol/L or lower but with an ongoing risk of rising	
YES » EMERGENT THERAPY	**NO » NON-EMERGENT THERAPY**
(1) Antagonize membrane effects*: - **Calcium gluconate 10%** 0.5-1 mL/kg in 5 to 10 minutes, max 20 mL in NaCl 0.9% (10 mg/mL, max 50 mg/mL)	
(2) Promote cellular potassium uptake*: - **Insulin 0.1 U/kg** (Max 10U): Take 1 mL (100U/mL) and dilute in NaCl 0.9% until 100 mL, *then remove the required amount according to patient weight* **+** **Glucose infusion 10%** 0.5-1 mL/kg in 30 minutes - **Inhaled β2-agonists 0.3-0.5 mg/kg/ dose** - **IV sodium bicarbonate (?) 1 mEq/kg** (Max 50 mEq) over 10-15 minutes *Repeat if necessary*	*Proceed to Point 3*
(3) Promote potassium removal - **Furosemide 1 mg/kg** (Max 40 mg) - **Cation exchange resins 1g/kg** - **Renal replacement therapy**	
(4) Treat reversible causes	

CONCLUSION

Despite quite common in the clinical practice, the diagnosis and prompt treatment of potassium disorders (whether hypo or hyperkalemia) is challenging. The causes of hypokalemia mirror those of hyperkalemia, and even though these entities represent two sides of the same coin, each has its particularities and should be individually addressed. ECG monitoring is crucial in the management of both. In hypokalemia, potassium supplementation depends on symptom severity and/or ECG changes. In hyperkalemia, emergent situations should be initially addressed with stabilization of the cardiac cell membrane, followed by potassium shift into cells, simultaneously increasing potassium renal or GI removal. In both cases, the underlying cause should be corrected.

AUTHORSHIP

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Writing – review & editing

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