Electrolyte Disorders

Mark Malesker, Pharm.D., FCCP, FCCP, FASHP, BCPS
Professor of Pharmacy Practice and Medicine
Creighton University
Learning Objectives

- Define/describe each of the following electrolyte disorders

  - Hyponatremia
  - Hypernatremia
  - Hypokalemia
  - Hyperkalemia
  - Hypocalcemia
  - Hypercalcemia
  - Hypophosphatemia
  - Hyperphosphatemia
  - Hypomagnesemia
  - Hypermagnesemia
For the electrolyte disorders listed above

- List common etiologies of each disorder
- List common medications that may predispose a patient to each disorder
- List common and/or severe signs/symptoms associated with each disorder
- Outline a rational treatment regimen for each disorder, including total doses, maximum rates of replacement, and recommended order of use of each treatment strategy
Recommended Reading

- **Pharmacotherapy 9E**
  - Chapter 34, *Disorders of Sodium and Water Hemostasis*
  - Chapter 35, *Disorders of Calcium and Phosphorous*
  - Chapter 36, *Disorder of Potassium and Magnesium*

- **Additional reading**
  - *Disorders of Fluid and Electrolyte Balance* in Porth’s *Pathophysiology, 9E*, chapter 39, p 1019-1061
Electrolytes

- Electrolyte Distribution
- Total number of anions = total number of cations in each fluid compartment
- Critical that cell membranes keep the ICF and ECF separate and biochemically distinct
- Serum concentrations reflect total body stores of ECF electrolytes rather than that of ICF electrolytes
- Concentrated electrolytes should not be stored in patient care areas (potassium chloride, hypertonic saline, magnesium, calcium)
<table>
<thead>
<tr>
<th></th>
<th>ECF</th>
<th>ICF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ion Species</td>
<td>Ion Species</td>
</tr>
<tr>
<td></td>
<td>Plasma (mEq/L)</td>
<td>Interstitial Fluid (mEq/L)</td>
</tr>
<tr>
<td></td>
<td>Cations</td>
<td>Cations</td>
</tr>
<tr>
<td>Na</td>
<td>142</td>
<td>144</td>
</tr>
<tr>
<td>K</td>
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<td>4</td>
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<tr>
<td>Ca</td>
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<td>3</td>
<td>1.5</td>
</tr>
<tr>
<td>Total</td>
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<tr>
<td></td>
<td>Anions</td>
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<tr>
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<td>2</td>
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<tr>
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<td>0</td>
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<tr>
<td>Total</td>
<td>154</td>
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</table>
# Serum Electrolyte Normal Values

<table>
<thead>
<tr>
<th>Electrolyte</th>
<th>Normal Range</th>
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<tbody>
<tr>
<td>Sodium</td>
<td>135 – 145 mEq/L</td>
</tr>
<tr>
<td>Potassium</td>
<td>3.5 – 5.0 mEq/L</td>
</tr>
<tr>
<td>Chloride</td>
<td>98 – 106 mEq/L</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>21 – 30 mEq/L</td>
</tr>
<tr>
<td>Magnesium</td>
<td>1.5 – 1.9 mEq/L</td>
</tr>
<tr>
<td>Calcium Total</td>
<td>4.4 – 5.2 mEq/L (9 – 10.5 mg/dl)</td>
</tr>
<tr>
<td>Ionized</td>
<td>2.2 – 2.8 mEq/L (4.5 – 5.6 mg/dl)</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>1.0 – 1.4 mmol/L (3 – 4.5 mg/dl)</td>
</tr>
</tbody>
</table>
Daily Requirements for Electrolytes

- Sodium: 1-2 mEq/kg/d
- Potassium: 0.5-1 mEq/kg/d
- Calcium: 800 - 1200 mg/d
- Magnesium: 300 - 400 mg/d
- Phosphorus: 800 - 1200 mg/d
Charting Labs

\[
\begin{array}{c|c|c}
\text{Na} & \text{Cl} & \text{Bun} \\
\text{K} & \text{HCO}_3^- & \text{Cr} \\
\end{array}
\]

\[
\begin{array}{c|c|c}
\text{Na} & \text{Cl} & \text{Bun} \\
\text{K} & \text{HCO}_3^- & \text{Cr} \\
\end{array}
\]

\[
\text{Gluc}
\]

\[
\text{Ca}
\]

\[
\text{pH} / \text{PCO}_2 / \text{PO}_2
\]
**Electrolytes**

- **Extracellular**
  - Na – helps nerve cells and muscle cells interact
  - Cl – maintains osmotic pressure, helps gastric mucosal cells produce HCl

- **Intracellular**
  - K – cell excitability, nerve impulse conduction, resting membrane potential, intracellular osmolality
  - PO$_4$ – energy metabolism
  - Mg – enzyme reactions, neuromuscular contractions, protein synthesis, NA and K ion transport
Osmolality

- Measure of the number of osmotically-active particles per unit of solution; independent of the weight or nature of the particle
- Equimolar concentrations of all substances in the undissociated state exert the same osmotic pressure
- The plasma osmolality is determined by the ratio of plasma solutes (sodium salts) and plasma water
  - Plasma [sodium] is maintained with narrow limits by appropriate variations in water intake and excretion resulting from changes in ADH and sensation of thirst
Calculated Osmolality

- The plasma osmolality (280-300 mOsm/kg) can be calculated as follows

\[2[Na^+] + [\text{Glucose}]/18 + [\text{BUN}]/2.8\]

- Body regulates water to maintain plasma osmolality
  - TBW depletion → increase in serum osmolality
  - TBW excess → decrease in serum osmolality
Osmolality Clinical Uses

- Helps determine deviations in TBW content
  - ↑ in osmolality = loss of water > solute (dehydration)
  - ↓ in osmolality = retention of water > solute (CHF, cirrhosis)
- Osmolar gap = measured serum osmolality > calculated serum osmolality by 10 or more
  - Ethanol
  - Methanol (wood denatured alcohol)
  - Ethylene glycol (antifreeze)
  - Isopropanol (isopropyl alcohol)
  - Lorazepam (Ativan)
  - Mannitol
Osmolality Case

Your ICU patient’s laboratory results include sodium 125 mEq/L, potassium 3.2 mEq/L, chloride 90 mEq/L, bicarbonate 22 mEq/L, BUN 2 mg/dL, Cr 1.2 mg/dL, and glucose 194 mg/dL.

The measured osmolality is 284 mOsm/L.

Calculate the osmolality for this patient?
Calculate the osmolar gap?
Sodium Disorders [135-145 mEq/L]

- **Physiology**
  - Sodium is the predominant cation of the ECF
  - Sodium is the primary electrolyte in establishing osmotic pressure relationships between the ICF and ECF
  - All body fluids are in osmotic equilibrium and changes in serum sodium concentration [Na] are associated with shifts of water in and out of body fluid compartments; thus, by adding sodium to the intravascular compartment we can cause fluid to enter this compartment from the interstitial fluid and, ultimately, from the ICF
Sodium Disorders

- A patient's [Na] should not be used as an index of sodium need because this parameter does not reflect total body sodium content; the [Na] primarily detects disturbances of TBW balance.

- Sodium imbalances, therefore, cannot be properly assessed without first assessing the body's fluid status.

- **Na disorders are water disorders**

- Normal maintenance sodium requirement is 1.0-1.5 mEq/kg/day (or ~ 80-120 mEq/day)
Hyponatremia Signs and Symptoms

- Usually exhibited at < 120 mEq/L
  - Irritability
  - Mental slowing
  - Headache
  - Unstable gait/falls
  - Confusion/delirium
  - Nausea/vomiting
  - Disorientation

- Usually exhibited at < 110 mEq/L
  - Stupor/coma
  - Seizures
  - Respiratory arrest
Hyponatremia: Incidence and Need to Treat

- Hyponatremia is a common electrolyte disorder occurring in 15-30% of hospitalized patients.
- Euvolemic hyponatremia, most often caused by SIADH, accounts for about 60% of all types of chronic hyponatremia.
- If not treated appropriately euvolemic hyponatremia may lead to significant morbidity and death.
Hypertonic Hyponatremia

- Usually associated with hyperglycemia; for every 60 mg/dL ↑ in serum glucose (above 200 mg/dL), [Na] is expected to ↓ by ~ 1 mEq/L
  - Osmotic shift of water from the ICF to the ECF which produces a dilutional ↓ in serum sodium
- Treat the hyperglycemia; as this is corrected, the [Na] will return to normal
Classification of Hyponatremia

- **Hypovolemic hyponatremia**
  - Patients usually have a deficit of both total body sodium and TBW, with the deficit of total body sodium > deficit of TBW

- **Euvolemic hyponatremia**
  - Patients usually have a slight excess of TBW and a relatively normal total body sodium content; in other words, an excess of "free water"

- **Hypervolemic hyponatremia**
  - Patients usually have an excess of both total body sodium and TBW, with the excess of TBW > excess of total body sodium
Diagnostic Algorithm for Hyponatremia

Assessment of volume status

Hypovolemia
- Total body water ↓
- Total body Na ↑

Euvolemia (no edema)
- Total body water ↑
- Total body Na± ↔

Hypervolemia
- Total body water ↑↑

Renal losses
- Diuretic excess
- Mineralocorticoid deficiency
- Salt-losing deficiency
- Bicarbonaturia with renal tubal acidosis and metabolic alkalosis
- Ketonuria
- Osmotic diuresis

U_{[Na^+]}>20 \text{ mEq/L}

Extrarenal losses
- Vomiting
- Diarrhea
- Third spacing of fluids
- Burns
- Pancreatitis
- Trauma

U_{[Na^+]} < 20 \text{ mEq/L}

Glucocorticoid deficiency
- Hypothyroidism
- Syndrome of inappropriate ADH secretion
- Drug-induced
- Stress

U_{[Na^+]} > 20 \text{ mEq/L}

Acute or chronic renal failure
- Nephrotic syndrome
- Cirrhosis
- Cardiac failure

U_{[Na^+]} < 20 \text{ mEq/L}

Legend: ↑ increase; ↑↑ greater increase; ↓ decrease; ↓↓ greater decrease; ↔ no change.

Hypovolemic Hyponatremia

- **Common causes**
  - Diuretic use (especially thiazides)
  - Sweat losses
  - GI losses (vomiting, diarrhea)
  - Hypoadrenalism (low cortisol, low aldosterone)
  - Renal tubular acidosis (leads to excess loss of sodium and water via the kidneys)
  - Third space losses (bowel obstruction, pancreatitis, burns)

- **Treatment**
  - Normal saline will begin to correct hyponatremia without developing signs of volume overload
Euvolemic Hyponatremia

- **Causes – Syndrome of Inappropriate ADH (SIADH)**
  - Carcinomas (especially lung and pancreas)
  - Pulmonary disorders (pneumonias, tuberculosis)
  - CNS disorders (meningitis, strokes, tumors, trauma)
  - Drugs
    - Chlorpropamide, carbamazepine, antineoplastic agents, barbiturates, morphine, antipsychotics, TCAs, SSRIs, NSAIDs, omeprazole, esomeprazole, nicotine

- **Treatment**
  - Fluid restriction (daily intake of 500 to 1000 mL)
  - Hypertonic saline
    - Consider if [Na] < 110 and/or severe symptoms (e.g. seizures)
  - Pharmacologic options
Causes of SIADH

**Pulmonary Disorders**
- Acute respiratory failure
- Infections
- Positive-pressure ventilation

**Tumors**
- Extrathoracic
- Mediastinal
- Pulmonary

**CNS Disorders**
- Acute psychosis
- Hemorrhage
- Inflammatory and demyelinating diseases
- Mass lesions
- Stroke
- Trauma

**Drugs**
- Carbamazepine
- Chlorpropamide
- Clofibrate
- Cyclophosphamide
- Desmopressin
- Nicotine
- Opiates
- Oxytocin
- Phenothiazines
- Prostaglandin-synthesis inhibitors
- Serotonin reuptake inhibitors
- Tricyclics
- Vincristine

**Miscellaneous**
- HIV infection
- Pain
- Postoperative state
- Severe nausea

CNS=central nervous system.
Hypervolemic Hyponatremia

- AKA dilutional hyponatremia
- Common causes
  - CHF
  - Hepatic cirrhosis
  - Nephrotic syndrome
  - Renal failure (acute and chronic)
- Treatment
  - Sodium/fluid restriction
  - Treatment of underlying disorder
    - Loop diuretics, ACE-inhibitors, spironolactone
## Treatments for Hyponatremia

<table>
<thead>
<tr>
<th>Short-term</th>
<th>Long-term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isotonic normal saline infusion</td>
<td>Fluid restriction</td>
</tr>
<tr>
<td>Hypertonic saline infusion</td>
<td>Demeclocycline</td>
</tr>
<tr>
<td>Vaptan (conivaptan, tolvaptan)</td>
<td>Furosemide + NaCl</td>
</tr>
<tr>
<td></td>
<td>Mineralcorticoids</td>
</tr>
<tr>
<td></td>
<td>Urea</td>
</tr>
<tr>
<td></td>
<td>Vaptan (tolvaptan)</td>
</tr>
</tbody>
</table>
Administration of Sodium

- Most patients can be adequately and much more safely rehydrated with 0.9% NaCl, which is a "hypertonic" solution compared to a hypotonic serum.
- 3% NaCl generally reserved for patients with coma/seizures and high urine Na loss
  - 7.5% NaCl in traumatic brain injury and stroke
  - Each bolus of 2 ml/kg 3% NaCl increases plasma approx 2 mEq/L
- Goal is to raise the [Na] relatively slowly (0.5-1.0 mEq/L/hr) to 125 mEq/L
  - A 4-6 mEq/L daily increase in Na should be the goal for most pts
  - Roughly one-third of the deficit can be replaced over the first 12 hours at a replacement rate of less than 0.5 mEq/hour
  - The remaining amounts can be administered over several days
Central Pontine Myelinolysis

- Avoid rises > 12 mEq/L in 24 hours and > 18 mEq/L in 48 hours
- Overly-rapid correction may lead to irreversible neurologic damage

Hyponatremia Example (1)

- Calculation of sodium deficit in a 75 kg male with a serum sodium of 123 mEq/L

Na deficit (mEq) = (TBW) (Desired - current Na concentration)

TBW = 0.6 \times 75 \text{ kg} = 45 \text{ liters}

Desired sodium = 140 \text{ mEq/L}

Current sodium = 123 \text{ mEq/L}

Example

Sodium deficit = (45 \text{ liters})(140 \text{ mEq/L} - 123 \text{ mEq/L}) = 765 \text{ mEq}
Hyponatremia Example (2)

- Estimate the anticipated change in serum sodium concentrations after the infusion of one liter of 3% sodium chloride in a 75 kg male with a serum sodium of 123 mEq/L.

\[
\text{Change in serum Na}^+ = \frac{\text{Infusate sodium} - \text{Serum sodium}}{\text{TBW} + 1}
\]

**Example**

\[
\frac{512-123}{(0.6 \text{ L/kg})(75 \text{ kg}) + 1} = \frac{389}{46} = 8.45 \text{ mEq}
\]
## Conventional Treatments for Euvolemic Hyponatremia

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Features and Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demeclocycline</td>
<td>No need to limit water intake, blocks effects of AVP on target organs, dosed 600-1200 mg/day: nephrotoxicity, 3-6 days for clinical effect, Not FDA approved</td>
</tr>
<tr>
<td>Fluid restriction</td>
<td>Inexpensive, Limited efficacy, slow to see effect, adherence</td>
</tr>
<tr>
<td>Lithium</td>
<td>Blocks effects of AVP on target organs, Slow onset of action, CNS side effects, cardiotoxicity, GI disturbances</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>Allow relaxation of fluid restriction, Volume depletion, K(^+) and Mg(^+) depletion, potential for ototoxicity</td>
</tr>
<tr>
<td>Saline</td>
<td>No consensus on infusion rate, Rapid response in symptomatic patients, Careful monitoring and complex calculations, not suitable long-term</td>
</tr>
<tr>
<td>Urea</td>
<td>Relaxation of fluid restriction, no USP formulation, Not FDA approved, Poor palatability, contraindicated in impaired renal function, intracranial bleeding, and liver failure</td>
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# Vasopressin Antagonists for Treating Hyponatremia

<table>
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<tr>
<th></th>
<th>Conivaptan (Vaprisol)</th>
<th>Tolvaptan (Samsca)</th>
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<tbody>
<tr>
<td>Vasopressin receptor</td>
<td>V1A/V2</td>
<td>V2</td>
</tr>
<tr>
<td>Administration</td>
<td>IV</td>
<td>Oral</td>
</tr>
<tr>
<td>Half-life (hrs)</td>
<td>3.1-7.8</td>
<td>6-8</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hepatic (CYP 3A4)</td>
<td>Hepatic (CYP 3A4)</td>
</tr>
<tr>
<td>Dose</td>
<td>20 mg in 30 minutes, then 20-40 mg/day</td>
<td>15-60 mg once daily</td>
</tr>
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</table>

- Expert panel recommendations for use of vaptans in treatment of hyponatremia (Am J Med 2013;126(Suppl 1)S1-S42.)
Conivaptan (Vaprisol)

- Arginine vasopressin (AVP) receptor antagonist
  - Short-term IV treatment of euvolemic hyponatremia in hospitalized patients (SIADH, hypothyroidism, adrenal insufficiency, or pulmonary disorders)
  - Treatment of hypervolemic hyponatremia in hospitalized patients
- Antagonizes $V_2$ receptors in the renal collecting duct, resulting in excretion of free water
- Drug interaction potential (3A4 inhibitor, substrate)
  - Ketoconazole, itraconazole, clarithromycin, ritonavir, and indinavir are contraindicated
- No recommendations for renal or hepatic dosing
- No comparative trials of efficacy (3% saline)
Conivaptan (Vaprisol)

- **Dose**
  - LD of 20 mg IV over 30 minutes, then
  - 20-40 mg infusion over 24 hours for up to 4 days

- **Side effects**
  - Injection site reactions - must rotate injection site every 24°
  - Over rapid correction of serum sodium [$> 12 \text{ mEq/L/24 hr}$] (9%)
Tolvaptan (Samsca)

- Oral alternative to IV conivaptan ($V_2$ receptor antagonist)
- Indicated for treatment of clinically significant hypervolemic and euvolemic hyponatremia (sodium < 125 mEq/L) or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction (CHF, cirrhosis, SIADH)
- Boxed warning for initiation in hospital because of need of close sodium monitoring (medication guide)
- MedWatch (2013) for potential risk of liver injury
- Initial dose 15 mg PO daily (titrated to 30 to 60 mg daily)
- Avoid with 3A4 inhibitors (ketoconazole, clarithromycin, ritonavir, diltiazem, verapamil, fluconazole, grapefruit juice)
- If CrCl 10-79 ml/min → no dose adjustment
- Frequently monitor for changes in electrolytes and volume
Tolvaptan (Samsca) Contraindications

- Do not administer to patients requiring urgent intervention to raise serum sodium acutely
- Do not use in patients who are unable to sense or respond appropriately to thirst
- Do not use in patients with hypovolemic hyponatremia
- Do not use with strong CYP 3A inhibitors
- Do not administer in patients who are anuric as no benefit is expected
Hyponatremia Case (1)

- Phyllis Glass is 77 year old female who was admitted to a LTC secondary to overall decline in health.
- She was previously living at home with her husband but has agreed to LTC secondary to progressive limitations in mobility.
- PMH: COPD, HTN, AF, obstipation, depression.
- Vital Signs: BP 140/80, P 84; RR 19; T: 97.8°F (36.6°C); SpO₂ (0.94) room air, Wt 127.6 lbs (58 kg).
- No signs of edema, clubbing or cyanosis; warm to touch; 2+ pulses noted bilaterally.
Hyponatremia Case (2)

- **Meds:** Fluticasone/salmeterol inhaler, albuterol HFA inhaler, levothyroxine, sertraline, famotidine, loratidine, metoprolol tartrate, diltiazem, apixaban, lisinopril, vitamin D, calcium carbonate, tramadol, fiber capsules, polyethylene glycol

- **Labs:** sodium 123 mEq/L, potassium 4 mEq/L, CO₂/HCO₃ 26 mEq/L, BUN 16 mg/dL, Cr 1.1 mg/dL, glucose 90 mg/dL, osmolality 259 mOsm/kg
Hyponatremia Case (3)

- How do you interpret these results?
  - A. The patient has hypovolemic hypotonic hyponatremia
  - B. The patient has euvoletic hypotonic hyponatremia
  - C. The patient has hypervolemic hypertonic hyponatremia
  - D. The patient has hypervolemic hypotonic hyponatremia
Hypernatremia

- Signs/Symptoms - these are the same as those found in TBW depletion
  - Usually exhibited at concentration > 160 mEq/L
    - Thirst
    - Confusion
    - Dry mucous membranes
    - Hallucinations
    - Acute weight loss
    - Intracranial bleed
    - Decreased skin turgor
    - Coma
Hypernatremia Causes

- First four lead to **TBW depletion**
- Dehydration = loss of hypotonic fluid (respiratory, skin losses)
- Decreased water intake
- Osmotic diuresis (glycosuria, mannitol, urea)
- Diabetes insipidus (decreased ADH activity)
  - May be induced by certain drugs (lithium, foscarnet, ifosamide, amphotericin B, phenytoin)
- Iatrogenic (administration of too much hypertonic saline - uncommon)
Hypernatremia Treatment

- Calculate TBW deficit
  - **Water Deficit (L) = Normal TBW - Present TBW**
  
  $$= 0.6 \text{ (LBW)} \left(\frac{\text{Present Na Concentration}}{\text{Normal Na Concentration}} - 1\right)$$

  where 140 mEq/L is used as a normal Na concentration

- Replace deficit over **48-72 hours** with solution hypotonic to patient's serum
Hypernatremia Treatment

- Overly-rapid correction may lead to cerebral edema and death
- The rate at which hypernatremia should be corrected depends on the severity of symptoms and the degree of hypertonicity
- For asymptomatic patients, the rate of correction probably should not exceed 0.5 mEq/L/hour
- A rule of thumb is to replace half the calculated deficit with hypotonic solutions over 12 to 24 hours
  - The rest of the deficit then can be replaced over the ensuing 24 to 48 hours
Hypernatremia Example (1)

- Calculate the water deficit in a 75 kg male with a serum sodium of 156 mEq/L

Water deficit (L) = TBW x \[(\text{serum sodium}/140) - 1\]

**Example**

Water deficit = (0.6 L/kg)(75 kg) \[156/140 - 1\]

= 45 \times 0.1 = 5.14 L
Hypernatremia Example (2)

What is the anticipated change in serum sodium concentrations after IV infusion of 1 L of 5% dextrose in a 75 kg male with a serum sodium of 156 mEq/L?

\[
\text{Change in serum Na}^+ = \frac{\text{Infusate Na} - \text{Serum Na}}{\text{TBW} + 1}
\]

Example

\[
\text{Change in serum Na}^+ = \frac{0 - 156}{45 + 1} = \frac{-156}{46} = -3.39 \text{ mEq}
\]
Potassium Disorders [3.5 – 5 mEq/L]

 Physiology

- Potassium is the predominant cation of the ICF
- Serum potassium concentration is not a good measure of total body potassium, however, clinical manifestations of disturbances in potassium balance correlate quite well with the [K]
- [K] is closely related to the acid/base balance of the body ($\downarrow$ pH → $\uparrow$[K])
- Most potassium is excreted from the body via the kidneys
- Normal maintenance potassium requirement = 0.5-1.0 mEq/kg/day (or ~ 40-80 mEq/day)
Hypokalemia

- **Signs/Symptoms/Manifestations**
  - Muscle weakness/cramps
  - N/V, paralytic ileus
  - Polyuria
  - EKG changes *(flattening of T-wave, elevation of u-wave)*
  - Cardiac arrhythmias *(bradycardia, heart block, α-flutter, PATs, A-V dissociation, PVCs, V-fib)*
  - Increased risk of digoxin toxicity *(try to maintain [K] > 4.0 mEq/L if patient on digoxin therapy)*
  - ↑ pH and bicarbonate levels
Hypokalemia Causes

- GI losses
  - Vomiting, diarrhea, NG suction
- Renal losses
  - High aldosterone, low [Mg]
- Inadequate intake (IVs fluids or PO)
- Alkalosis
- Medications
Medications and Hypokalemia

- Cellular redistribution
  - $B_2$ agonists and insulin

- Renal potassium wasting
  - Diuretics (loops, thiazides)
  - High dose antibiotics (penicillins)
  - Corticosteroids

- Hypokalemia secondary to Mg depletion
  - Aminoglycosides
  - Amphotericin B
  - Cisplatin
  - Foscarnet (Foscavir)
Hypokalemia Treatment

- Estimate total body potassium deficit
  - 1 mEq/L fall in serum potassium from 4 mEq/L to 3 mEq/L represents approximately a 200 mEq deficit
  - When the serum potassium falls below 3.0 mEq/L, the total body deficit increases by 200 to 400 mEq for each 1 mEq reduction in serum concentration
  - Other data suggest that a deficit of 100 mEq per 0.27 mEq/L fall in serum potassium concentration
  - Transcellular redistribution of potassium may significantly alter the relationship between serum concentration and total body deficit
  - Potassium repletion should be guided by close monitoring of serum concentrations instead of using a predetermined amount
# mEq/g of Various Potassium Salts

<table>
<thead>
<tr>
<th>Potassium salt</th>
<th>mEq/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium gluconate</td>
<td>4.3</td>
</tr>
<tr>
<td>Potassium citrate</td>
<td>9.8</td>
</tr>
<tr>
<td>Potassium bicarbonate</td>
<td>10</td>
</tr>
<tr>
<td>Potassium acetate</td>
<td>10.2</td>
</tr>
<tr>
<td>Potassium chloride</td>
<td>13.4</td>
</tr>
</tbody>
</table>

Hypokalemia/alkalosis – use KCl
Hypokalemia/acidosis – use bicarbonate, citrate, acetate, or gluconate salts
# PO Potassium Replacement Products

<table>
<thead>
<tr>
<th>Product</th>
<th>Salt</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extended/Control-release Tablets</td>
<td>Chloride</td>
<td>8 mEq (600mg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 mEq (750mg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15 mEq (1125mg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20 mEq (1500mg)</td>
</tr>
<tr>
<td>Effervescent tabs</td>
<td>Chloride and bicarbonate</td>
<td>10 mEq, 20 mEq, 25 mEq, 50 mEq</td>
</tr>
<tr>
<td>Liquid</td>
<td>Chloride</td>
<td>20 mEq/15ml (10%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40 mEq/15ml (20%)</td>
</tr>
<tr>
<td>Powder packets</td>
<td>Chloride</td>
<td>20 mEq, 25 mEq</td>
</tr>
</tbody>
</table>
IV Potassium Replacement Products

- **Potassium acetate**
- **Potassium chloride premixed**
  - Saline solution is ideal
  - 10-20 mEq diluted in 100 ml 0.9% NaCl
  - No concentrated potassium vials on patient units
Hypokalemia Treatment

- **Moderate hypokalemia (2.5-3.5 mEq/L) without EKG changes**
  - Usually can replace orally at a dose of 40-120 mEq/day
  - Oral route is preferred “sticks” to body better
  - If an ongoing source of potassium loss is present, consider long-term replacement therapy
  - If rapid response desired, recommend liquid or powder product vs. controlled-release.
  - Rule of thumb is $4.0 - K^+ \times 100$
Hypokalemia Treatment

- **Severe hypokalemia (< 2.5 mEq/L) and/or EKG changes**

- **Initiate IV replacement**
  - Maximum infusion rate = 40 mEq/hr (> 10 mEq/hr requires cardiac monitoring)
  - Maximum concentration = 80 mEq/L (max = 40 mEq/L for routine replacement)
  - Causes vein irritation/thrombophlebitis - **avoid** > 10 mEq/hr in peripheral vein
Hypokalemia Treatment

- Initiate IV replacement (continued)
  - Avoid glucose solution as vehicle (augments intracellular movement of potassium)
  - Initial increase in $[K]$ may be transient
  - Magnesium deficits must be corrected concomitantly
  - Consider alternative salts to KCl if acidotic (K-acetate) or low phosphate (K-phos)
### Empiric Treatment of Hypokalemia

<table>
<thead>
<tr>
<th>Severity</th>
<th>Serum K (meq/L)</th>
<th>IV Potassium Dose (meq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild to moderate</td>
<td>2.5 – 3.4</td>
<td>20 – 40</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt;2.5</td>
<td>40 – 80</td>
</tr>
</tbody>
</table>
Recommended Potassium Dosage/Infusion Rate Guidelines

<table>
<thead>
<tr>
<th></th>
<th>Max Conc Small Vol</th>
<th>Max Conc 1000 mL</th>
<th>Max Rate not on EKG</th>
<th>Max Rate on EKG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral</td>
<td>10 mEq/50 ml</td>
<td>40 mEq/L</td>
<td>10 mEq/hr</td>
<td>10 mEq/hour</td>
</tr>
<tr>
<td>Central</td>
<td>10 mEq/50 ml</td>
<td>80 mEq/L</td>
<td>10 mEq/hr</td>
<td>40 mEq/hour</td>
</tr>
</tbody>
</table>
Hyperkalemia

- Signs/Symptoms/Manifestations
  - Muscle weakness
  - Paresthesias
  - GI hypermotility
  - Hypotension
  - EKG changes (peaked T-wave, shortening of Q-T interval, widened QRS complex)
  - Cardiac arrhythmias (↓ cardiac conduction, V-fib, asystole)
  - ↓ pH causes ↑ potassium
Hyperkalemia Causes

- **Increased potassium intake**
  - Excessive intake (watch salt-substitutes)
  - Blood transfusions (increased concentration in stored blood)
  - Rapid excessive IV administration
  - Medications
Medications and Hyperkalemia

- K-sparing diuretics (spironolactone)
- Cyclosporine
- ACE-inhibitors (captopril, lisinopril, etc)
- ß-blockers
- TMP/SMX
- NSAIDs (ibuprofen, naproxen, etc)
- Pentamidine
- Heparin or LMWH (enoxaparin)
- Digoxin (severe toxicity)
- Succinylcholine (Anectine)
- Tacrolimus (Prograf)
- Potassium supplements (excessive doses)
Hyperkalemia Causes

- Decreased potassium excretion
  - Acute and chronic renal failure
  - Addison’s disease (↓ ADH production)
- Potassium release from cells
  - Tissue breakdown (surgery, trauma, hemolysis, rhabdomyolysis)
  - Metabolic acidosis
Hyperkalemia
Treatment Strategies (1)

- Directly oppose effects on cardiac tissue
  - IV calcium - indicated if \([K] > 7.0 \text{ mEq/L} \) and/or EKG changes

- Promote intracellular movement of potassium ions:
  - Dextrose + insulin ± sodium bicarbonate - consider if \([K] > 6.0 \text{ mEq/L} \) and/or EKG changes
    - Bicarb is 50 meq (1 amp of 8.4% solution) infused over 5 min
  - \(\beta_2\) agonists (albuterol) - consider in non-acute situations
    - 10-20 mg nebulized over 10 minutes
Hyperkalemia

Treatment Strategies (2)

- Potassium binding agents
  - Sodium polystyrene sulfonate (Kayexalate)
  - Patiromer (Veltassa)
  - Sodium zirconium cycloilicate (ZS-9)
    - Binds potassium in exchange for sodium and hydrogen
- Loop or thiazide diuretics
- Hemodialysis - usually only used in CRF patients
- Avoid aggravating the problem
  - D/C potassium-sparing drugs, potassium supplements, salt substitutes
Sodium Polystyrene Sulfonate (Kayexalate)

- Exchanges Na for K in the gut
- Oral dose: oral is 15 g (60mL) 1-4 times/day
- Rectal dose: 30-50 g every 6 hours (less effective)
  - Available as powder, suspension 15 g/60mL
- FDA approval based upon a clinical trial of 32 patients in 1961 (before dialysis available)
- MedWatch 2009
  - Cases of colonic necrosis and other serious gastrointestinal adverse events (bleeding, ischemic colitis, perforation) have been reported in association with co-administration of 70% sorbitol
- FDA Drug Safety Communication October 2015
  - Concern for binding other oral medications
  - Separate by 6 hours until more information available
Patiromer (Veltassa) (1)

- Nonabsorbed polymer that binds potassium in exchange for calcium
- Oral suspension used for outpatient treatment of hyperkalemia
  - Not for life-threatening hyperkalemia
- Option for patients with chronic kidney disease and diabetes who have $K > 5$ mEq who would benefit from ACEI, ARB, or aldosterone inhibitor
- Boxed warning for binding to other oral medications (give 6 hours before/after patiromer)
Patiromer (Veltassa) (2)

- Dose is 8.4 g given orally once daily with food, with adjustments at weekly intervals (or longer)
  - Available as single use packets (8.4 g, 16.8 g, 25.2 g)
  - Take with food, mix with water only
  - Max dose is 25.2 g daily
- Side effects: constipation (7.2%), hypomagnesemia 5.3%, diarrhea (4.8%), nausea (2.3%), abdominal discomfort (2%), flatulence (2%)
Suggested Treatment Regimens
Hyperkalemia

- Calcium chloride 1 gm (13.5 mEq) by direct injection or diluted in 50 mL D5W IV over 15 min
  - Works in 1-2 min, lasts 10-30 min
  - May repeat as often as needed
- Dextrose 50% (50 mL, 25 gm) IV over 5 min
- Dextrose 10% with 20 units regular insulin IV over 1-2 hr
  - Works in 30 min, lasts 2-6 hours
- Sodium polystyrene - PO or PR
  - 15-60 gm (60 gm in four divided doses)
## Treatments for Acute Hyperkalemia

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose</th>
<th>Time to Onset</th>
<th>Duration of Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium gluconate</td>
<td>1-2 g IV</td>
<td>1-2 min</td>
<td>10-30 min</td>
</tr>
<tr>
<td>Sodium bicarb</td>
<td>50-100 mEq IV</td>
<td>30 min</td>
<td>2-6 hr</td>
</tr>
<tr>
<td>Insulin + dextrose</td>
<td>5-10 units/50 ml</td>
<td>15-45 min</td>
<td>2-6 hr</td>
</tr>
<tr>
<td>50% dextrose</td>
<td>50 ml (25g)</td>
<td>30 min</td>
<td>2-6 hr</td>
</tr>
<tr>
<td>10% dextrose</td>
<td>1000 ml (100g)</td>
<td>30 min</td>
<td>2-6 hr</td>
</tr>
<tr>
<td>Furosemide</td>
<td>40-80 mg</td>
<td>15 min</td>
<td>2-3 hr</td>
</tr>
<tr>
<td>Sodium polystyrene sulfonate</td>
<td>15-60 g</td>
<td>1 hr</td>
<td>4-6 hr</td>
</tr>
<tr>
<td>Albuterol</td>
<td>10-20 mg</td>
<td>30 min</td>
<td>1-2 hr</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>2-4 hr</td>
<td>Immediate</td>
<td>Variable</td>
</tr>
</tbody>
</table>

Crit Care Med 2008;36:3246-3251
An 85 year-old man is brought to the ED for evaluation of weakness and nausea. He was diagnosed 10 days ago with prostatitis.

His medical history is positive for HTN, CHF, and chronic renal insufficiency.

Current meds include carvedilol, furosemide, enalapril, verapamil, and digoxin; TMP/SMX was recently added because of new diagnosis of prostatitis.
Postassium Case (1)

- The BP is 100/60 mm Hg, temp is 98.4°F. Nonpitting edema is noted in lower extremities bilaterally.
- Labs include sodium of 132 mEq/L, potassium 6.8 mEq/L, BUN 27 mg/dL, Cr 2.3 mg/dL.
- What is the most probable cause of this patient’s hyperkalemia?
Potassium Case (2)

- A 67-year-old female with a history of CHF presents to the clinic with a potassium of 3.1 mEq/L. Her medication list includes digoxin 0.125 mg daily, atorvastatin 20 mg daily, furosemide 40 mg daily, enalapril 10 mg twice daily, aspirin 81 mg daily and fluticasone nasal spray.

What strategy would you recommend with regard to potassium in this patient?

- A. No action is necessary
- B. Begin potassium chloride tablets 20 mEq PO daily
- C. Begin potassium liquid 20 mEq/15ml as 30 ml PO three times daily
- D. Admit to the hospital and give potassium chloride 40 mEq/L IV over one hour
Calcium Disorders [9-10.5 mg/dL]

- **Physiology**
  - > 99.5% of total body calcium found in bone
  - Functions as enzyme co-factor in blood clotting
  - Reciprocal relationship between serum calcium concentration [Ca] and serum phosphate concentration [Phos]
  - [Ca] and [Phos] regulated by complex interaction between
    - Parathyroid hormone (PTH): ↑PTH → ↑[Ca]
    - Vitamin D
    - Calcitonin: ↑calcitonin → ↓[Ca]
Physiology: (continued)

- If the above homeostatic mechanisms are intact, the reservoir of calcium in bone maintains the [Ca] within normal limits despite pronounced changes in the external balance of calcium.
- Normal maintenance calcium requirement = 800-1200 mg/day.
- Corrected Calcium (CC) - accounts for a decrease in percent of protein binding due to a decrease in serum albumin concentration.

\[
CC = \text{Observed } [\text{Ca}] + 0.8 (\text{Normal Albumin}^* - \text{Observed Albumin})
\]

\(^*\)Normal albumin = 4 g/dL
Calcium Case (1)

- A 25 year-old has been hospitalized secondary to a suspected seizure. She has a calcium of 6.5 mg/dL and albumin of 2.0 g/dL.

- The corrected calcium is calculated to be:
  - A. 7.3 mg/dL
  - B. 8.1 mg/dL
  - C. 8.8 mg/dL
  - D. 9.7 mg/dL
Hypocalcemia

- **Signs/Symptoms/Manifestations**
  - Usually seen at serum concentration < 6.5 mg/dL or ionized calcium* of less than 1.12 mmol/L
    - Tetany (digital/circumoral tingling, muscle spasms, cramps, convulsions)
    - Hypoactive reflexes
    - Depression/hallucinations
    - Hypotension/acute myocardial failure
    - Lethargy/stupor
    - Trousseau’s and Chvostek’s signs

*Ionized calcium concentrations are typically used to assess calcium status in the critically ill patient
Hypocalcemia Causes

- Hypoparathyroidism (low PTH)
- Hypomagnesemia (↓ PTH secretion and activity)
- Hyperphosphatemia
- Chronic renal failure (inability to form active vitamin D)
- Vitamin D deficiency
- Acute pancreatitis
- Alkalosis (↑ binding of calcium ions to serum proteins)
- Hypoalbuminemia
Hypocalcemia Causes

Medications
- Loop diuretics (furosemide)
- Corticosteroids
- Phenytoin/phenobarbital
- Cisplatin
- Foscarnet
- Interferon-alpha
- Aminoglycosides (secondary to hypomagnesemia)
- Pentamidine
- Phosphate-replacement products
Checking for Trousseau’s and Chvostek’s Signs

- **Trousseau’s sign**
  - Apply a BP cuff to pts upper arm and inflate
  - Pt will experience adducted thumb, flexed wrist and metacarpophalangeal joints
  - Carpopedal spasm – indicating tetany

- **Chvostek’s sign**
  - Tap on pts facial nerve adjacent to the ear
  - Brief contraction of upper lip, nose, or side of face indicates tetany
## Calcium Supplements

<table>
<thead>
<tr>
<th>Calcium Salt</th>
<th>Elemental Ca (meq/g)</th>
<th>Elemental Ca %</th>
<th>Formulation</th>
<th>Admin Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium chloride</td>
<td>13.6</td>
<td>27</td>
<td>1 g/10 ml</td>
<td>IV</td>
</tr>
<tr>
<td>Calcium gluconate</td>
<td>4.56</td>
<td>9</td>
<td>1 g/10 ml, 500 mg tab</td>
<td>IV or PO</td>
</tr>
<tr>
<td>Calcium acetate</td>
<td>12.7</td>
<td>25</td>
<td>667 mg tab</td>
<td>PO</td>
</tr>
<tr>
<td>Calcium carbonate</td>
<td>20</td>
<td>40</td>
<td>500 mg tab</td>
<td>PO</td>
</tr>
<tr>
<td>Calcium citrate</td>
<td>10.5</td>
<td>21</td>
<td>950 mg tab</td>
<td>PO</td>
</tr>
</tbody>
</table>
PO Calcium Replacement Products

- **Calcium carbonate**
  - 400 mg/g (500 mg to 1500 mg tabs)
  - Os-Cal, Tums, generics

- **Calcium citrate**
  - 211 mg/g (950 mg tabs)
IV Calcium Replacement Products

- **Calcium gluconate**
  - 10 ml of a 10% solution contains 90 mg (4.5 mEq) of elemental Ca (IM or IV use)
  - Generally preferred → less irritating

- **Calcium chloride**
  - 10 ml of a 10% solution contains 270 mg (13.5 mEq) of elemental Ca (IV use)
  - Irritating to veins → central line

- Preparations given as slow push or added to 500 ml to 1000 ml of 0.9% NaCl, LR, or D5W for slow infusion
Indications for IV Calcium for Acute Hypocalcemia

- Patient symptomatic (paresthesias, tetany, Chvostek sign)
- Clinically relevant hypocalcemia (serum ionized calcium < 1 mmol/L)
- Massive blood transfusion (especially with preexisting cardiac disease)
- Calcium channel blocker overdose
- Receiving inotropic or vasopressor support
- Emergent hyperkalemia
Hypocalcemia Treatment

- **Acute symptomatic hypocalcemia**
  - 200-300 mg of elemental calcium IV and repeat until symptoms fully controlled
    - 1 gram of calcium chloride or 2-3 grams of calcium gluconate
    - No faster than 30-60 mg of elemental calcium per minute
    - Caution if serum phosphate elevated or if on digoxin therapy

- **To effectively correct calcium deficiency, magnesium body stores must be replete**
Hypocalcemia Treatment

- **Chronic hypocalcemia**
  - Oral calcium supplementation
    - Usually 2-4 gm/day of *elemental* calcium
  - Different salts have varying amounts of elemental calcium
  - Many patients must also be supplemented with vitamin D
Signs/Symptoms/Manifestations

- Usually at serum concentration > 12 mg/dL
  - Lethargy, somnolence, confusion, coma
  - Muscle weakness, myalgias, arthralgias
  - Polyuria, kidney stone development, ECF depletion, renal failure, metabolic alkalosis
  - EKG changes (↓ QT interval), ventricular arrhythmias, HTN, heart failure
  - Constipation, N/V, anorexia, acute pancreatitis
  - ↑ risk of digoxin toxicity
Hypercalcemia Causes (1)

- Malignant disease
- Hyperparathyroidism
- Thyrotoxicosis
- Total parenteral nutrition
- Granulomatous diseases
  - Sarcoidosis, tuberculosis, leprosy, histoplasmosis
- Immobilization/multiple fractures
- Acidosis (decreases affinity of albumin for calcium)

Hypercalcemia Causes (2)

- Milk-alkali syndrome (high use of milk + antacids)
- Medications
  - Thiazide diuretics (HCTZ)
  - Estrogens and antiestrogens (tamoxifen)
  - Lithium
  - Vitamins A and D
  - Calcium supplements
Hypercalcemia Treatment

- Consider if patient symptomatic and/or serum concentration > 12 mg/dL
- 0.9% NaCl ± furosemide
  - Infusion rates as high as 200-300 mL/hr may be necessary
  - Only add loop diuretic after initial ECF depletion has been corrected
  - Functioning kidneys necessary (the alternative is hemodialysis)
  - Monitor [K] and [Mg] carefully
# Hypercalcemia Treatment Strategies

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Modalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapy of primary disease</td>
<td>Surgery, stop causal drug</td>
</tr>
<tr>
<td>Enhancement of urinary calcium excretion</td>
<td>Volume expansion (NaCl), loop diuretics</td>
</tr>
<tr>
<td>Inhibition of bone resorption</td>
<td>Calcitonin, mithramycin, prostaglandin synthesis inhibitors, bisphosphonates, gallium, PTH antagonists</td>
</tr>
<tr>
<td>Reduction of intestinal calcium absorption</td>
<td>Low calcium diet, glucocorticoids</td>
</tr>
<tr>
<td>Increased calcium deposition</td>
<td>PO/IV phosphate</td>
</tr>
<tr>
<td>Other</td>
<td>Dialysis</td>
</tr>
</tbody>
</table>

Rev Endocr & Metabol Disord 2003;4:167-175
Hypercalcemia Treatment

- Calcitonin - rapid onset/tachyphylaxis
- Corticosteroids
- Biphosphonates
  - Zoledronic acid (Zometa)
  - Etidronate
  - Pamidronate (Aredia)
- Mithramycin (also known as plicamycin)
- Phosphate replacement (if hypophosphatemic and/or secondary to hyperparathyroidism)
# Treatment of Hypercalcemia

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Dose</th>
<th>Onset</th>
<th>Duration</th>
<th>Efficacy*</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS</td>
<td>3-6 L/D IV</td>
<td>Hours</td>
<td>Hours</td>
<td>1-2 mg/dL</td>
</tr>
<tr>
<td>Furosemide</td>
<td>80-160 mg/day IV</td>
<td>Hours</td>
<td>Hours</td>
<td>1-2 mg/dl</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>200 mg/day IV</td>
<td>Hours</td>
<td>Days</td>
<td>0.5-3 mg/dL</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>4-8 units/Kg SC, IV</td>
<td>Hours</td>
<td>Hours</td>
<td>1-2 mg/dL</td>
</tr>
<tr>
<td>Mithramycin</td>
<td>25 mcg/Kg IV</td>
<td>12°</td>
<td>Days</td>
<td>1-5 mg/dL</td>
</tr>
<tr>
<td>Pamidronate</td>
<td>30-90 mg/wk IV</td>
<td>Days</td>
<td>1-4 weeks</td>
<td>1-5 mg/dL</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>4-8 mg IV</td>
<td>Days</td>
<td>Weeks</td>
<td>1-5 mg/dL</td>
</tr>
</tbody>
</table>

* = expected decrease in serum Ca
Because of polyuria, patient is usually dehydrated.

Normal saline 200-300 mL/hr, checking for continued dehydration or fluid overload. Goal: up to 4 L on day one.

Once rehydrated, add furosemide (blocks Ca reabsorption) 40-80 mg IV Q 1-4 hours until urine output = 200-250 mL/hr.

Monitor serum K and Mg.
A 38 year-old male with a history of severe GERD presented with altered mental status and a recent history of anorexia, lethargy, myalgia.

He reports taking 20-40 tablets of calcium carbonate per day for the past few years. He was tachycardiac with BP 191/102. Labs revealed a calcium of 19.9 mg/dL, phosphorous 1.8 mg/dL, a low parathyroid level, potassium of 2.2 mEq/L, serum creatinine 6.4 mg/dL.

What is the differential diagnosis for hypercalemia?

How should the hypercalcemia be managed in this patient?
A nursing student calls the hospital pharmacy for advice administering IV calcium to her assigned patient.

What patient specific information would you ask about to help answer her question?
Phosphorus Disorders [3 – 4.5 mg/dL]

- Physiology
  - Primarily found in bone (80-85%) and ICF (< 1% in ECF) - major anion within cells
  - Source of phosphate for ATP and phospholipid synthesis
  - Rapid shifts between ECF and ICF may frequently confound assessment of total body phosphorus
  - ~ 90% excreted in urine - regulated by GFR and proximal tubular reabsorption
  - Express phosphate in milligrams (mg) or millimoles (mmol or mM) - not milliequivalents (mEq)
    - # millimoles = [(amount in mg) / (atomic or molecular wt)]
  - Normal maintenance phosphate requirement = 800-1200 mg/day (250 mg = 8 mmol)
**Hypophosphatemia Mechanisms**

- **Redistribution of phosphate from ECF into cells**
  - ↑ insulin secretion (refeeding)
  - Acute respiratory alkalosis

- **Decreased intestinal absorption of phosphate**
  - Inadequate intake
  - Antacids containing aluminum or magnesium
  - Steatorrhea or chronic diarrhea
  - Vitamin D deficiency or resistance

- **Increased urinary phosphate excretion**
  - Primary and secondary hyperparathyroidism
  - Osmotic diuresis, acetazolamide, acute volume expansion
Hypophosphatemia

- **Signs/Symptoms/Manifestations**
- **Usually at serum concentration < 1.0 mg/dL (0.32 mmol/L)**
  - Paresthesias
  - Muscle weakness; myalgias
  - Bone pain
  - Anorexia; N/V
  - RBC hemolysis
  - Acute respiratory failure
  - Congestive heart failure
  - Confusion; seizures; coma
Hypophosphatemia Causes

- Malnutrition; GI malabsorption; alcoholism
- TPN without adequate supplementation
- Aggressive feeding of malnourished patients (refeeding syndrome)
- Alkalosis; hyperventilation
- Recovery from severe burns
- Vitamin D deficiency
- Hyperparathyroidism
- Hypokalemia/hypomagnesemia

Hypophosphatemia Causes

- Medications
  - Diuretics
  - Sucralfate
  - Corticosteroids
  - Cisplatin
  - Antacids
  - Foscarnet
  - Phenytoin/phenobarbital
  - Phosphate binders (sevelamer, calcium acetate)
Hypophosphatemia Treatment

- **Mild hypophosphatemia (2.0-2.5 mg/dL)**
  - **Eat high phosphorous diet**
    - Eggs, nuts, whole grains, meat, fish, poultry, milk products
Hypophosphatemia Treatment

- Moderate hypophosphatemia (1.0-2.5 mg/dL)
  - Oral therapy usually adequate
    - 1.5-2.0 gm/day (30-60 mmol/day) divided in 3-4 doses
    - Diarrhea may be dose-limiting
  - IV therapy may be given to NPO patients in ICU
Hypophosphatemia Treatment

- **Severe hypophosphatemia (< 1.0 mg/dL)**
  - Parenteral therapy indicated
    - Select replacement product based on need for other electrolytes (Na vs. K)
    - Caution in patients with hypercalcemia, renal dysfunction, or evidence of tissue injury
    - Switch to oral supplement when level 2-2.5 mg/dL or patient able to tolerate PO or NG dosing
# PO Phosphate Replacement Products*

<table>
<thead>
<tr>
<th>Product</th>
<th>Route</th>
<th>Mg PO4</th>
<th>mmol PO4</th>
<th>mEq Na+</th>
<th>mEq K+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uro-KP-Neutral Tablets</td>
<td>PO</td>
<td>250</td>
<td>8</td>
<td>10.9</td>
<td>1.27</td>
</tr>
<tr>
<td>K-Phos Neutral</td>
<td>PO</td>
<td>250</td>
<td>8</td>
<td>13.1</td>
<td>1.1</td>
</tr>
<tr>
<td>K-Phos Original</td>
<td>PO</td>
<td>114</td>
<td>3.7</td>
<td>--</td>
<td>3.7</td>
</tr>
<tr>
<td>PHOS-NaK</td>
<td>PO</td>
<td>250</td>
<td>8</td>
<td>7.2</td>
<td>7</td>
</tr>
</tbody>
</table>

*In Fall 2008 Neutra-Phos and Neutra-Phos K were discontinued

3 mmol = 93 mg phosphorus
## Suggested PO Treatment Regimens for Hypophosphatemia

<table>
<thead>
<tr>
<th>Product</th>
<th>Dosage Form</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uro-KP-Neutral</td>
<td>Tablets</td>
<td>1-2 tabs dissolved in 6-8 oz of water 4 times/day PC &amp; HS. For best results, soak tabs in water for 2-5 min then stir and swallow</td>
</tr>
<tr>
<td>K-Phos Neutral</td>
<td>852 mg tabs</td>
<td>1-2 tabs 4 times/day after PC &amp; HS</td>
</tr>
<tr>
<td>K-Phos Original</td>
<td>500 mg potassium acid phosphate</td>
<td>2 tabs (dissolved in 6-8 oz water) 4 times daily with meals, bedtime</td>
</tr>
<tr>
<td>PHOS-NaK</td>
<td>1.5 g packet</td>
<td>1-2 packets 4 times/day PC &amp; HS Dilute in 75 ml of water or juice</td>
</tr>
</tbody>
</table>
### IV Phosphate Replacement Products

<table>
<thead>
<tr>
<th>Product</th>
<th>Route</th>
<th>Mg PO₄</th>
<th>mmol PO₄</th>
<th>mEq Na⁺</th>
<th>mEq K⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPO₄/ml</td>
<td>IV</td>
<td>94</td>
<td>3</td>
<td>0</td>
<td>4.4</td>
</tr>
<tr>
<td>NaPO₄/ml</td>
<td>IV</td>
<td>94</td>
<td>3</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>
IV Phosphorous Replacement

- **Mild** [2.3-3 mg/dL]
  - 0.32 mmol/kg over 4-6 hr
- **Moderate** [1.6-2.2 mg/dL]
  - 0.64 mmol/kg over 4-6 hr
- **Severe** [≤ 1.5 mg/dL]
  - 1 mmol/kg over 8-12 hr

- K+ < 4 mEq/L → KPO₄ given
- K+ ≥ 4 mEq/L → NaPO₄ given

Give no faster than 7.5 mmol/h

*JPEN 2006;30:209-14*
Hyperphosphatemia

- **Signs/Symptoms/Manifestations**
  - Hypocalcemia; tetany
  - **Metastatic calcification**
    (at ↑ risk if [Ca] x [Phos] > 60)
Hyperphosphatemia Causes (1)

- Renal failure
- Severe tissue breakdown (rhabdomyolysis, tumor lysis syndrome)
- Hypoparathyroidism
- Acidosis
- Vitamin D excess
- Overuse of phosphorous supplements
Hyperphosphatemia Causes (2)

- Medications
  - Etidronate (bisphosphonates)
  - Interferon-alpha
  - Phosphate-containing enemas / laxatives
  - Phosphorous supplements
Safety of Phosphate Bowel Preps

- MedWatch [Dec 11, 2008] Fleet Phospho-soda, OsmoPrep, Visicol are frequently used for bowel preps
  - High phosphate content can accelerate decline in renal function
  - Be cautious with age > 65, diabetes, diuretics, ACEIs, ARBs, NSAIDs
  - PEG (polyethylene glycol) solutions as alternative (CoLyte, GoLytely, NuLytely)

- MedWatch [Jan 8, 2014] Sodium Phosphate OTC products
  - Using more than one dose (Fleet, others) in 24 hours to treat constipation can cause rare but serious harm to kidneys, heart, even death
Hyperphosphatemia Treatment

- Dietary restriction of phosphate and protein
- If tetany, administer calcium salts IV (see hypocalcemia above)
- Oral phosphate binders
Hyperphosphatemia Treatment

- **ALOH antacids (Alternagel, Amphogel)**
  - For many years, the agent of choice
  - Osteomalacia, encephalopathy have been observed
  - Now recognized problem of aluminum intoxication with long term use

- **Magnesium hydroxide (Milk of Magnesia)**
  - 1-6 tabs/day
  - Can cause diarrhea

- **Calcium carbonate (Tums): 1-2 g/each meal**
  - Inexpensive, tablets can be crushed
  - Numerous dosage formulations
  - Not for patients with hypercalcemia
Hyperphosphatemia Treatment

- **Calcium acetate (Phos-Lo)**
  - 2 tabs/caps each meal initially (1 tablet/capsule = 667 mg)
  - Maintenance dose is 3-4 caps/tabs with each meal
  - Less systemic absorption than calcium carbonate

- **Sevelamer carbonate (Renvela)**
  - Replaced sevelamer hydrochloride (Renagel)
    - Exacerbated metabolic acidosis in dialysis patients
  - Cationic polymer, contains neither calcium or aluminum
  - 1600-3200 mg tid with meals
  - Available in tablets and powder suspension

- **Lanthanum carbonate (Fosrenol)**
  - Initial dose 250-500 mg PO 3x daily to max of 3750 mg/day
  - Most require 500 mg - 1 g tid (1500 – 3000 mg/day)
  - Large tablets must be crushed or chewed to be effective
Sucroferric Oxyhydroxide (Velphoro)

- Calcium-free phosphate binder, for treatment of hyperphosphatemia in patients with chronic kidney disease on dialysis
- First iron-based phosphate binder to be approved for this indication (500 mg chewable tabs, may be crushed)
- Starting dose is 1 tab chewed with each meal TID with dose adjusted weekly or based on phosphate levels until serum phosphorus levels are <5.5 mg/dL
- Separate dosing of levothyroxine by 4 hours
- Side effects include diarrhea, discolored feces (black), nausea, abnormal taste
Ferric Citrate (Auryxia)

- Oral iron based therapy used for hyperphosphatemia in patients with chronic kidney disease receiving dialysis
- Each tablet contains 210 mg ferric iron (equivalent to 1 g ferric citrate)
- Initial dose is 2 tabs, 3 times per day with meals, then titrated by 1-2 tabs daily at 1 week intervals to achieve target phosphorous levels (max 12 tablets daily)
- Monitor for iron overload, drug interaction with doxycycline
- Side effects include diarrhea, discolored feces (dark), constipation, nausea, vomiting
# Phosphate Binders Comparison

<table>
<thead>
<tr>
<th>Agent</th>
<th>Patient Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium carbonate (Tums)</td>
<td>• Inexpensive</td>
</tr>
<tr>
<td></td>
<td>• Hypercalcemia</td>
</tr>
<tr>
<td></td>
<td>• Efficacy affected by gastric pH</td>
</tr>
<tr>
<td>Calcium acetate (PhosLo)</td>
<td>• Large tablet/capsule</td>
</tr>
<tr>
<td></td>
<td>• Hypercalcemia</td>
</tr>
<tr>
<td>Sevelamer HCL (Renagel)</td>
<td>• Binds fat soluble vitamins</td>
</tr>
<tr>
<td>Sevelamer carbonate (Renvela)</td>
<td>• Acidosis in some patients (Renagel)</td>
</tr>
<tr>
<td></td>
<td>• Lowers total cholesterol and LDL</td>
</tr>
<tr>
<td></td>
<td>• Available in powder/suspension (Renvela)</td>
</tr>
<tr>
<td>Lanthanum carbonate (Fosrenol)</td>
<td>• Must be chewed completely</td>
</tr>
<tr>
<td>Suroferric oxyhydroxide (Velphoro)</td>
<td>• Must be chewed completely</td>
</tr>
<tr>
<td></td>
<td>• GI adverse effects, abnormal taste</td>
</tr>
<tr>
<td>Ferric citrate (Auryxia)</td>
<td>• GI adverse effects</td>
</tr>
<tr>
<td></td>
<td>• Avoid in patients with iron overload</td>
</tr>
</tbody>
</table>
A 76-year-old intubated man (90 kg) is in your ICU with suspected pneumonia.

His morning labs are sodium 142 mEq/L, potassium 4.1 mEq/L, chloride 106 mEq/L, bicarbonate 17 mEq/L, BUN 29 mg/dL, creatinine of 1.2 mg/dL, and phosphorus of 1.0 mg/dl.

What would you recommend for phosphorus replacement in this patient?
A 56 year old man (CrCl 18 ml/min), takes calcium acetate 667 mg with each meal. He is found to have a Ca of 10.8 mg/dL and a phosphate level of 7.2 mg/dL. He says that he follows the physician’s and dietician’s orders very strictly.

- Explain the mechanism for hyperphosphatemia in the patient?
- Why is his serum Ca level so high?
- How would you treat his hyperphosphatemia?
Magnesium Disorders

[1.5 – 1.9 mEq/L or 1.7 – 2.2 mg/dL]

- **Physiology**
  - Primarily found in ICF - serum concentrations are relatively poor measure of total body stores
  - Responsible for catalyzing and/or activating more than 300 separate enzymes
  - Usually must be ordered as separate lab; generally not part of normal chemistry panels
  - Normal maintenance magnesium requirement = 320 mg/day (women) to 420 (men) mg/day

*Int Urol Nephrol 2009;41:357-362*
Hypomagnesemia

- **Signs/Symptoms/Manifestations**
  - Usually at serum concentration < 1.0 mEq/L
  - Muscle weakness; cramps
  - Agitation; confusion; hallucinations; tetany; seizures
  - Apathy; depression; hyperactive deep tendon reflex
  - Anorexia; N/V
  - EKG changes (↑ PR, QRS, and QT intervals; presence of u-waves); cardiac arrhythmias
  - Refractory hypokalemia / hypocalcemia
  - Increased risk of digoxin toxicity
Hypomagnesemia Causes

- **Inadequate intake**
  - Alcoholism, dietary restriction, inadequate Mg in TPN

- **Inadequate absorption**
  - Steatorrhea, cancer, malabsorption syndromes, excess calcium, or phosphorous in the GI tract

- **Excessive GI loss**
  - Diarrhea, laxative abuse, NG tube suctioning, acute pancreatitis

- **Excessive urinary loss**
  - Primary hyperaldosteronism, medications, DKA and renal disorders
Medications and Hypomagnesemia

- Diuretics (loop and thiazides)
- Cyclosporine
- Aminoglycosides
- Proton pump inhibitors
  - Be alert for unexplained hypomagnesemia, hypokalemia or hypocalcemia in PPI users (most are long-term users)
- Insulin
- Cisplatin
- Amphotericin B
- Foscarnet
- Etidronate/pamidronate
- Vitamin D excess
IV Magnesium Sulfate

- 10 mL of 10% solution = 1 g of Mg
  - (98 mg Mg = 8.12 mEq)
- Uses: magnesium deficiency, torsades de pointes, premature labor, seizures in eclampsia/preeclampsia, severe asthma
- MedWatch (2013) FDA avoids use > 5-7 days for stop preterm labor, risk of low calcium and bone problems
- 1-2 g IV over 10 min, then a separate infusion depending on the dose
- If given too quickly – flushing, bradycardia, cardiac arrhythmia or cardiac arrest can occur
  - Slower infusion allows better tissue distribution
- No concentrated magnesium on patient care areas
- Often given empirically to critically ill (2 gm IV q 8°)
  - Replace cautiously in renal dysfunction
# Empirical Treatment of Hypomagnesemia

<table>
<thead>
<tr>
<th>Severity</th>
<th>Serum Mg (mg/dL)</th>
<th>IV Mg Replacement Dose*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild to moderate</td>
<td>1.0 – 1.5</td>
<td>8 - 32 meq (1- 4 g mag sulfate) up to 1.0 meq/kg</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt; 1.0</td>
<td>32 - 64 meq (4 - 8 g mag sulfate) up to 1.5 meq/kg</td>
</tr>
</tbody>
</table>

*Max rate of infusion = 8 meq (1 g) per hour up to 12 g over 12 hours if asymptomatic, up to 32 meq (4 g) over 4-5 min if severely symptomatic.
PO Magnesium Supplements

- Used when [Mg] > 1.0 mEq/L and < 1.5 mEq/L without symptoms
- Magnesium oxide (Mag-Ox)
  - 400 mg = 241 mg Mg = 20 mEq Mg
- Magnesium chloride hexahydrate (Slo-Mag)
  - 64 mg elemental mg, enteric coated
- Both products are OTC
- Limiting side effect is diarrhea
Hypermagnesemia

- Rare - secondary to kidney’s ability to excrete high loads
- Signs/Symptoms/Manifestations
  - 2-3 mEq/L = drowsiness, lethargy, hyporeflexia
  - 3-5 mEq/L = N/V; somnolence, areflexia, hypocalcemia, hypotension, Bradycardia, prolonged PR and QT interval, increase in QRS duration
  - Above 5 mEq/L = muscle paralysis, quadraplegia, apnea, complete heart block, cardiac arrest
Hypermagnesemia Causes

- Renal failure (often in conjunction with use of Mg-containing medications)
  - Magnesium cathartic abuse (magnesium citrate)
  - Increased intake with antacids (MOM, Maalox)
  - Magnesium supplements

- Lithium therapy (overdose)
Hypermagnesemia Treatment

- IV calcium gluconate – (1-2 grams IV) temporarily reverses neuromuscular and cardiovascular effects
  - Indicated if [Mg] > 5.0 mEq/L with symptoms or if > 8.0 mEq/L without symptoms
- 0.9% NaCl + furosemide (good renal function) or hemodialysis (renal failure)
- D/C all Mg-containing medications (MOM, Maalox)
AA is a 47-year-old male admitted to the ICU with acute pancreatitis due to alcohol ingestion. He is suffering from alcohol withdrawal and is started on a lorazepam drip to help manage the symptoms.

Today’s laboratory results include sodium 125 mEq/L, potassium 3.2 mEq/L, chloride 90 mEq/L, bicarbonate 22 mEq/L, magnesium 2 mEq/L, BUN 2 mg/dL, Cr 1.1 mg/dL, glucose 194 mg/dL.

The attending physician wishes to start IV magnesium, what dose do you recommend?

A staff pharmacist questions the dose because the Mg lab is normal. How do you respond?
Magnesium Case (2)

- A 22 year-old pregnant female in her 3rd trimester was admitted for severe hypertension (180/110 mmHg) and proteinuria. She was started on IV magnesium sulfate and IV labetalol. Her BP was controlled at 140/90.

- A few days later, she developed nausea and vomiting and progressively became lethargic. Her BP dropped to 100/70 mmHg. Deep tendon reflexes were decreased. Her Cr was 2.0 mg/dL and Mg was 6.2 mEq/dL.

- Why did the patient develop hypermagnesemia?
- How would you recognize Mg intoxication at the bedside?
- How would you treat this patient?