

# Chapter 25

## Approach to Hyperkalemia in the ICU



### 25.1 Introduction

Hyperkalemia, defined as a serum potassium level greater than 5.0 mmol/L, is a potentially life-threatening condition that requires prompt assessment and management. Potassium plays a crucial role in maintaining cellular membrane potential, particularly in cardiac and neuromuscular tissues. Severe hyperkalemia can lead to dangerous cardiac arrhythmias and muscle weakness, making it critical to quickly identify and treat the underlying cause.

This approach to hyperkalemia is structured to guide healthcare providers through a systematic evaluation and management process. The initial step is to differentiate between acute and chronic hyperkalemia, as the management strategies may differ. Subsequent steps focus on immediate stabilization, diagnosis, and long-term treatment strategies [1] [Ref: Algorithm 25.1].

#### A. Initial Assessment: Differentiating Between Acute and Chronic Hyperkalemia

- The first step in managing hyperkalemia is determining whether the hyperkalemia is acute (less than 48 h) or chronic (more than 48 hours or unknown duration). This differentiation is important because acute hyperkalemia is more likely to cause severe cardiac arrhythmias due to the rapid rise in potassium levels, while chronic hyperkalemia might allow time for some adaptation in the body.

#### Pseudohyperkalemia

Pseudohyperkalemia refers to a falsely elevated serum potassium level that does not reflect the actual in vivo potassium concentration. This condition often arises due to the release of potassium from cells during or after blood sample collection,

particularly if there is hemolysis, thrombocytosis, or leukocytosis. It is essential to distinguish pseudohyperkalemia from true hyperkalemia because the management of true hyperkalemia involves urgent therapeutic interventions to prevent life-threatening complications. In contrast, pseudohyperkalemia requires no specific treatment. Clinicians should suspect pseudohyperkalemia if there are elevated potassium levels without corresponding clinical symptoms or ECG changes indicative of hyperkalemia. Confirmation can be achieved by rechecking the serum potassium level using plasma rather than serum and ensuring proper sample handling techniques.

**Clinical features:** Muscle weakness and cramps and arrhythmias are the most common features. Gastrointestinal disturbances may also be seen. Involvement of respiratory muscles can lead to hypoventilation and apnea.

**ECG changes:** PR interval prolonged, P wave flattening, shortening of QT interval, Pointed T waves, Wide QRS complex.

#### **B. Immediate Stabilization: Administering Calcium (presence of ECG changes)**

- **Calcium Gluconate:** Administer 10 mL of 10% solution intravenously over 2–3 min. Calcium gluconate is preferred for peripheral administration because it is less irritating to veins compared to calcium chloride.
- **Calcium Chloride:** Administer 5–10 mL of 10% solution intravenously. This option provides more potent calcium but is generally administered through a central line due to the risk of tissue necrosis if extravasation occurs.
- **Rationale:** Calcium does not lower serum potassium levels but stabilizes the cardiac membrane, reducing the risk of arrhythmias associated with hyperkalemia [2].

#### **C. Lowering Potassium levels:**

##### **Shifting Potassium Intracellularly**

- **Insulin and Dextrose:** Administer 10 units of regular insulin IV followed by 50 mL of 50% dextrose. Insulin promotes the uptake of potassium into cells, temporarily lowering serum potassium levels. Onset of time: 20 min.
- **Beta-2 Agonist (Albuterol):** Administer 20 mg via nebulization in 4 mL of saline as an adjunct to insulin. This can also drive potassium into cells. Onset of time: 30 to 60 min.
- **Sodium Bicarbonate:** Consider this if there is metabolic acidosis. Sodium bicarbonate can help shift potassium into cells, particularly in patients with acidosis. Onset of time: 30 to 60 min.
- **Potassium elimination:** Potassium binding agents, loop diuretics, and hemodialysis.

#### D. Electrocardiogram (ECG) Evaluation

- An ECG should be performed immediately to assess for signs of hyperkalemia, such as tall peaked T waves, widened QRS complex (seen with potassium level greater than 6 mmol/L). These findings necessitate urgent treatment.

#### E. Identifying the Cause: History and Assessment

- Gather a detailed history to identify potential causes of hyperkalemia, including increased potassium intake, decreased renal excretion, or transcellular shifts (e.g., acidosis, tissue breakdown).
- Assess for conditions that could contribute to a transcellular shift of potassium or an increased potassium load.

#### F. Transtubular Potassium Gradient (TTKG)

- **TTKG Calculation:** This is calculated to assess the kidney's ability to excrete potassium. A TTKG greater than 8 suggests appropriate renal excretion in the presence of hyperkalemia.

#### TTKG >8:

When the Transtubular Potassium Gradient (TTKG) is greater than 8, it typically indicates that the kidneys are appropriately excreting potassium in response to hyperkalemia, suggesting that the tubular function is intact. However, the high TTKG in the presence of persistent hyperkalemia may indicate reduced tubular flow, which can result from advanced kidney failure or reduced extracellular volume (ECV) [3].

##### 1. Advanced Kidney Failure:

- In the context of chronic kidney disease (CKD) or acute kidney injury (AKI), the kidney's ability to filter blood is severely compromised. Even though the renal tubules may still be responding to aldosterone by excreting potassium effectively (reflected by a high TTKG), the overall decrease in glomerular filtration rate (GFR) means that the total amount of potassium excreted in the urine is insufficient to balance intake, leading to hyperkalemia.
- Management in this scenario focuses on addressing the underlying renal failure. This may include optimizing volume status, managing comorbid conditions like hypertension or diabetes, and considering dialysis in cases of severe kidney dysfunction.

##### 2. Reduced Extracellular Volume (ECV):

- Reduced ECV can occur in conditions such as dehydration, heart failure, or cirrhosis. In these situations, the body perceives a low blood volume, leading to increased aldosterone secretion and enhanced renal potassium excretion

(reflected by a high TTKG). However, the reduced overall urine flow due to the low volume status results in insufficient potassium clearance, contributing to hyperkalemia.

- Management in these cases focuses on restoring the ECV. This might involve administering intravenous fluids to correct dehydration; optimizing heart failure management (e.g., with diuretics, vasodilators), or addressing underlying liver disease. Care must be taken to balance fluid replacement with the risk of fluid overload, especially in patients with heart failure or cirrhosis.

In both scenarios, addressing the underlying cause is crucial to restoring normal potassium balance. While acute measures to lower serum potassium levels (e.g., using insulin, beta-agonists) may be necessary, long-term management must focus on improving kidney function or correcting volume status to prevent recurrent hyperkalemia. Additionally, careful monitoring and adjustment of medications that affect potassium levels (e.g., RAAS inhibitors, potassium-sparing diuretics) are essential in the management plan.

**TTKG  $\leq 5$ :** Suggests inadequate aldosterone (resistance) activity or tubular dysfunction, and indicates the need for further investigation.

#### **Administering 9 $\alpha$ -Fludrocortisone.**

- If TTKG is less than 5, consider the administration of 9 $\alpha$ -Fludrocortisone to promote renal potassium excretion by enhancing the effects of aldosterone.
- **Rationale:** 9 $\alpha$ -Fludrocortisone is a synthetic mineralocorticoid that helps in cases where aldosterone deficiency or resistance is suspected.

#### **TTKG $\geq 8$ : Low Aldosterone**

A TTKG (Transtubular Potassium Gradient) greater than or equal to 8, along with low aldosterone levels, suggests that the kidney's ability to excrete potassium is intact, but the issue lies in the regulation of aldosterone itself. Aldosterone is a hormone that plays a crucial role in regulating potassium and sodium balance in the body. When aldosterone levels are low, potassium excretion is reduced, leading to hyperkalemia. The evaluation of renin levels, which regulates aldosterone production, can further help determine the underlying cause of low aldosterone.

## **25.2 High Renin Levels: Causes and Implications**

When renin levels are high in the setting of low aldosterone and hyperkalemia, it usually indicates a problem with the adrenal glands or a blockade in the pathway that produces aldosterone:

**1. Primary Adrenal Insufficiency:**

- Also known as Addison's disease; this condition results in the destruction or dysfunction of the adrenal cortex, leading to inadequate production of aldosterone (and cortisol). This insufficiency results in hyperkalemia due to the inability to excrete potassium properly.

**2. Isolated Aldosterone Deficiency:**

- This rare condition involves a specific deficiency in aldosterone production, leading to hyperkalemia and sometimes hyponatremia, without affecting cortisol levels. It can be due to genetic mutations or acquired conditions affecting aldosterone synthesis.

**3. Heparin/Low Molecular Weight Heparin:**

- These anticoagulants can cause hyperkalemia by reducing aldosterone production, particularly with long-term use. This effect is more pronounced in patients with underlying renal impairment or those on other medications that affect potassium balance.

**4. ACE Inhibitors/ARBs (Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers):**

- These drugs interfere with the renin-angiotensin-aldosterone system (RAAS) by blocking the conversion of angiotensin I to angiotensin II (in the case of ACE inhibitors) or by blocking angiotensin II receptors (in the case of ARBs). Both mechanisms reduce aldosterone production, leading to hyperkalemia.

**5. Ketoconazole:**

- This antifungal agent inhibits adrenal steroidogenesis, including aldosterone synthesis, leading to hyperkalemia. The effect is dose-dependent and reversible upon discontinuation of the drug.

## **25.3 Low Renin Levels: Causes and Implications**

Low renin levels, in the presence of low aldosterone and hyperkalemia, point to conditions where renin production is suppressed or where there is resistance to the action of renin:

**1. Diabetes Mellitus:**

- Long-standing diabetes can lead to a state known as hyporeninemic hypoaldosteronism. This condition is characterized by low renin and aldosterone

levels, often leading to hyperkalemia. It is particularly common in diabetic nephropathy.

**2. Acute Glomerulonephritis (GN):**

- Inflammatory conditions of the glomeruli can reduce the kidneys' ability to excrete potassium. This reduction is often accompanied by a decrease in renin production due to altered renal function.

**3. Tubulointerstitial Diseases:**

- Chronic kidney diseases affecting the renal tubules and interstitium can impair renin release and aldosterone synthesis, leading to hyperkalemia.

**4. Pseudo-hypoaldosteronism (PHA) Type II:**

- Also known as Gordon's syndrome, this genetic condition is characterized by hypertension, hyperkalemia, and normal or low levels of renin and aldosterone. The disorder is caused by mutations that lead to increased sodium reabsorption and potassium retention in the distal nephron.

**5. Nonsteroidal Anti-inflammatory Drugs (NSAIDs):**

- These drugs reduce the production of prostaglandins, which are necessary for the release of renin. Chronic use of NSAIDs can therefore lead to decreased renin and aldosterone levels, contributing to hyperkalemia.

**6. Beta-Blockers:**

- Beta-adrenergic blockers reduce renin secretion by inhibiting the sympathetic nervous system's stimulation of the juxtaglomerular cells in the kidney. This suppression can lead to reduced aldosterone production and subsequent hyperkalemia.

## **25.4 Management Strategies**

The management of hyperkalemia in the context of low aldosterone and varying renin levels involves addressing the underlying cause:

- For conditions like primary adrenal insufficiency, hormone replacement therapy with fludrocortisone may be necessary.
- Adjusting or discontinuing medications like ACE inhibitors, ARBs, or NSAIDs may be required, particularly if these are contributing to hyperkalemia [4].

- In cases of drug-induced hyperkalemia (e.g., with heparin or ketoconazole), discontinuation or dose adjustment of the offending drug is the primary treatment.
- For patients with conditions like diabetes mellitus, careful management of blood glucose and monitoring of kidney function are critical to preventing and treating hyperkalemia.

#### I. **TTKG < 8: Tubular Resistance and Its Implications**

A Transtubular Potassium Gradient (TTKG) less than 8 in the setting of hyperkalemia suggests that the renal tubules are not responding appropriately to aldosterone. This condition is often referred to as **tubular resistance** to aldosterone. Several factors can lead to this resistance, including certain medications and underlying medical conditions.

## 25.5 Drugs Leading to Tubular Resistance

Several medications can impair the renal tubules' ability to respond to aldosterone, thereby reducing potassium excretion and contributing to hyperkalemia:

1. **Amiloride, Spironolactone, and Triamterene:** These are potassium-sparing diuretics that act on the distal nephron. They inhibit sodium reabsorption in exchange for potassium and hydrogen ion secretion, effectively reducing potassium excretion.
2. **Trimethoprim:** This antibiotic, often used in treating urinary tract infections, acts similarly to potassium-sparing diuretics and can cause hyperkalemia, particularly in patients with renal impairment.
3. **Pentamidine:** An antimicrobial agent used in the treatment of *Pneumocystis jirovecii* pneumonia, especially in immunocompromised patients, can cause renal potassium retention through a mechanism similar to that of potassium-sparing diuretics.
4. **Eplerenone:** Another potassium-sparing diuretic, it acts as an aldosterone antagonist and is used in the management of heart failure. Like spironolactone, it can impair potassium excretion.
5. **Drospirenone:** A synthetic progestin found in some oral contraceptives, it has antimineralocorticoid properties, which can lead to increased potassium retention.
6. **Calcineurin Inhibitors (e.g., cyclosporine, tacrolimus):** These immunosuppressants, commonly used in organ transplantation, can cause hyperkalemia by reducing renal potassium excretion.

## 25.6 Other Causes of Tubular Resistance

1. **Tubulointerstitial Diseases:** Conditions affecting the renal interstitium, such as chronic interstitial nephritis, can impair the kidney's ability to respond to aldosterone, leading to reduced potassium excretion.
2. **Urinary Tract Obstruction:** Chronic obstruction can cause tubular dysfunction, leading to impaired potassium excretion and hyperkalemia.
3. **Pseudo-hypoaldosteronism (PHA) Types I:** These rare genetic disorders are characterized by a lack of response to aldosterone. In PHA type I, there is a mutation in the mineralocorticoid receptor or in the epithelial sodium channel (ENaC), leading to severe hyperkalemia and metabolic acidosis.
4. **Sickle Cell Disease:** Chronic sickle cell nephropathy can cause tubular damage and lead to aldosterone resistance, contributing to hyperkalemia.
5. **Renal Transplant:** Post-transplant patients may develop hyperkalemia due to calcineurin inhibitors, tubular damage from ischemia-reperfusion injury, or rejection episodes that impair tubular function.
6. **Systemic Lupus Erythematosus (SLE):** Lupus nephritis can cause interstitial nephritis and other forms of renal damage that impair the kidney's ability to excrete potassium effectively.

## 25.7 Management Implications

When a low TTKG suggests tubular resistance, the management of hyperkalemia involves addressing the underlying causes, such as discontinuing or adjusting medications that contribute to hyperkalemia. Additionally, managing the underlying conditions like urinary tract obstruction or treating tubulointerstitial diseases is essential. In cases of genetic conditions like PHA, management may involve specific dietary modifications, and in some cases, medications that help enhance potassium excretion or bypass the defective pathway.

### 25.7.1 Consideration of Contemporary Pharmacotherapies

In addition to traditional therapies, newer pharmacological agents such as sodium zirconium cyclosilicate (SZC) and patiromer have emerged as effective options for managing chronic hyperkalemia. These agents work by binding potassium in the gastrointestinal tract, helping to lower serum potassium levels without significant systemic absorption. They offer an advantage in patients with chronic kidney disease (CKD) by reducing the risk of hyperkalemia without requiring discontinuation of renin-angiotensin-aldosterone system inhibitors (RAASi), which are crucial for managing CKD and heart failure.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors have emerged as a valuable tool in managing hyperkalemia, particularly in patients who are on RAAS inhibitors. By promoting renal excretion of potassium and glucose, SGLT2 inhibitors allow patients to continue on RAAS inhibitors without significantly increasing the risk of hyperkalemia. This helps in managing patients with CKD or heart failure where RAAS inhibition is crucial for long-term outcomes [5].

### ***25.7.2 Chronic Hyperkalemia Management***

Chronic hyperkalemia, unlike its acute counterpart, develops over a longer period and is often seen in patients with CKD, diabetes, or heart failure. Management involves reviewing medications, particularly RAAS inhibitors, and ensuring effective diuretic therapy. When chronic hyperkalemia persists, newer agents such as SZC and patiromer can be introduced to maintain potassium homeostasis without discontinuing RAAS inhibitors. Dietary potassium restriction is another component of management, although recent evidence suggests that moderate, individualized adjustments may be more appropriate than severe restriction.

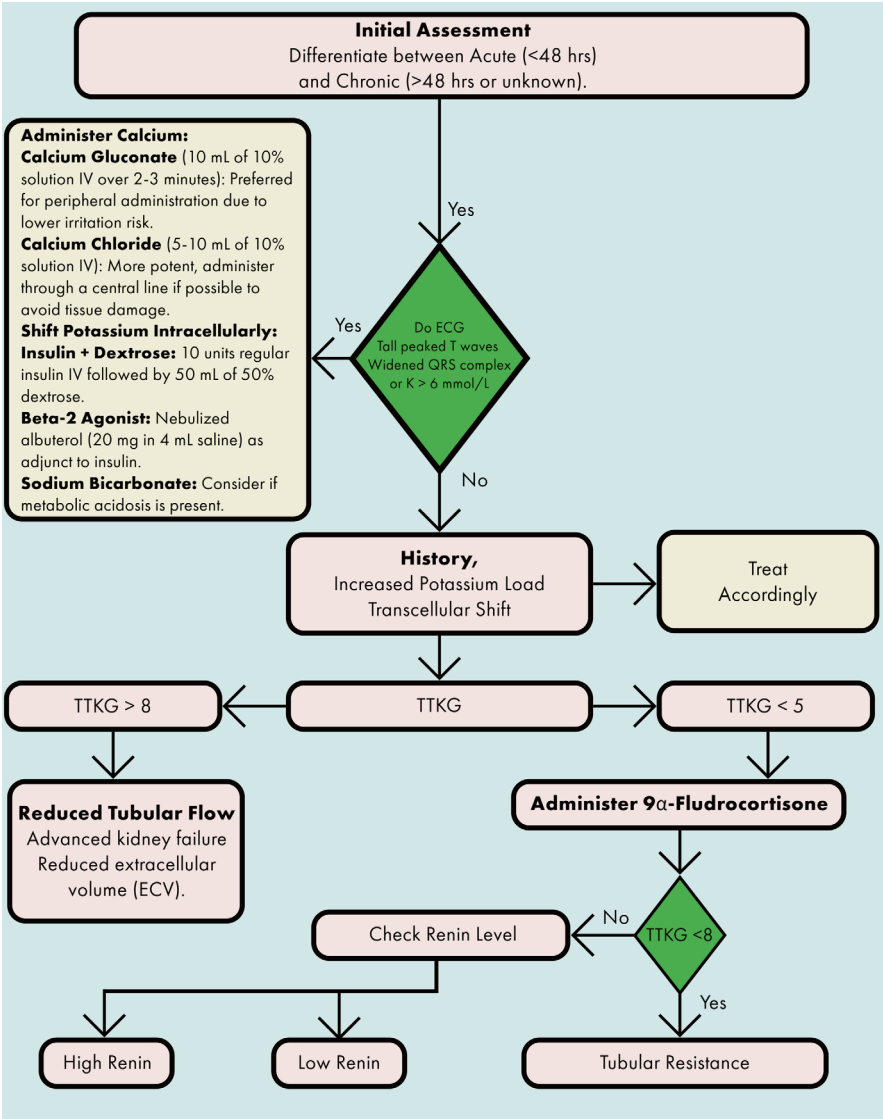
### ***25.7.3 Dietary Considerations***

In patients with CKD, dietary potassium intake can be managed without entirely restricting healthy foods like fruits and vegetables. Individualized and stepwise reduction in potassium intake is recommended, focusing on avoiding processed foods with hidden potassium sources and employing methods like soaking or boiling to reduce potassium content in foods. This approach allows for a more balanced diet while mitigating the risk of hyperkalemia.

## **25.8 Conclusion**

Effective management of hyperkalemia requires a systematic approach, beginning with the differentiation between acute and chronic cases, immediate stabilization to prevent life-threatening complications, and a thorough investigation to identify and address the underlying cause. Using tools like the TTKG, ECG, and renin levels, clinicians can tailor treatment to the specific needs of the patient, ensuring the best possible outcomes.

Algorithm 25.1: Approach to hyperkalemia in the ICU



## Bibliography

1. Emektar E. Acute hyperkalemia in adults. *Turk J Emerg Med.* 2023;23(2):75–81.
2. Massicotte-Azarniouch D, Canney M, Sood MM, Hundemer GL. Managing hyperkalemia in the modern era: a case-based approach. *Kidney Int Rep.* 2023;8(7):1290–300.
3. Palmer BF, Clegg DJ. Hyperkalemia treatment standard. *Nephrol Dial Transplant.* 2024;39(7):1097–104.
4. AlSahow A. Moderate stepwise restriction of potassium intake to reduce risk of hyperkalemia in chronic kidney disease: a literature review. *World J Nephrol.* 2023;12(4):73–81.
5. Sinnathamby ES, Banh KT, Barham WT, Hernandez TD, De Witt AJ, Wenger DM, et al. Hyperkalemia: pharmacotherapies and clinical considerations. *Cureus.* 2024;16(1):e52994.