Hypokalemia

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physiology: potassium pharmacokinetics

the potassium deficit is often large

- Patients with hypokalemia often have a large total-body potassium deficit. This varies depending on acid/base status, but to get a general idea: (31227226)
  - K of 3 mEq/L may correlate with a potassium deficit of 100-200 mEq.
K of 2 mEq/L may correlate with a potassium deficit of 400-600 mEq.

- The relationship between potassium level and total-body potassium deficit is exponential (figure below). As the potassium level falls progressively lower, this represents an exponentially large increase in the total body potassium deficit.

![Graph showing exponential relationship between serum potassium and total body potassium deficit](image)

**Segal equation for potassium deficit**: Although often approximated as a linear function, the potassium deficit is better estimated as an exponential function.


**estimating the potassium deficit in clinical context**

- This depends on two factors:
  - The serum potassium level.
  - The presence of any factors which may cause shifting of potassium in or out of the cells.
- For example, diabetic ketoacidosis causes potassium to shift out of the cells. Therefore, the potassium deficit may be even larger than would be estimated based on the above formula.

**most of the deficit occurs intracellularly**

- The vast majority of potassium in the body is located intracellularly. Thus, most of the total body potassium deficit represents deficient intracellular potassium.
- The intracellular nature of the potassium deficit means that IV potassium must be administered slowly:
  - Time is required for potassium to enter the cells.
  - Rapid administration may cause serum levels to be elevated (even though there is a total-body potassium deficit!). Serum hyperkalemia is dangerous. Furthermore, serum hyperkalemia may cause poor retention of potassium (as it will tend to encourage potassium excretion in the urine).
- Bedside clinical implications:
  - (1) IV potassium should never be given as a bolus.
  - (2) Even in severely hypokalemic patients, aggressive IV potassium administration can be dangerous (more on this below).

**causes of spuriously low lab values (pseudo-hypokalemia)**

- (1) Delayed sample analysis (cells absorb potassium while the blood tube is sitting around).
- (2) Markedly elevated cell counts.
  - Leukocytes take up potassium while the blood is awaiting analysis.
T-wave abnormalities
- May flatten or invert.
- Inverted T-wave followed by prominent U-wave may create a biphasic “down-up” morphology.

U-wave prominence
- May fuse with the T-wave to produce a prolonged QT interval (technically a Q-T-U interval).
- ST segments may appear depressed.
- QT prolongation, which may predict risk of arrhythmia.

Arrhythmias
- Torsades de pointes may be the most classic.
- Other possibilities include atrial fibrillation, ventricular tachycardia, and ventricular fibrillation.

Clinical significance

Causes

Reduced potassium intake (rarely the sole cause)
- Anorexia nervosa
- Alcoholism

Potassium shifts into the cells
- Insulin (e.g. during DKA resuscitation)
- Beta-agonists (albuterol, terbutaline, epinephrine – including endogenous epinephrine surges from stress)
- Hypothermia
- Alkalemia (small effect)
- Hypokalemic periodic paralysis ([31227226](https://www.ncbi.nlm.nih.gov/pubmed/31227226))
  - Familial form with onset <20 years old.
  - Acquired form associated with hyperthyroidism, typically in Asian and Mexican men.

**extra-renal potassium loss**

- Diarrhea
- Vomiting or large-volume gastric suction
- Profound sweating

**renal potassium loss**

- Secondary to another electrolyte abnormality
  - Hypomagnesemia
  - Metabolic alkalosis
- Polyuria with increased distal delivery of sodium and water to the tubule
  - Non-potassium-sparing diuretics (e.g. thiazides, loop diuretics, acetazolamide, mannitol)
  - Sodium-wasting nephropathy (e.g. post-ATN or post-obstructive)
- High-dose penicillins
- Mineralocorticoid excess
  - Cushing's syndrome
  - Primary hyperaldosteronism
  - Exogenous steroid
  - Licorice ingestion
- Renal tubular acidosis types I or II (see table below)
The magnesium level is the most important contributing factor, for several reasons:

(a) Hypomagnesemia is common (most patients with hypokalemia have hypomagnesemia as well) (29540487)

(b) Treatment of hypomagnesemia may be required to effectively treat hypokalemia.

(c) Expedient treatment of hypomagnesemia may reduce the risk of Torsade de pointes.

May consider checking a full electrolyte panel (including Calcium, Magnesium, and Phosphate):

Electrolyte abnormalities often occur in pairs and triplets ("electrolytic disarray").

(2) review the medication list, focusing on:

- Diuretics
- Insulin
- Beta-agonists
- Steroid
- Antibiotics
  - High-dose penicillins
  - Amphotericin
  - Aminoglycosides
  - Tenofovir, anti-retrovirals
  - Foscarnet
- Chemotherapeutics
  - Platinum agents
  - Ifosfamide
- Miscellaneous
  - Mafenide acetate
  - NSAIDs
  - Lithium
  - Topiramate
  - Valproic acid

(3) review recent history & data

- Historical clues:
  - Diarrhea
  - Polyuria
  - Profound sweating
  - Vomiting or gastric suction
- Lab clues:
  - Nonanion-gap metabolic acidosis (look for RTA-1 or RTA-2)
  - Metabolic alkalosis (may cause hypokalemia, but can also result from hypokalemia!)

(4) additional diagnostic tests?

- Fancy evaluations usually aren't needed.
  - Careful consideration of the above etiologies combined with the clinical context will usually provide an explanation for the hypokalemia.
  - Urine potassium measurement may be more helpful for outpatients (who may have surreptitious vomiting or laxative abuse).
- Persistent hypokalemia despite repletion usually implies renal potassium-wasting (in an ICU patient with no evidence of extra-renal potassium loss).
  - Among patients with hypertension, metabolic alkalosis, and ongoing potassium wasting, evaluation of the renin-angiotensin-aldosterone system may be considered. This may be accomplished by checking renin and aldosterone levels.
- An approach to further evaluation of hypokalemia is shown below:
risk stratification

risk factors for complications from hypokalemia

- Severe hypokalemia (potassium < 2.5 mM).
- Clinical context where potassium is likely to fall further (e.g. DKA or re-feeding syndrome).
- EKG changes due to hypokalemia (e.g. QT prolongation).
- Increased risk of arrhythmia:
  - Patients on digoxin
  - Myocardial ischemia or scarring
  - Concomitant deficiency of magnesium

hypokalemia is generally well tolerated

- Overall, hypokalemia is much more dangerous than hypokalemia.
- In the absence of the above factors, hypokalemia is well tolerated (and can be treated gradually).
- For patients with hypokalemia plus hypomagnesemia, a reasonable strategy is often to treat the hypomagnesemia fairly aggressively (because this is safe), but to be a bit more conservative with treatment of hypokalemia.
  - 🍎 For patients with hypokalemia and hypomagnesemia, rapid correction of hypomagnesemia is safe and may quickly decrease the risk of arrhythmia.

target potassium level?

most patients: target > 3.5 mM?

- Targeting a potassium level > 3.5 mM seems reasonable for most patients.
- Cardiac patients
  - Traditionally, the target has been > 4 mM in efforts to reduce the risk of arrhythmia.
  - Larger, modern studies have shown that the safest potassium range in patients with myocardial infarction may be 3.5-4.5 mM (22235086, 26714972, 24560065). Either higher or lower potassium values correlate with worse outcomes (figure below).
  - This is admittedly correlational data, but it's the best data that we have.
  - An evidence-based potassium target for cardiac patients would therefore seem to be > 3.5 mM.
renal failure: target >3 mM?

- It's usually best to be conservative in the absence of any specific factors which increase the risk of arrhythmia (see "risk stratification" above). In renal failure, the primary concern is generally development of hyperkalemia (rather than hypokalemia). For patients with acute or worsening renal failure, potassium is likely to rise over time.
- A target potassium of >3 mM may be reasonable in most patients with severe renal failure. This is particularly true in oliguric renal failure, wherein there is little risk that the patient will suddenly develop worsening hypokalemia.

diabetic ketoacidosis: target >5.3 mM?

- Patients being resuscitated from DKA will generally tend to drop their potassium levels over time.
- In the absence of renal dysfunction, it's often useful to target a high-normal potassium level (e.g. >5 mM).

enteral route generally preferred

reasons that enteral potassium is preferred

- (1) Cheaper and generally easier.
- (2) Doesn't irritate veins.
- (3) Safer (oral potassium is overall more idiot-proof than IV potassium).

formulations of oral potassium

- Potassium chloride (KCl)
  - Most commonly used formulation.
  - Especially useful in patients with metabolic alkalosis (it will increase the serum chloride level).
  - Slow-release microencapsulated (wax-matrix) KCl formulations are suboptimal if an immediate effect is desired. However, they may be better tolerated with less emesis (31227226 (https://www.ncbi.nlm.nih.gov/pubmed/31227226)).
- Potassium citrate
  - May be useful in patients with nonanion-gap metabolic acidosis (NAGMA). The citrate will be converted into bicarbonate, thereby improving the acidosis.

dose & schedule
- This involves clinical judgement based on consideration of two factors: total body potassium deficit and renal function.
- If the renal function is adequate and stable (e.g. GFR > 30 ml/min and the patient is not oliguric), then it's unlikely that oral potassium will cause hyperkalemia. In this scenario, oral doses of potassium may be scheduled and the potassium level can be checked intermittently.
  - For example: In a patient with normal renal function and K = 3 mM (estimated deficiency of ~100-200 mEq), a dose of 40 mEq KCl could be given q8hr with daily measurement of electrolytes.
  - For patients with oliguria or renal insufficiency, closer monitoring is required to avoid overshoot hyperkalemia.

### intravenous potassium

#### indications for IV potassium

- (1) Lack of gut access or function.
- (2) Severe hypokalemia in need of emergent treatment (see "risk stratification" above).
- (3) Profound shock plus severe hypokalemia (unclear whether potassium would be adequately absorbed from the gut).

#### typical rates of IV potassium administration

- 10 mEq/hour
  - Commonly used rate for routine potassium repletion.
- 20 mEq/hr
  - Commonly used for severe hypokalemia or DKA.
    - Ideally, this shouldn't be run through a single peripheral IV line (to prevent vein sclerosis). This can be run either through a central line, or split into two 10 mEq/hr infusions through two different peripheral lines.
  - The frequency of monitoring electrolytes depends on clinical acuity and renal function (similar to the monitoring of oral repletion above).

#### high-dose IV potassium administration

- Using high-dose IV potassium is rarely necessary. However, this might be preferable to the combination of simultaneously given intravenous and enteral potassium (which can lead to erratic pharmacology in critically ill patients, if the enteral potassium is absorbed in a delayed fashion).
- Possible regimens are listed below (none of which are supported by high-level evidence). A useful concept is that potassium levels should be repeated after every ~60 mEq of potassium administered (22901631). If potassium is given more rapidly, then it must be monitored more frequently.
  - (1) Cardiac arrest due to hypokalemia (e.g. VT, VF, or asystole)
    - Start with 20 mEq potassium IV over 2-3 minutes (16600469).
  - (2) Recurrent malignant arrhythmias with a pulse
    - Start with 20 mEq potassium IV over 10-20 minutes (infusion rate of 60-120 mEq/hr) (16600469).
    - Down-titrate the rate rapidly as the EKG improves and the patient stabilizes.
  - (3) Severe hypokalemia plus (DKA or overdose of beta-blocker/calcium channel blocker)
    - Hypokalemia itself isn't immediately life-threatening here, but hypokalemia impedes the ability to provide insulin (which is needed for the treatment of DKA or for high-dose insulin therapy for poisoning).
    - Infusion of potassium at a rate of 40-60 mEq/hr could be reasonable if the patient is extremely unstable (with the judgement that the inability to provide insulin is a life-threatening problem).
    - Check potassium level very frequently (e.g. q40 minutes to q60 minutes) with a point-of-care monitor to allow for real-time titration of potassium at the bedside. Don't give more than ~60 mEq potassium without repeating the level.

### magnesium repletion

- Magnesium depletion is very common in patients with hypokalemia.

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https://emcrit.org/ibcc/hypokalemia/
• Failure to treat the magnesium deficiency will make it difficult or impossible to fix the hypokalemia (hypomagnesemia causes renal potassium-wasting, so the patient will keep on spilling potassium until their magnesium level is repleted).

• Magnesium repletion is also useful because it will reduce the risk of Torsade de pointes in these patients.
  • Magnesium can be repleted rapidly (faster than potassium). This may be the fastest approach to decrease the patient’s risk of arrhythmia.

• Hypomagnesemia is discussed further in this chapter (https://emcrit.org/ibcc/hypomagnesemia/).

other measures

gastric losses

• For patients with ongoing gastric fluid loss, initiation of a proton pump inhibitor may minimize electrolyte derangements being caused by this. (The main driver of hypokalemia due to gastric fluid loss is the metabolic alkalosis, so avoiding loss of gastric acid will prevent this.)

potassium-sparing diuretics

• These may be useful for patients with severe volume overload who require ongoing diuresis.
  • Spironolactone may be useful (e.g. 50-100 mg BID), but it takes awhile for it to take effect.
  • Amiloride or triamterene have the advantage of working more rapidly.

checklist

podcast

https://emcrit.org/ibcc/hypokalemia/
The Podcast Episode

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questions & discussion

To keep this page small and fast, questions & discussion about this post can be found on another page here.

- Failure to check and replete magnesium levels.
- Excessive use of intravenous potassium repletion, when enteral potassium would be a safer and easier strategy.
- Aggressive repletion of mild hypokalemia in patients with renal failure (hyperkalemia is generally much more dangerous than hypokalemia, so better to err on the low side).

Going further:
- Hypokalemia (CORE EM, Anand Swaminathan)
- Hypokalemia (Chris Nickson, LITFL)
- Hypokalemia (WikEM)

The Internet Book of Critical Care is an online textbook written by Josh Farkas (@PulmCrit), an associate professor of Pulmonary and Critical Care Medicine at the University of Vermont.