CRYSTALLOD SOLUTIONS

- Used to increase the intravascular space
- Isotonic crystalloids stay in the extracellular compartment and distribute between the interstitial and intravascular compartments— for every one liter of NS, 250 ml remain in the intravascular compartment
Normal saline-induced hyperchloremic metabolic acidosis

- When you give your patient NS (hyperchloremic solution) you are increasing the chloride significantly and it is the chloride anion that is causing the acidosis.
- When you give NaCl it combines with water:
  \[ \text{NaCl} + \text{H}_2\text{O} \rightarrow \text{HCl} + \text{NaOH}. \]
- The strong acid (HCl) and the strong base (NaOH) should cancel each other out with no effect on pH.
- HOWEVER because the normal concentrations of Na and Cl in the serum are 140 and 100 respectively, adding saline (154 meq Na and 154 meq Cl) cause the chloride to increase more than the sodium.
- This increase in chloride tips the acid-base balance toward HCl thus causing a non anion gap metabolic acidosis.

---

SMART (Isotonic Solutions and Major Adverse Renal Events) Trial

- Randomized multiple-crossover trial in 5 ICU at an academic center
- Assigned 15,802 adults to either normal saline or balanced crystalloids (lactated ringer’s solution or plasma-lyte A).
- Primary outcomes – major adverse kidney event within 30 days, a composite of death from any cause, new renal replacement therapy, or persistence of renal dysfunction which were all censored at hospital discharge or 30 days, whichever occurred first.
- 7942 pt in the balanced crystalloids group, 1139 (14.3%) had a major adverse kidney event as compared with 1211 of 7860 patients (15.4%) in the saline group (marginal odds ratio, 0.91; 95% confidence interval; p= 0.04).
- In hospital mortality at 30 days was 10.3% in the balanced crystalloids and 11.1% in the saline group (p = 0.006).
- Incidence of new RRT was 2.5% and 2.9% respectively (p = 0.08)
- Incidence of persistent renal dysfunction was 6.4% and 6.6% (p = 0.6)

CONCLUSIONS:
Among critically ill adults, the use of balanced crystalloids for intravenous fluid administration resulted in lower rates of the composite outcome of death for any cause, new RRT, or persistent renal dysfunction than use of saline.

SMART-EM trial

- Single-center, pragmatic, multiple-crossover trial comparing balanced crystalloids (lactated Ringer’s solution or Plasma-Lyte A) with saline among adults in the emergency department and were subsequently hospitalized outside an ICU. The type of crystalloid administered in the emergency department was assigned to each patient on the basis of calendar month, with the entire emergency department crossing over between balanced crystalloids and saline monthly during the 16-month trial.
- The primary outcome was hospital-free days (days alive after discharge before day 28). Secondary outcomes included major adverse kidney events within 30 days—a composite of death from any cause, new renal replacement therapy, or persistent renal dysfunction—all censored at hospital discharge or 30 days, whichever occurred first.
- A total of 13,347 patients were enrolled. Median crystalloid volume administered in the emergency department of 1079 ml and 88.3% of the patients exclusively receiving the assigned crystalloid.
- A total of 13,347 patients were enrolled. Median crystalloid volume administered in the emergency department of 1079 ml and 88.3% of the patients exclusively receiving the assigned crystalloid.
- The number of hospital-free days did not differ between the balanced crystalloids and saline groups (median, 25 days in each group; adjusted odds ratio with balanced crystalloids, 0.98; 95% confidence interval; P=0.41).
- Balanced crystalloids resulted in a lower incidence of major adverse kidney events within 30 days than saline (4.7% vs. 5.6%; adjusted odds ratio, 0.82; 95% CI: 0.64-1.05).

CONCLUSIONS:
Among noncritically ill adults treated with intravenous fluids in the emergency department, there was no difference in hospital-free days between treatment with balanced crystalloids and treatment with saline.
So, does the type of fluid matter?

- The main concern with isotonic saline is felt to be related to the high Chloride concentration relative to the plasma Chloride concentration. The excessive Chloride concentration:
  - May decrease renal perfusion by causing renal vasoconstriction and reductions in renal blood flow and thus leading to acute kidney injury.
  - It also causes a dilutional non-anion-gap metabolic acidosis and may also cause inflammation, hypertension, all of which have the potential to increase mortality.

- What is the relative precautions of balanced crystalloids?
  - The relative hypotonicity of the balanced crystalloids (276 mOsm) may increase intracranial pressure so need to be cautious when treating traumatic brain injury and in patients who are hyperkalemic, hypercalcemic, liver failure.

- Recent data suggest that the use of balanced solutions was associated with a lower rate of major adverse renal events and death in hypovolemic patients as compared with isotonic saline. This difference, while meager, may still warrant its use since the cost difference between the two solutions is minimal. The effects on morbidity and mortality may be more important in septic patients in which the use of large volume resuscitation is often required.

- The case for balanced crystalloids is growing BUT....

DYSNATREMIAS – hyponatremia and hypernatremia

**HYPONATREMIA**

- Low serum sodium < 136 mEq
  - Increased free water retention
  - Urinary sodium loss

- Signs and symptoms:
  - Neurologic – nausea, vomiting, weakness, confusion, forgetfulness, disorientation, obtundation, noncardiogenic pulmonary edema, headache, falls, seizure, coma, decorticate posturing, dysgeusia
ADH release

- Physiologic release:
  - Increased serum osm where the increased ADH leads to retention of free water to "hydrate" the patient thereby producing a CONCENTRATED urine
  - Decreased BP/perfusion where the increased ADH leads to preservation of the intravascular volume and some degree of vasoconstriction

- NON-physiologic release:
  - Increased hypothalamic production of ADH:
    - Neurotrophic factors
    - Infections like meningitis, encephalitis
    - Traumatic brain injury
  - Drugs
    - Lung disease
      - PNA
      - TB
      - Lung abscess, empyema
  - Ectopic (non-hypothalamic) production of ADH:
    - CA like small cell, bronchogenic
    - Hodgkin's, leukemia
    - Pulmonary TB
  - Exogenous administration of ADH:
    - Vasopressin, desmopressin
    - Others
Evaluation of hyponatremia

- Step 1: Is renal failure present? What is the serum osm, urine osm, urine sodium.

- Step 2: Are there signs of ECFV depletion?
  - History of nausea, vomiting or other source of depletion with water ingestion. Is the urine sodium low (<20)?

- Step 3: Are there signs of ECFV overload?
  - Careful history and physical: signs of CHF with increased JVP, rales, effusions, ascites, S3, edema
  - Cirrhosis with edema and ascites
  - Nephrotic syndrome: check urine protein
  - Is urine sodium low? Due to decreased effective circulating volume leading to increased sodium retention by the kidney

- Step 4: Is the patient taking thiazide diuretics?

- Step 5: Is there a condition or drug capable of producing SIADH?

- Step 6: Is there evidence of thyroid or adrenal insufficiency?

- Step 7: Elderly/poor solute intake?
  - Leads to lower medullary solute concentration gradient and less ability to concentrate the urine.
  - 24 hr total solute excretion < 600 mOsm/24 hr
DIAGNOSIS SIADH

**Essential features:**
- Decreased effective osmolality (<275 mOsm/kg of water)
- Urine osmolality > 100 mOsm/kg of water during hypotonicity

**Clinical manifestations:**
- No clinical signs of volume depletion of extracellular fluid
- No anasarca, kaliopenia, decreased urine volume, or dry mucous membranes
- No clinical signs of excessive volume of extracellular fluid

**Other features:**
- No edema or ascites
- Urinary sodium > 40 mmol/liter with normal dietary salt intake
- Normal thirst and adrenal function

**Supplemental features:**
- Plasma osmol gap > 4 mg/dl
- Blood urea nitrogen > 10 mg/dl
- Fractional sodium excretion > 3%, fractional urea excretion > 5%
- Failure to correct hypotension despite 20-40% or >40% rehydration
- Connection of hypotension through fluid restriction

**Elevated plasma AVP levels:** Despite the presence of hypotonicity and clinical manifestations.

**Table 1 Causes of the syndrome of inappropriate antidiuretic hormone secretion**

<table>
<thead>
<tr>
<th>Cause of Deserved Antidiuretic Hormone Secretion</th>
<th>Diagnoses of the Central Nervous System</th>
<th>Drugs</th>
<th>Other Causes</th>
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<tbody>
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</table>
Severe hyponatremia (serum sodium <125 mmol/L)

Duration of illness:
- Acute (<48 hours)
- Chronic (>48 hours)

Hyperosmolar:
- Diagnostic evaluation
- Fluid restriction
- Oral Na supplementation
- High protein diet

Symptomatic:
- Diagnostic evaluation
- Fluid restriction
- Saline infusion + Furosemide
- Consider vasopressin receptor antagonists

Immediate correction:
- 3% saline at 1-2 ml/kg/hr OR 100 ml 3% saline bolus over 10-15 min and can repeat if needed (2-3 more times)
- +/- DDAVP
- +/- Furosemide 20 mg IV

Aim for 1-2 mmol/L/hr correction until symptoms improve (max 4-6 over 24 hours) KEEP correction ≤8 meq over 24 h and about 8 meq over the next 24 hours

Monitor serum sodium q2h and adjust the infusion rate as needed.

WATCH URINE OUTPUT

Duration >48 hours (chronic)

Asymptomatic:
- Diagnostic evaluation
- Fluid restriction
- Salt supplementation (avoid in hypervolemia)
- High protein diet

Symptomatic:
- Begin diagnostic evaluation
- Fluid restriction
- Saline infusion + Furosemide
- Consider vasopressin receptor antagonists
- 3% saline (50 ml)

Aim for 0.5-1 mmol/L/hr, maximum correction 4-6 mmol/L/day. No more than 8 total over 24 h. Then 6 over the next 24 h +/− DDAVP

** UREA
- Monitor lab and urine output

Treatment of symptomatic non-emergent hypoxonatremia

- Calculate the amount of sodium needed to bring the serum sodium up by only 4 to 6 mEq/liter in a 24 h period (usually enough to reverse symptoms without over shoot):
  - Na deficit: 0.6 x wt (in kg) (desired sNa – present sNa)
  - Example: a 60 kg woman (use 0.5 instead of 0.6) with a serum sodium of 110 and lethargy and no evidence of volume depletion or CHF; want to correct no more than 6 mEq/l in first 24 hr. Correction to 116.
    - 0.5 x 60 x (116 – 110) = 180 mEq
    - 1 liter of 3% saline contains 513 mEq salt; therefore 350 ml of 3% saline over next 24 hr. Order would read 3% saline at 15 ml/hr for 24 hr with frequent repeat serum sodium levels

** patients with volume depletion will correct with normal saline as soon as volume stimulation of ADH is shut off

** Patients with active CHF and severe symptomatic hyponatremia are better treated with AVP antagonists
Hyponatremia correction equations:

<table>
<thead>
<tr>
<th>Source</th>
<th>Step 1</th>
<th>Step 2</th>
<th>Example of use (mEq/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditions³</td>
<td>No required - 1 LBS x (Na⁺ - Na⁺)</td>
<td>No required - 1 LBS</td>
<td>21</td>
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<tr>
<td>Arginine and Lysine⁴</td>
<td>ρNa x (Na⁺ - Na⁺)</td>
<td>Volume (mL) x 1 LBS</td>
<td>187</td>
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<tr>
<td>Serum and Lysine⁴</td>
<td>ρNa x (Na⁺ - Na⁺)</td>
<td>Volume (mL) x 1 LBS</td>
<td>187</td>
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<tr>
<td>Hyponatremia and Nutritional</td>
<td>ρNa x (Na⁺ - Na⁺)</td>
<td>Volume (mL) x 1 LBS</td>
<td>70</td>
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<tr>
<td>Jones and Donald</td>
<td>ρNa x (Na⁺ - Na⁺) / 12 H x 50 LBS</td>
<td>Weight (lbs) / 20</td>
<td>70</td>
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Why DDAVP????

Usual approach to hypovolemic hyponatremia: Timid initial therapy followed by endogenous over-correction

Reactive DDAVP strategy

Proactive DDAVP strategy in asymptomatic hyponatremia
PROACTIVE or responsive DDAVP?

- Patients with reversible cause of hyponatremia who are likely to develop a water diuresis
- Pt at risk for osmotic demyelination:
  - Very low serum sodium at the start (≤105 mmol/L)
  - Concomitant hypokalemia
  - Cirrhosis
  - Malnutrition
  - Advanced liver disease
- DDAVP (with the 3% at 15-30 ml/hour) 1-2 mcg of desmopressin (DDAVP) IV or SQ every 6-8 hours — “DDAVP clamp” it prevents the body from autocorrecting the sodium and allows for a well-regulated, slow rise in sodium. Also need to restrict free water intake

Who should not get DDAVP?

- If the cause of hypotnatremia is UNLIKELY to be rapidly reversible (those who are unlikely to develop a water diuresis) such as:
  - Edematous pt (Heart failure or cirrhosis). Desmopressin (DDAVP) may increase the amount of hypertonic saline required to achieve the desired increase in serum sodium concentration and the likelihood of overly rapid correction is low in these patients. In such patients, it may be better to give Furosemide with the hypertonic saline to prevent hypervolemia.
- In patients with recurrent hyponatremia that is caused by a chronic SIADH secretion.

When treating severe hyponatremia don't forget!!!
Appropriate uses for VAPTANS

- Hyponatremia from syndrome of inappropriate antidiuretic hormone secretion
- Malignancy, especially small cell lung cancers
- Cirrhosis
- Pulmonary disorders
- Medications, when chronic use is required
- Nausea or pain, when chronic and intractable
- Idiopathic
- Hyponatremia from heart failure
- Non-severe hyponatremia
- Hyponatremia that is not amenable to correction with fluid restriction or other therapies
HYPERNATREMIA

Hypernatremia

- Reason for water loss or sodium gain:
  - Increased insensible losses (fever, tachypnea); sweat losses; diarrhea; renal water loss (>3L/24hr); administration of hypertonic sodium
  - Reason for inadequate water intake:
  - Impaired thirst; altered mental status; primary neurological disorder (stroke, infection, tumor); no access to water
  - Is polyuria present:
    - Urine Osm >300 mOsm/L (osmotic diuresis): urea, glucose, mannitol, saline
    - Urine Osm <150 mOsm/L (diabetes insipidus):
      - Response to vasopressin:
        - No response: nephrogenic DI
        - Urine Osm increases to >300 mOsm/L: central DI

Hypernatremia: treatment

- If volume depleted/ hypotensive, begin correction with isotonic saline
- Aim to correct the sodium by about 0.5 to 1 mEq/L/hr
- Slowly correct over 36 to 72 hrs to avoid cerebral edema
- Calculate the water deficit:
  - TBW x (measured Na – desired Na)/ desired Na
  - Example: a 70kg man has a serum sodium of 170 and you desire to correct to 160 over the next 12 hrs:
    - deficit= 0.6 x 70 x (170-160)/160 = 2.6L
    - Add to this any ongoing insensible (0.5 to 1L/day depending on fever) or urinary or GI losses.
DEXTROSE and WATER SOLUTIONS

- D5 W will deliver water according to the natural distribution of body water
- If it is D5 normal saline it will distribute according to normal saline
- 2/3 of the fluid moves intracellularly
- 8% (or 80 ml of every 1000 ml) remains in the intravascular space

POTASSIUM – hyperkalemia and hypokalemia

- Total content 3500 mmol
- 98% INTRACELLULAR
- 2% in the extracellular compartment
- Average diet contain about 100 mmol potassium
- 90-95% is renal excreted

POTASSIUM HOMEOSTASIS

- Total content 3500 mmol
- 98% INTRACELLULAR
- 2% in the extracellular compartment
- Average diet contain about 100 mmol potassium
- 90-95% is renal excreted
Determinants of CCD K+ Secretion

- Mineralocorticoid activity
- Distal delivery of Na+
- Luminal flow rate

Mineralocorticoid activity

Distal sodium delivery
HYPERKALEMIA

• Exact incidence and prevalence of hyperkalemia is unknown.
  - 5-10% of hospitalized patients.
  - Up to 11% of patients on ACE inhibitors at VA.
  - As high as 40-50% in CKD patients.
  - 3-24% in heart failure patients.

• The most common predisposing factor is CKD. Other co-morbid conditions:
  - Heart failure
  - DM2
  - Advanced age
  - Use of RAAS inhibitors.

Exact incidence and prevalence of hyperkalemia is unknown:
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The most common predisposing factor is CKD. Other co-morbid conditions:
- Heart failure
- DM2
- Advanced age
- Use of RAAS inhibitors.
Causes of hyperkalemia

- Pseudohyperkalemia
- Excess intake
- Cell shifts
- Impaired renal excretion

Pseudohyperkalemia

- Hemolysis during venipuncture
- Excessive blood sample clotting
- Hemolytic spherocytosis
- Increased WBC and platelet count
- Familial hyperkalemia

- Suspect by history OR can find a lower potassium concentration in plasma versus serum:
  - Serum is made up of non-clotting proteins, glucose, nutrients, electrolytes, hormones, antigens, antibodies and other particles.
  - Plasma components are same as that of serum, except for fibrinogens and clotting factors that are absent in serum.
  - Serum = plasma after removal of clotting factors.

  Potassium is released from leukocytes and platelets when a blood sample is allowed to clot in vitro... Usually the serum potassium is about 0.1-0.4 meq/L less than measured in the plasma, in which the clotting is prevented by drawing the blood into a heparinized tube...

CELL SHIFTS

- Cell injury
  - Rhabdomyolysis
  - Tumor lysis
  - Massive hemolysis
  - Ischemia

- Toxins/Drugs:
  - Digoxin
  - Succinylcholine

- DKA and NKHS
Impaired renal excretion

- Primary decrease in mineralocorticoid activity:
  - NSAIDS
  - Beta blockers
  - Cyclosporine and tacrolimus
  - Ace inhibitors and ARBs
  - Ketoconazole
  - Spironolactone
- Primary decrease in distal sodium delivery:
  - Oliguric AKI
  - Acute GN
- Abnormal cortical collecting duct:
  - Drugs
  - Tubulointerstitial nephritis
  - Urinary obstruction

WHY is hyperkalemia important?

Manifestations of hyperkalemia

- Ascending muscle weakness
- Flaccid Paralysis
- Cardiac conduction abnormalities:
  - Normal
  - Right and left BBB
  - Bifascicular block
  - Advanced AV block
- Cardiac arrhythmias:
  - Sinus bradycardia
  - Sinus arrest
  - Slow idioventricular rhythm
  - Ventricular tachycardia and fibrillation
  - Asystole
- EKG changes
**Renal Metabolic Disorders**
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**EKG Changes**
- Peak T waves are the initial finding
- Shortened Q-T interval
- Widened QRS
- Arrhythmia

K⁺: 5.0 mEq/L, K⁺: 6.5 mEq/L, K⁺: 7.0 mEq/L, K⁺: 8.0 mEq/L

**Diabetes**
- Begins in 10-20 min
- Peaks in 30-60 min
- Lasts 4-6 hours
- Average decrease in potassium: 0.5-1.2 mEq/L
- Effect within minutes
- Lasts 30-60 min
- Watch with digoxin toxic!!

**Contraindicated in IV infiltrate**
- Can cause skin necrosis!

**Decrease within minutes**
- Peaks within 90 min
- Lasts 4-6 hours
- Lowers potassium by 0.5-1.5 mEq/L
- 1/3 pt will not respond!!!

**Kayexylate**
- 15-30 gms PO
- Starts about 2 hours
- Peaks within 4-6 hr
- In 24 hr, may decrease by 0.4-1 mEq/L
- Bowel necrosis!!

**Approximately 1.5 meq/l per hour of dialysis**

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However

- 60% of patients with serum potassium of >6 meq/L did not have any EKG changes!!
- V fib occasionally may occur WITHOUT antecedent peaked T-waves or QRS prolongation
- Rare case reports of patients with normal EKG with K >9!!

So……

- If there are EKG changes emergent therapy should be initiated.
- Should also consider emergent therapy with potassium >6.5 mEq/L even in the ABSENCE of EKG changes because of the significant risk of rapid development of such changes
- CLOSE monitoring key!!!

Kayexalate (sodium polystyrene sulfonate)

- Is a cation-exchange resin that was approved in 1958 as a treatment for hyperkalemia
- Kayexalate, Kionex, SPS
- Works by exchanging sodium for potassium in the colon and thus excreting potassium from the body.
- Usual dose:
  - Oral: 15 g 1 to 4 times daily.
  - Rectal: 30 to 50 g every 6 hours
**What is the evidence for Kayexalate (sodium polystyrene)?**

  - Population: 10 patients with severe oliguria
  - Intervention: Sorbitol + a cation exchange resin (+ a low potassium diet)
  - Control: Sorbitol alone (+ a no potassium diet)
  - Findings: Serum potassium levels were reduced by about 1 mEq/L in all 10 patients. The serum potassium levels in the control group did not change.

  - Population: 32 patients with acute or chronic renal failure.
  - Intervention: Oral (or rectal) cation exchange resin and a low potassium diet
  - Control: None
  - Findings: Scherr and colleagues found a decrease in serum potassium by 1.0 mEq/L on average.

  - Population: 6 patients with renal failure
  - Intervention: Single dose of a cation exchange resin + sorbitol
  - Control: None
  - Findings: The authors found no difference in serum potassium levels at 12 hours.

- Cochrane Review (Mahoney 2005) that states that potassium-absorbing resins have never been found to be effective in the first hours of treatment.

**Kayexalate (sodium polystyrene) complications**

- Complications: COLONIC NECROSIS
  - FDA added a warning back in 2011 cautioning against the use of the drug for this reason.

- SO What now?

**Veltassa (Patiromer)**

- Indication:
  - Treatment of Hyperkalemia.
  - NOT to be used as EMERGENCY treatment for life threatening hyperkalemia given its delayed onset of action

- May bind to many orally administered medications and should be separated from other meds 6 hours pre and 6 hours post
Veltassa (Patiromer) – warnings and precautions

- **Worsening of gastrointestinal motility**
  - Avoid use of veltassa in patients with severe constipation, bowel obstruction or impaction including abnormal post-operative bowel motility disorders
  - It may be ineffective and may worsen gastrointestinal conditions
- **Hypomagnesemia**
  - Veltassa binds to magnesium in the colon, which can lead to hypomagnesemia.
  - It was reported as an adverse reaction in 5.3%
  - Monitor serum magnesium
- **Mild to moderate hypersensitivity reaction** reported in 0.3% and included edema of the lips.
- **Can bind to other oral medications**
Causes of hypokalemia

- Pseudohypokalemia:
  - Uptake by metabolically active cells as in AML
- Cell shifts:
  - Alkalosis effect is small
  - Increased ß-adrenergic activity
  - Increased ß-adrenergic activity
  - Stress-related release of epinephrine
  - Increased ß-adrenergic activity
  - Hypertension, diabetes, calcitonin, alcohol
  - Treatment for pernicious anemia
  - TPN
  - Rapidly growing leukemias and lymphomas
  - Hypothermia
  - Barium and chloroquine intoxication
- Insufficient intake:
  - Unusual as the only cause of hypokalemia
  - Kidney can decrease the potassium excretion to 5-15 meq/day
- GI losses
- Renal losses

Hypokalemia – GI losses

- Urine potassium is < 20 meq/L a day
- Diarrhea is the most common cause
  - Can lose 30-50 meq/l in GI secretions
- Vomiting
  - Can lose 5-10 meq/L in vomitus
  - SO…. Most of the hypokalemia you see is ultimately RENAL loss

Hypokalemia – Renal losses

- Urinary potassium > 20 meq/day
- No history of diarrhea
- Examples:
  - Liddle’s
  - Bartter’s
  - Gitelman’s
  - Primary hyperaldosteronism (Conn syndrome)
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TREATMENT
- estimate of the amount of potassium you will need:
  - \((4 - \text{current K}) \times 100\)
  - example: potassium of 3.2
    - \((4 - 3.2) \times 100 = 80\) meq

Treatment of Hypokalemia
- Address underlying cause
- Chronic treatment
  - \(\text{IV} \) (slow or slow K)
  - Acute treatment
    - \((IV \text{KCl}) 40-80\) mEq/L at rate \(<20\) mEq/hr
  - If hypokalemia is accompanied by acidoses, treat hypokalemia before correction of acidoses

ANION GAP DIFFERENTIAL
- M ethanol
- U remia
- D KA
- P araldhyde
- I ron, isoniazid
- L actic Acid
- E thylene glycol
- S alcylates

- C yanide
- I oniazid, iron
- T oluene
- E thanol
- G lycols (ethylene, propylene)
- O xoproline (ich acetaminophen use)
- L lacate
- D lacate (short bowel syndrome)
- M ethanol
- A sa
- R enal failure
- K etotic acidosis (starvation, diabetic)
THE END