HYPOKALEMIA IN CHILDERN

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Introduction

Normal serum potassium levels in children*

Age	Range (mEq/L or mmol/L)
Premature infant	4 to 6.5
Newborn	3.7 to 5.9
Infant	4.1 to 5.3
Child >1 year old	3.5 to 5

* Local laboratory reference ranges for normal may vary depending on laboratory and assay technique. Clinical implications of variation from normal or reference range levels must be considered individually.

Graphic 86501 Version 2.0

- Lower limit for normal serum potassium is ۳/۵ mmol/L.
- Mild when the serum potassium level is ۳ to ۳/۴ mmol/L,
- Moderate when the serum potassium level is ۲/۵ to ۳ mmol/L,
- Severe when the serum potassium level is less than ۲/۵ mmol/L.
- Compared to plasma levels, serum levels are usually slightly higher due to delays in processing and/or the effect of clotting.

Etiology

١. Decreased potassium intake
٢. Transcellular shifts (increased intracellular uptake)
٣. Increased potassium loss (skin, gastrointestinal, and renal losses)

Pathophysiology

- Decreased potassium intake, in isolation, rarely results in hypokalemia due to the ability of the kidneys to effectively minimize potassium excretion.
- However, reduced intake can be a contributor to hypokalemia in the presence of other causes, such as malnutrition or diuretic therapy.
- Cellular uptake of potassium is promoted by alkalemia, insulin, beta-adrenergic stimulation, aldosterone and xanthines, such as caffeine.
- Renal potassium losses are associated with increased mineralocorticoid-receptor stimulation such as occurs with primary hyperreninism and primary aldosteronism.
- Increased delivery of sodium and/or non-absorbable ions (diuretic therapy, magnesium deficiency, genetic syndromes) to the distal nephron can also result in renal potassium wasting.

Gastrointestinal losses

- GI losses are a common cause of hypokalemia with severe or chronic diarrhea being the most common extrarenal cause of hypokalemia.
- Diarrheal potassium content (٢٠ to ٥٠ mEq/L) is relatively high compared with other body fluids.
- In contrast, upper GI losses (eg, vomiting, nasogastric drainage) are initially minimal as the potassium content is relatively low (٥ to ١٠ mEq/L).
- However, the loss of gastric secretions results in metabolic alkalosis that leads to increased urinary potassium losses.
- Metabolic alkalosis leads to increased distal delivery of sodium bicarbonate, which in combination with hypovolemia-induced hyperaldosteronism results in enhanced potassium excretion as potassium is exchanged for sodium.

Increased urinary losses

- Increased delivery of sodium and water to the distal nephron
- Increased mineralocorticoid activity

Diuretics

- Diuretic therapy (loop and thiazide diuretics) impairs sodium reabsorption in more proximal nephron segments leading to distal delivery of sodium.
- In addition, volume depletion leads to increased aldosterone activity.
- Bartter and Gitelman syndromes are autosomal recessive diseases that are caused by mutations in genes encoding tubular transport proteins involved in sodium reabsorption.

Tubular injury

- Tubular injury due to tubulointerstitial diseases or cisplatin results in decreased sodium reabsorption in more proximal nephron segments, leading to distal delivery of sodium, where potassium is exchanged for sodium.
- Renal tubular acidosis
- In distal (type ١) RTA, increased urinary potassium loss is due to enhanced potassium secretion needed to maintain electroneutrality because of the impaired distal acidification (ie, defective secretion of protons) .
- In addition, tubular cellular membrane permeability is also increased, leading to potassium loss into the lumen along with protons.
- In proximal (type ٢) RTA, as noted above, urinary potassium loss is due to increased distal delivery of sodium bicarbonate due to the reduced proximal tubule's absorptive capacity for bicarbonate.

Increased mineralocorticoid activity

- Hypovolemia

Other etiologies :

- Aldosterone-secreting adenomas
- Glucocorticoid remediable aldosteronism (GRA) is an autosomal dominant disorder due to a fusion of the promoter of the gene encoding aldosterone synthase in the adrenal zona fasciculata (involved in cortisol synthesis) with the coding region of the related gene in the zona glomerulosa (involved in aldosterone synthesis).
- This mutation increases the production of aldosterone, which can be suppressed by glucocorticoid administration. GRA typically presents with hypertension before ٢١ years of age.
- Apparent mineralocorticoid excess (AME) is an autosomal recessive disorder due to mutations of the gene that encodes ١١-beta-hydroxysteroid dehydrogenase type ٢ isoform, which normally breaks down cortisol to cortisone.
- This genetic defect results in increased levels of renal cortisol, which binds to the mineralocorticoid receptor. AME typically presents in infancy or early childhood with severe hypertension, failure to thrive, and muscle weakness due to hypokalemia.
- Chronic ingestion of licorice containing glycyrrhetinic acid has a similar effect.

Drugs (besides beta-adrenergic agonists)

- Heavy metals–
- Barium toxicity is a rare cause of hypokalemia, caused by blockade of potassium channels limiting their efflux from cells.
- Cesium has been reported as a rare cause of hypokalemia in adults due to its use as an alternative therapy for cancer, but has not been reported in children.
- Antipsychotic drugs
- risperidone and quetiapine in adults.
- Chloroquine intoxication is an uncommon cause of severe hypokalemia in children due to intracellular movement of potassium.
- Penicillin is an anion excreted in the urine, resulting in increased K+ excretion because the penicillin anion must be accompanied by a cation.

Other causes of urinary loss

- **Amphotericin B nephrotoxicity**
- Amphotericin B causes hypokalemia by disrupting cellular membranes and increasing membrane permeability.
- **Liddle syndrome**
- Liddle syndrome is caused by an autosomal dominant gain-of-function mutation in subunits of the epithelial sodium channel (ENaC) that presents in childhood as hereditary hypokalemic metabolic alkalosis and hypertension.

- **Cystic fibrosis and skin losses**

- Sweat losses of K+ can be significant during vigorous exercise in a hot climate. Associated volume depletion and hyperaldosteronism increase renal losses of K+.
- Both the polyuric phase of acute tubular necrosis and postobstructive diuresis cause transient, highly variable K+ wasting and may be associated with metabolic acidosis. Tubular damage, which occurs either directly from medications or secondary to interstitial nephritis, is often accompanied by other tubular losses, including magnesium, Na + , and water. Such tubular damage may cause a secondary RTA with metabolic acidosis.
- Isolated magnesium deficiency causes renal K+ wasting.

- Both endogenous (epinephrine in stress) and exogenous (albuterol) β-adrenergic agonists stimulate cellular uptake of K+ .
- Theophylline overdose, barium intoxication, administration of cesium chloride (a homeopathic cancer remedy), and toluene intoxication from paint or glue sniffing can cause a transcellular shift hypokalemia, often with severe clinical manifestations.
- Children with hypokalemic periodic paralysis, a rare autosomal dominant disorder, have acute cellular uptake of K. **Hypokalemic periodic paralysis is due to defects in muscle calcium and sodium channels.**
- **Most cases are hereditary and are primarily associated with a mutation in the gene that codes for the alpha-١ subunit of the dihydropyridine-sensitive calcium channel in skeletal muscle. These patients typically present in late childhood or adolescence.**
- **Acquired cases have been reported in patients with hyperthyroidism (referred to as thyrotoxic periodic paralysis), and typically present in older patients between ٢٠ and ٣٠ years of age.**

- Hypokalemia can occur during refeeding syndrome.
- Inadequate K+ intake occurs in anorexia nervosa ; accompanying bulimia and laxative or diuretic abuse exacerbates the K+ deficiency.
- Urinary K+ wasting is often accompanied by a metabolic alkalosis. This condition is usually associated with increased aldosterone, which increases urinary K+ and acid losses, contributing to the hypokalemia and the metabolic alkalosis.
- **In general, serum potassium concentration falls by less than ٠/٤ mEq/L for every ٠/١ unit rise in pH.**

- In congenital chloride-losing diarrhea , an autosomal recessive disorder, there is high stool loss of Cl^- , leading to metabolic alkalosis, an unusual sequela of diarrhea.
- Some patients with hypoparathyroidism and hypocalcemia caused by an activating mutation of the calcium-sensing receptor (autosomal dominant hypoparathyroidism) have hypokalemia, hypomagnesemia, and metabolic alkalosis.
- The reason is that activation of the calcium-sensing receptor in the loop of Henle impairs tubular resorption of sodium and chloride, causing volume depletion and secondary hyperaldosteronism.

- EAST syndrome , an autosomal recessive disorder caused by mutations in the gene for a potassium channel in the kidney, inner ear, and brain, consists of e pilepsy, a taxia, s ensorineural hearing loss, and tubulopathy (hypokalemia, metabolic alkalosis, hypomagnesemia, and hypocalciuria).
- In the presence of high aldosterone levels, there is urinary loss of K+ , hypokalemia, metabolic alkalosis, and elevated urinary [Cl −].
- Also, renal retention of Na + leads to hypertension.
- Glucocorticoid-remediable aldosteronism , an autosomal dominant disorder that leads to high levels of aldosterone (but low renin levels), is often diagnosed in childhood, although hypokalemia is not always present.
- A variety of disorders cause hypertension and hypokalemia without increased aldosterone levels.

- congenital adrenal hyperplasia
- ١١β-hydroxylase deficiency
- ١٧a-hydroxylase deficiency
- Cushing syndrome

Transcellular Shifts

- Alkalemia
- Insulin
- a-Adrenergic agonists Drugs/toxins (theophylline, barium, toluene, cesium chloride, hydroxychloroquine)
- Hypokalemic periodic paralysis
- Thyrotoxic period paralysis
- Refeeding syndrome

Extrarenal Losses

- Diarrhea
- Laxative abuse
- Sweating
- Sodium polystyrene sulfonate (Kayexalate) or clay ingestion

Decreased Intake

- Anorexia nervosa

Renal Losses

- With Metabolic Acidosis
- Distal renal tubular acidosis
- Proximal renal tubular acidosis
- Ureterosigmoidostomy
- Diabetic ketoacidosis

Without Specific Acid–Base Disturbance

- Tubular toxins: amphotericin, cisplatin, aminoglycosides
- Interstitial nephritis
- Diuretic phase of acute tubular necrosis
- Postobstructive diuresis
- Hypomagnesemia High urine anions (e.g., penicillin or penicillin derivatives)

With Metabolic Alkalosis

- Low urine chloride
- Emesis or nasogastric suction
- Chloride-losing diarrhea (OMIM ٢١٤٧٠٠) Cystic fibrosis (OMIM ٢١٩٧٠٠)
- Low-chloride formula
- Posthypercapnia
- Previous loop or thiazide diuretic use
- High urine chloride and normal blood pressure
- Gitelman syndrome
- Bartter syndrome
- Autosomal dominant hypoparathyroidism
- EAST syndrome
- Loop and thiazide diuretics (current)
- High urine chloride and high blood pressure
- Adrenal adenoma or hyperplasia
- Glucocorticoid-remediable aldosteronism (OMIM ١٠٣٩٠٠)
- Renovascular disease
- Renin-secreting tumor
- ١٧β-Hydroxylase deficiency (OMIM ٢٠٢١١٠) ١١β-Hydroxylase deficiency (OMIM ٢٠٢٠١٠) Cushing syndrome ١١β-Hydroxysteroid dehydrogenase deficiency (OMIM ٢١٨٠٣٠) Licorice ingestion Liddle syndrome (OMIM ١٧٧٢٠٠)

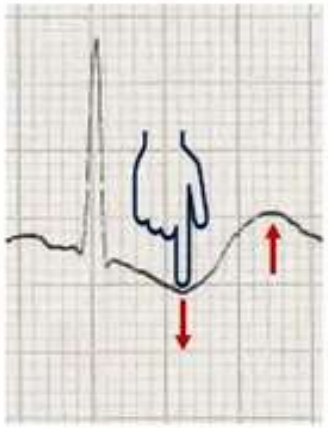
History and Physical

- Significant **muscle weakness** occurs at serum potassium levels below ۲٫۵ mmol/L but can occur at higher levels if the onset is acute.
- the pattern is **ascending** in nature affecting the lower extremities, progressing to involve the trunk and upper extremities and potentially advancing to paralysis.
- Affected muscles can include the muscles of respiration which can lead to respiratory failure and death.
- Involvement of GI muscles can cause an ileus with associated symptoms of nausea, vomiting, and abdominal distension.
- Severe hypokalemia can also lead to **muscle cramps**, **rhabdomyolysis**, and resultant **myoglobinuria**.
- Periodic paralysis is a rare neuromuscular disorder, which is inherited or acquired, that is caused by an acute transcellular shift of potassium into the cells.
- It is characterized by potentially fatal episodes of muscle weakness or paralysis that can affect the respiratory muscles.

History and Physical

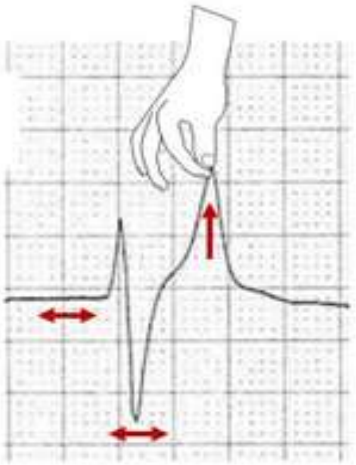
- Hypokalemia can result in a variety of cardiac dysrhythmias.
- The **ECG** changes that occur are:
- T-wave flattening initially,
- followed by ST depression and the appearance of a U wave that can be difficult to distinguish from the T wave.
- The U wave is often seen in the lateral precordial leads of V۴ to V۶.
- Prolongation of the PR and QT interval can also occur. Risk of arrhythmias is highest in older patients, those with heart disease and those receiving digoxin or antiarrhythmic drugs.
- Administration of anesthesia in the setting of hypokalemia is also a risk for dysrhythmias and impaired cardiac contractility but more so with acute rather than chronic hypokalemia.

The push-pull effect



Hypokalaemia

T wave inversion
ST depression
Prominent U wave

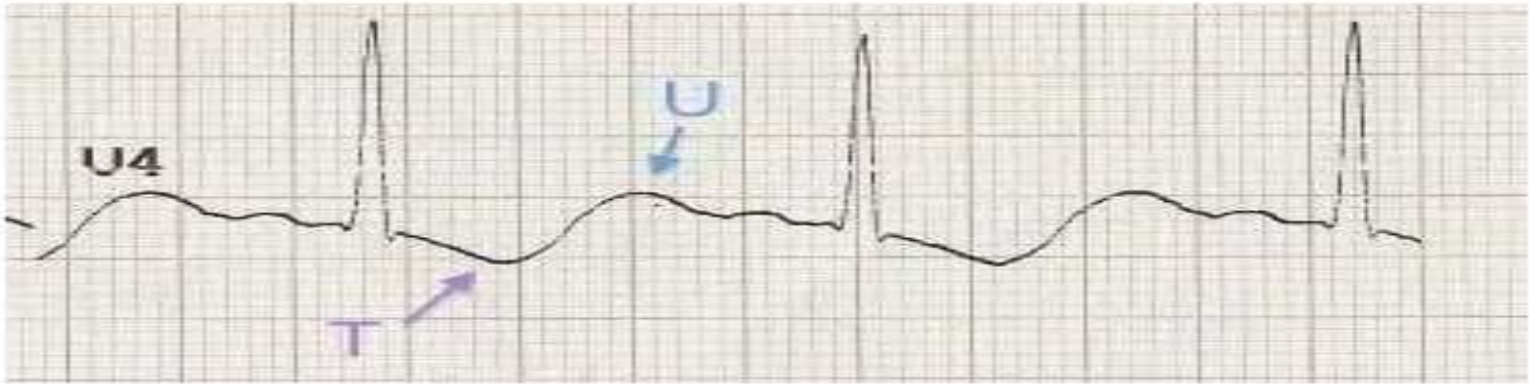


Hyperkalaemia

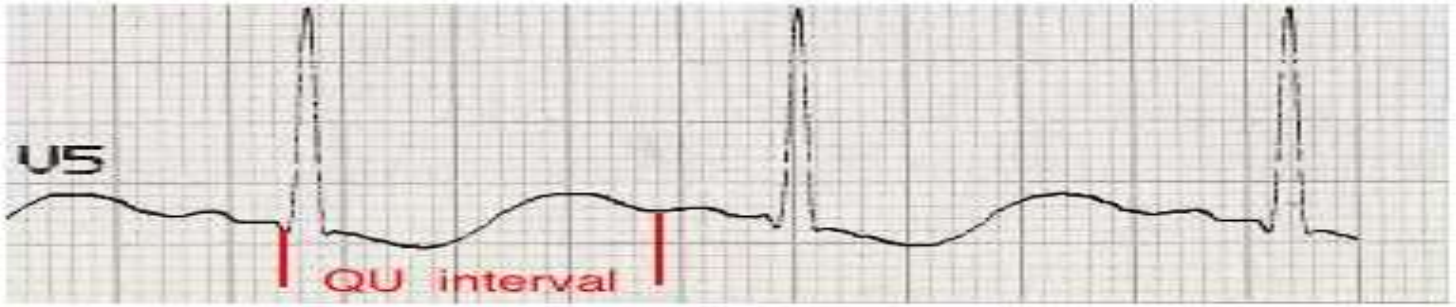
Peaked T waves
P wave flattening
PR prolongation
Wide QRS complex

LIFE IN THE FASTLANE

- Hypokalaemia creates the illusion that the T wave is "pushed down", with resultant T-wave flattening/inversion, ST depression, and prominent U waves
- In hyperkalaemia, the T wave is "pulled upwards", creating tall "tented" T waves, and stretching the remainder of the ECG to cause P wave flattening, PR prolongation, and QRS widening

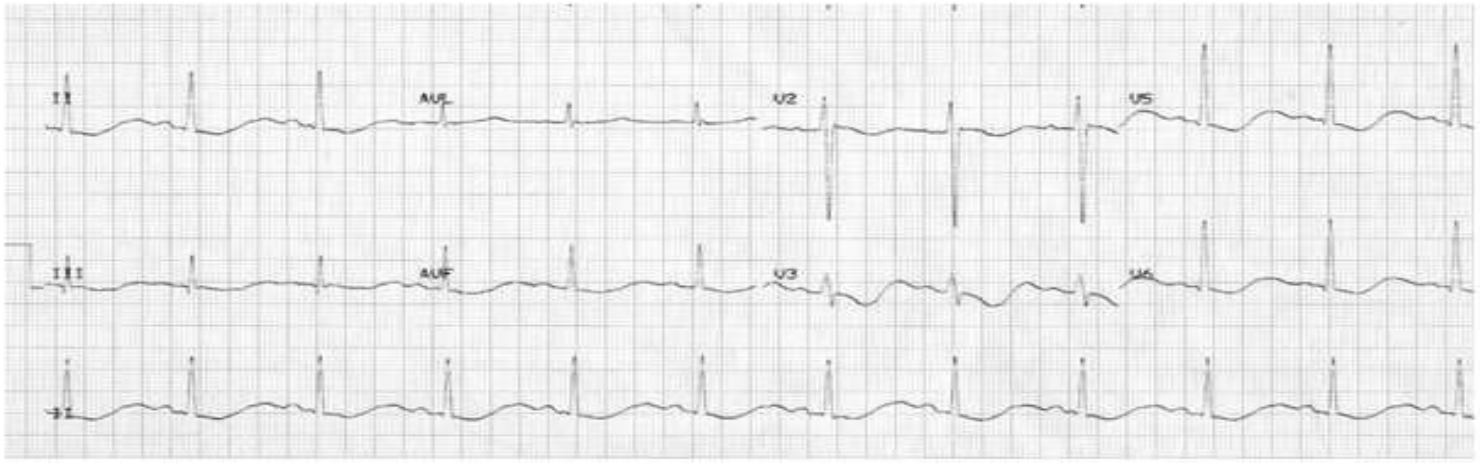


Hypokalaemia: T wave inversion and prominent U waves



QU interval: The apparent pseudo-prolonged QT interval is actually the QU interval with an absent T wave

MENU BLOG ECG CCC TOP 100 PODCASTS EPONYM TOX JOBS PART ONE

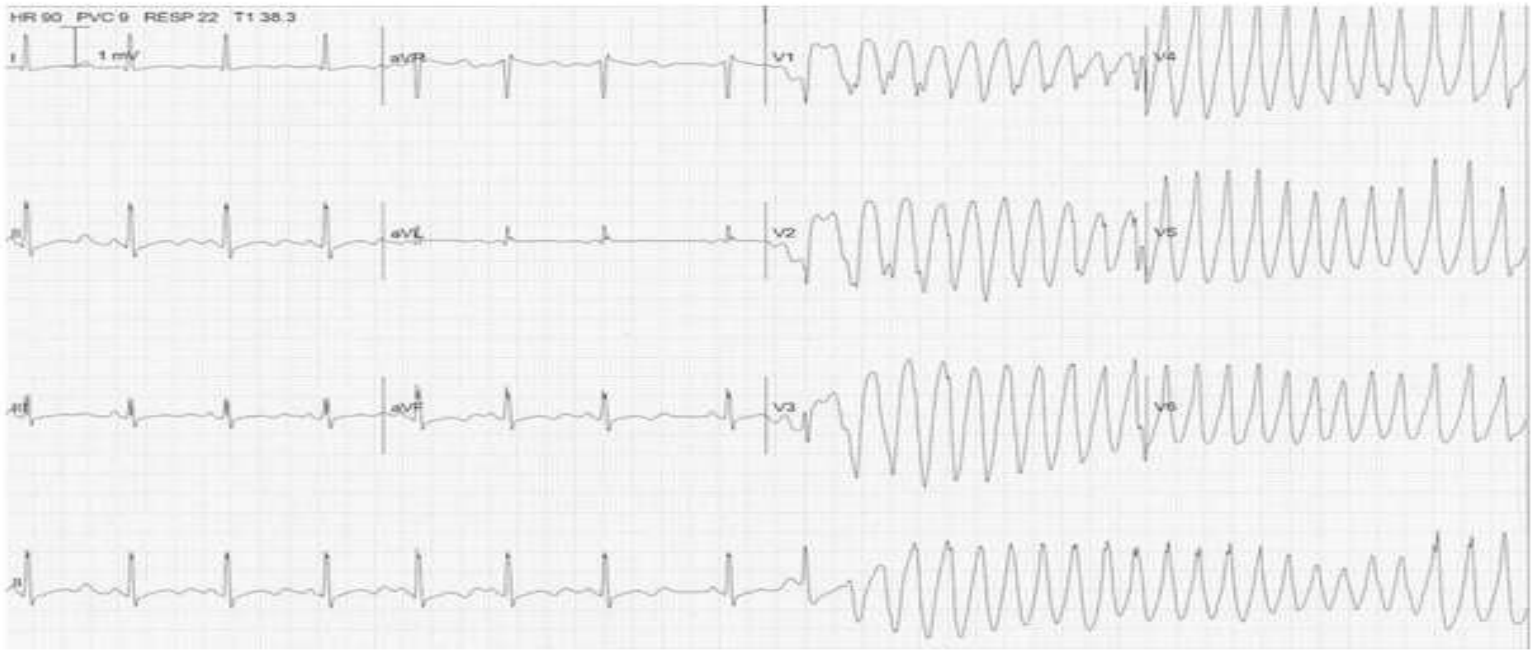


Hypokalaemia:

- Widespread ST depression and T wave inversion
- Prominent U waves
- Long QU interval

This patient had a serum K+ of 1.7

Example 3



Hypokalaemia causing **Torsades de Pointes**

- Another ECG from the same patient
- Note the atrial ectopic causing 'R on T' (or is it 'R on U'?) that initiates the paroxysm of TdP

History and Physical

- **Hypomagnesemia** often occurs with and may worsen hypokalemia especially in the presence of chronic diarrhea, alcoholism, genetic disorders, diuretic use and chemotherapy.
- The combination of **hypokalemia** and **hypomagnesemia** are associated with an increased risk of **torsades de pointes**, particularly in individuals receiving QT-prolonging medications.
- Additionally, hypomagnesemia can increase urinary potassium losses thus lowering the serum potassium level, as well as, prevent urinary potassium reabsorption thereby impeding potassium repletion.
- Lastly, prolonged hypokalemia can cause structural and functional changes in the kidney that include impairing concentrating ability, increased ammonia production, altered sodium reabsorption and increased bicarbonate absorption.
- Hypokalemia can also result in glucose intolerance by reducing insulin secretion.

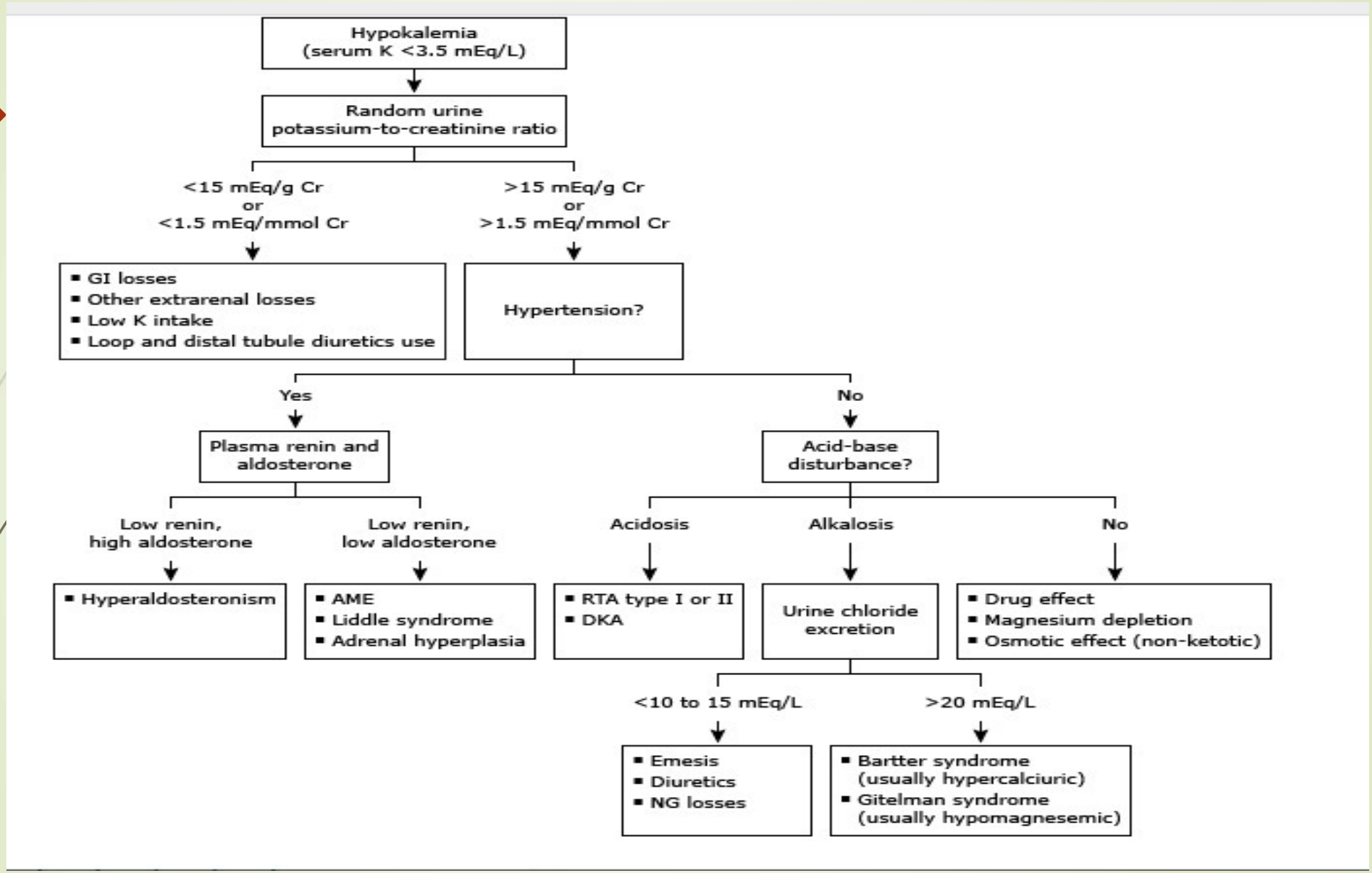
Evaluation

- Diagnostic evaluation involves assessment of urinary potassium excretion and assessment of acid-base status.
- Assessment of urinary potassium excretion can help distinguish renal losses from other causes of hypokalemia. Measurement of potassium excretion is ideally done via a ٢٤-hour urine collection.
- Excretion of more than ٣٠ mEq of potassium per day indicates inappropriate renal potassium loss.
- Alternative methods for measurement include a spot urine potassium concentration or urine potassium-to-creatinine ratio.
- A urine potassium concentration of greater than ١٥ mmol/L or a ratio greater than ١٣ mEq/mmol of creatinine, respectively, also indicates inappropriate renal potassium loss.
- After determining the presence or lack of renal potassium wasting, assessment of acid-base status should then be determined.
- The existence of metabolic acidosis or alkalosis with or without renal potassium wasting can further narrow the differential diagnosis.
- Aside from diagnostic evaluation, assessment of serum magnesium level, muscle strength, and electrocardiographic changes is warranted as the latter two would warrant immediate intervention.

Laboratory testing for pediatric hypokalemia of unknown etiology

Blood tests
Chemistries (sodium, potassium, chloride, bicarbonate, magnesium, creatinine)
Venous pH
Plasma renin activity
Plasma aldosterone
Urine tests
Chemistries (sodium, potassium, chloride, calcium, creatinine)

Graphic 98037 Version 1.0


Hypokalemia
(serum K <3.5 mEq/L)
Random urine
potassium-to-creatinine ratio
<15 mEq/g Cr
or
<1.5 mEq/mmol Cr
>15 mEq/g Cr
or
>1.5 mEq/mmol Cr
GI losses
Other extrarenal losses
Low K intake
Loop and distal tubule diuretics use
Hypertension?
Yes
No
Plasma renin and
aldosterone
Acid-base
disturbance?
Low renin,
high aldosterone
Low renin,
low aldosterone
Acidosis
Alkalosis
No
Hyperaldosteronism
AME
Liddle syndrome
Adrenal hyperplasia
RTA type I or II
DKA
Urine chloride
excretion
Drug effect
Magnesium depletion
Osmotic effect (non-ketotic)
<10 to 15 mEq/L
>20 mEq/L
Emesis
Diuretics
NG losses
Bartter syndrome
(usually hypercalciuric)
Gitelman syndrome
(usually hypomagnesemic)

Treatment / Management

The overarching goals of therapy for hypokalemia are to prevent or treat life-threatening complications, replace the potassium deficit, and to diagnose and correct the underlying cause.

- Clinical manifestations do not occur with mild to moderate hypokalemia; thus, repletion is not urgent. Mild to moderate hypokalemia is typically treated with oral potassium supplements. Providing ۶۰ to ۸۰ mmol/day in divided doses over days to weeks is usually sufficient.
- Oral supplementation can irritate GI mucosa leading to bleeding and/or ulceration but is associated with a lower risk of rebound hyperkalemia. It should be taken with plenty of fluids and food.
- A majority of cases of hypokalemia involve chloride depletion and respond best to replacement with potassium chloride. Intravenous (IV) repletion is administered if oral therapy is not tolerated.
- Replacement therapy must be given more rapidly with severe hypokalemia or when clinical symptoms are present.
- Potassium chloride of ۴۰ mmol given every ۳ to ۴ hours for ۳ doses is preferred. Rapid correction can be provided via oral and/or IV formulation. IV administration is preferred in the setting of cardiac dysrhythmias, digitalis toxicity and recent or ongoing cardiac ischemia.

Treatment / Management

- Pain and phlebitis usually occur with peripheral IV infusions when infusion rates exceed ١٠ mmol per hour.
- There is also a risk of rebound hyperkalemia when rates exceed a dose of ٢٠ mmol per hour.
- In general, ٢٠ mmol per hour of potassium chloride will increase serum potassium levels by an average of ٠/٢٥ mmol per hour.
- Potassium should not be given in dextrose-containing solutions because dextrose will stimulate insulin secretion which then exacerbates the hypokalemia.
- Serum potassium levels should be checked every ٢ to ٤ hours.
- Potassium repletion can occur more slowly once the serum potassium level is persistently above ٣ mmol/L or clinical symptoms have resolved.
- Every decrease in serum concentration of ٠/٣ mmol/L accounts for a reduction of approximately ١٠٠ mmol in total body potassium stores.

Treatment / Management

- A potassium-sparing diuretic should also be considered when the etiology of hypokalemia involves renal potassium wasting as potassium replacement therapy alone may not suffice.
- The presence of an acid-base disorder needs to be established as management may differ for etiologies of hypokalemia caused by redistribution of potassium from the extracellular fluid into cells (redistributive hypokalemia).
- When paralysis or cardiac dysrhythmias are present, in this setting, potassium repletion should be considered.
- Rebound hyperkalemia is a potential complication of potassium therapy when redistributive hypokalemia is the cause of hypokalemia.
- As the initial process causing redistribution resolves or is corrected, the transfer of potassium from intracellular to extracellular fluid in conjunction with potassium repletion can result in hyperkalemia.
- Potassium repletion in patients with periodic paralysis carries a high risk of rebound hyperkalemia.