Hypophosphatemia

May 9, 2019 by Josh Farkas

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phosphate physiology

phosphate basics

- 99% of phosphate is present within cells.
- Symptoms from phosphate deficiency result from intracellular phosphate deficiency. Unfortunately, we can measure only extracellular phosphate levels. This creates some variability among patients with hypophosphatemia:
  - Symptoms tend to occur in patients with chronic hypophosphatemia and total-body deficiency (e.g. alcoholism, chronic antacid ingestion, chronic malnutrition with re-feeding syndrome).
  - Symptoms are uncommon in patients with acute shifts of phosphate out of the blood (e.g. diabetic ketoacidosis).
- In practice, it is often difficult to tell whether hypophosphatemia represents a total-body deficiency or a transient phosphate shift. Given the potential consequences of true phosphate deficiency, it is generally better to err on the side of phosphate repletion.
endocrine physiology

- The most common endocrine causes of hypophosphatemia are as follows:
- (1a) Hyperparathyroidism — as shown above, this may cause hypophosphatemia and hypercalcemia.
- (1b) Hungry Bone Syndrome
  - Occurs immediately following resection of a parathyroid adenoma which was causing hyperparathyroidism.
  - Bone mineralization occurs, which pulls phosphate and calcium into the bone.
  - Clinically this should be easy to recognize because it occurs in the immediate postoperative period following parathyroid surgery.
- (2) Vitamin D deficiency — this causes impaired phosphate absorption in the gut and increased phosphate excretion.
- (3) Oncogenic osteomalacia
  - Extremely rare paraneoplastic disorder which usually occurs with small, benign tumors.
  - Tumor secretes phosphaturic hormones that reduce renal phosphate absorption and synthesis of 1,25-OH-vitamin D.
  - Clinical presentation: hypophosphatemia with paradoxically low 1,25-OH-vitamin D levels (this is paradoxical, because normally hypophosphatemia would stimulate elevation of 1,25-OH-vitamin D).

symptoms

- Seizures, paresthesias, tremor
- Confusion, dysarthria, stupor, coma
- May promote the development of central pontine myelinolysis

neurologic

- Impaired contractility, heart failure
- Arrhythmia (supraventricular and ventricular tachycardia)

muscular

- Rhabdomyolysis
  - Rare; May mask diagnosis of hypophosphatemia by release of phosphate from muscle!
- Muscle weakness, including diaphragm
May sometimes contribute to difficult weaning

Other rare manifestations

- Insulin resistance
- Hemolysis

Phosphate level

When checking a phosphate level, consider obtaining a complete electrolyte panel (including Ca/Mg/Phos). Electrolyte disorders tend to occur in pairs and triplets ("electrolytic disarray").

When should phosphate be checked?

- When initiating nutrition in patients at-risk for refeeding syndrome.
- Patients with diabetic ketoacidosis or hyperosmolar hyperglycemic nonketotic syndrome (HHNS).
- Patients on continuous renal replacement therapy (CRRT).
- Possibly once, upon admission for all patients entering the ICU?
- If there is clinical concern of symptoms due to hypophosphatemia.
  - In patients with difficulty weaning from ventilation (some evidence shows that hypophosphatemia may be a contributory factor by causing diaphragmatic weakness).

<table>
<thead>
<tr>
<th>rough interpretation of serum phosphorous levels</th>
<th>mg/dL</th>
<th>mM</th>
<th>clinical correlate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>2.5-5</td>
<td>0.81-1.6</td>
<td>Normal</td>
</tr>
<tr>
<td>Mild hypophosphatemia</td>
<td>2-2.5</td>
<td>0.65-0.81</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Moderate hypophosphatemia</td>
<td>1-2</td>
<td>0.32-0.65</td>
<td>Usually asymptomatic</td>
</tr>
<tr>
<td>Severe hypophosphatemia</td>
<td>&lt;1</td>
<td>&lt;0.32</td>
<td>Can be symptomatic</td>
</tr>
</tbody>
</table>

Spurious hypophosphatemia (pseudohypophosphatemia)

- Uncommon
- Potential causes: hyperbilirubinemia, mannitol, paraproteins, acute leukemia

Causes of hypophosphatemia

Shifting phosphate into cells

- Insulin
  - Diabetic ketoacidosis
  - Re-feeding syndrome
- Acute respiratory alkalosis
- Hungry bone syndrome (s/p surgery for hyperparathyroidism)

Reduced gastrointestinal uptake

- Inadequate oral intake
- Chronic diarrhea
- Drugs
  - Chronic use of antacids containing calcium, magnesium, or aluminum

Increased renal loss

- Diuresis or Dialysis
- Diuretics (loop diuretics, acetazolamide, thiazides)
Hypophosphatemia

- Osmotic diuresis (hyperosmolar hyperglycemic nonketotic syndrome, i.e. HHNS)
- Auto-diuresis following iatrogenic volume overload
- Post-ATN or post-obstructive polyuria
- Hypothermia (“cold diuresis”)
- Continuous renal replacement therapy (CRRT) – especially prolonged high-intensity runs for intoxication
- Proximal tubule dysfunction (Type II RTA, a.k.a. Fanconi Syndrome)
- Hyperparathyroidism
- Medications
  - Aminoglycosides
  - IV iron
  - Tenofovir
  - Chemotherapeutic agents (especially imatinib, VEGF inhibitors, and target of rapamycin inhibitors such as temsirolimus)
- Oncogenic osteomalacia

**multifactorial**

- Alcoholism
- Vitamin D deficiency
- Critical illness of most types:
  - Sepsis, systemic inflammation
  - Trauma (especially head trauma)
  - Major surgery (especially cardiothoracic, aortic, or hepatic)
  - Burns

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**Table 2 Prevalence and/or incidence of hypophosphatemia**

<table>
<thead>
<tr>
<th>Author (ref.)</th>
<th>Year</th>
<th>Population/disease</th>
<th>Number of patients</th>
<th>Definition of hypophosphatemia</th>
<th>Prevalence</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical ICU patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goldstein et al. [15]</td>
<td>1985</td>
<td>Thoracic surgery</td>
<td>34</td>
<td>&lt;0.80 mmol/L</td>
<td>-</td>
<td>56%</td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>40</td>
<td>&lt;0.80 mmol/L</td>
<td>-</td>
<td>50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zasso et al. [14]</td>
<td>1995</td>
<td>Surgical ICU</td>
<td>208</td>
<td>0.59 mmol/L</td>
<td>-</td>
<td>17.3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buell et al. [26]</td>
<td>1998</td>
<td>Hepatic surgery</td>
<td>35</td>
<td>&lt;0.80 mmol/L</td>
<td>-</td>
<td>2.4%</td>
</tr>
<tr>
<td>Cohen et al. [12]</td>
<td>2004</td>
<td>Cardiac surgery</td>
<td>566</td>
<td>&lt;0.80 mmol/L</td>
<td>-</td>
<td>67%</td>
</tr>
<tr>
<td>Salem et al. [17]</td>
<td>2005</td>
<td>Hepatic surgery</td>
<td>20</td>
<td>&lt;0.70 mmol/L</td>
<td>-</td>
<td>100%</td>
</tr>
<tr>
<td>Medical ICU patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily et al. [18]</td>
<td>1990</td>
<td>Trauma patients</td>
<td>12</td>
<td>&lt;0.80 mmol/L</td>
<td>-</td>
<td>75%</td>
</tr>
<tr>
<td>Kruse et al. [27]</td>
<td>1992</td>
<td>General ICU patients</td>
<td>418</td>
<td>&lt;0.80 mmol/L</td>
<td>-</td>
<td>56%</td>
</tr>
<tr>
<td>Mank et al. [28]</td>
<td>1996</td>
<td>Refeeding after &gt;48 h starvation</td>
<td>62</td>
<td>&lt;0.65 mmol/L</td>
<td>-</td>
<td>34%</td>
</tr>
<tr>
<td>Berger et al. [19]</td>
<td>1997</td>
<td>Burn injuries</td>
<td>16</td>
<td>&lt;0.80 mmol/L</td>
<td>-</td>
<td>100%</td>
</tr>
<tr>
<td>Bask et al. [7]</td>
<td>1998</td>
<td>Sepsis</td>
<td>99</td>
<td>&lt;0.80 mmol/L</td>
<td>-</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sepsis, infection without sepsis</td>
<td>32</td>
<td>&lt;0.80 mmol/L</td>
<td>-</td>
<td>65%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sepsis, negative blood culture</td>
<td>37</td>
<td>&lt;0.80 mmol/L</td>
<td>-</td>
<td>80%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sepsis, positive blood culture</td>
<td>30</td>
<td>&lt;0.80 mmol/L</td>
<td>-</td>
<td>80%</td>
</tr>
<tr>
<td>Polderman et al. [21]</td>
<td>2000</td>
<td>Head trauma</td>
<td>18</td>
<td>&lt;0.60 mmol/L</td>
<td>-</td>
<td>61%</td>
</tr>
<tr>
<td>Miklovs et al. [29]</td>
<td>2002</td>
<td>Severe heart failure</td>
<td>86</td>
<td>&lt;0.77 mmol/L</td>
<td>-</td>
<td>13%</td>
</tr>
<tr>
<td>Dominguez-Roldan et al. [30]</td>
<td>2005</td>
<td>Brain-dead patients</td>
<td>50</td>
<td>&lt;0.80 mmol/L</td>
<td>-</td>
<td>72%</td>
</tr>
</tbody>
</table>

**Hypophosphatemia is quite common in most cohorts of critically ill patients (note: 0.8 mM = 2.5 mg/dL).**

Generally, the cause of hypophosphatemia can be determined by a history and review of labs and medications. In rare situations where hypophosphatemia persists and the cause is unclear, a fractional excretion of phosphate might be helpful (Fe-Phos).

**Fractional excretion of phosphate**

- Calculated in the same fashion as fractional excretion of sodium (FeNa)
- You can use any calculator for FeNa (just insert phosphate in place of sodium).
- Or you can use this online calculator (https://hiv.uw.edu/page-clinical-calculators/fepo4) for fractional excretion of phosphate.
- Fe-Phos should be <5% as a normal response to hypophosphatemia. Thus:
  - Fe-Phos <5%: Gastrointestinal problem, shifting into cells
  - Fe-Phos >5%: Renal phosphate wasting
  - Multifactorial etiologies should be considered regardless of the Fe-Phos.

### Hypophosphatemia

#### Treatment

**Significant hypophosphatemia (phosphate level <2 mg/dL or <0.65 mM)**

- **Moderate/severe renal failure?**
  - Yes: Caution: Phosphate may accumulate. Give phosphate only if symptomatic or severe hypophosphatemia. Use ~50% lower doses than usual.
  - No

- **Abnormal calcium level?**
  - Yes: Caution: Increasing the calcium-phosphate product may result in precipitation of calciphylaxis.
    - **Hypercalcemia**: Rapid IV phosphate may worsen hypercalcemia.
  - No

**Indication for IV phosphate?**

- **Yes**
  - Either K-Phos or Na-Phos (depending on potassium level)
    - Initial dose:
      - Phosphate >1.5 mg/dL or >0.48 mM: 15 mM over 4 hr
      - Phosphate <1.5 mg/dL or <0.48 mM: 30 mM over 4 hr
    - Repeat electrolytes & re-dose Phos (if severe may require several doses)

- **No**
  - Oral phosphate
    - Choose formulation (dosed in terms of elemental phosphate equivalents, generally in increments of 8 mM phosphate) Potassium-containing formulation e.g. PHOS/NAK packets (8 mM phosphate, 7 mM potassium, 7 mM sodium); Potassium phosphate oral solution
    - Dosing depends roughly on phosphate level (but consider higher doses in active refeeding syndrome)
    - Phosphate < 1.5 mg/dL (<0.48 mM): 16 mM phosphate q4hr x 24 hours for a total dose of 64 mM
    - Phosphate > 1.5 mg/dL (<0.48 mM): 8 mM phosphate q4hr for a total of 32 mM

- **Follow & dose-litrate**
  - Follow electrolytes (including Ca/Mg/Phos)
  - Re-dose phosphate depending on levels & dynamic renal function (decrease doses if worsening renal function).

#### Cautions

- Significant hypophosphatemia (e.g. phosphate <2 mg/dL or <0.65 mM) should generally be repleted, with the following potential exceptions:
  - **(1) Renal insufficiency**
    - Phosphate should be given only if truly necessary, since these patients tend to develop hyperphosphatemia over time.
  - **(2) Hypercalcemia**
    - Increasing phosphate may result in precipitation of calcium-phosphate in tissues (calciphylaxis).
    - Try to keep the calcium-phosphate product <70 (calcium multiplied by phosphate, both in mg/dL).
  - **(3) Hypocalcemia**
    - Rapid infusion of IV phosphate may reduce calcium level.
    - If hypotension occurs during infusion of IV phosphate, consider possibility of hypocalcemia.

#### Intravenous phosphate

- **Indications**:
  - Severe hypophosphatemia (<1 mg/dL or <0.32 mM)
  - Symptoms
  - Lack of enteral access
  - Malabsorption
- Either potassium phosphate or sodium phosphate may be used, depending on the potassium level.
- **Typical dose**:
  - Phosphate <1.5 mg/dL (<0.48 mM) == Initial dose of 30 mM phosphate infused over 4 hours
  - Phosphate >1.5 mg/dL (<0.48 mM) == Initial dose of 15 mM phosphate infused over 2 hours
  - Repeat electrolytes and provide more as needed. Patients with severe hypophosphatemia often require several doses (e.g. 60-90 mM total).
  - Should probably be infused slowly.
Sources disagree about the safe rate of infusion.\(^1\)

Rapid infusion may cause transient hyperphosphatemia (which leads to hypocalcemia). However, studies suggest that infusion at rates up to 20 mM/hour are safe. A rate of 7.5 mM/h is definitely safe (as recommended in the algorithms here).\(^2\)

### Table 4 Intravenous treatment of hypophosphatemia

<table>
<thead>
<tr>
<th>Author [ref.]</th>
<th>Year</th>
<th>Serum phosphate (mmol/L)</th>
<th>Dose</th>
<th>Speed</th>
<th>Efficacy</th>
<th>Complications/safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown et al.</td>
<td>2006</td>
<td>0.73-0.96</td>
<td>0.32 mmol/kg</td>
<td>7.5 mmol/h</td>
<td>No significant increase in IP</td>
<td>Considered safe</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.51-0.72</td>
<td>0.64 mmol/kg</td>
<td>7.5 mmol/h</td>
<td>IP normalized in 59%</td>
<td>Considered safe</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;0.50</td>
<td>1 mmol/kg</td>
<td>7.5 mmol/h</td>
<td>IP normalized in 60%</td>
<td>Considered safe</td>
</tr>
<tr>
<td>Taylor et al.</td>
<td>2004</td>
<td>0.55-0.70</td>
<td>0.2 mmol/kg</td>
<td>33 μmol/kg/h</td>
<td>IP normalized in 76% (all patients)</td>
<td>Considered safe</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.32-0.55</td>
<td>0.4 mmol/kg</td>
<td>67 μmol/kg/h</td>
<td></td>
<td>Considered safe</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;0.32</td>
<td>0.8 mmol/kg</td>
<td>100 μmol/kg/h</td>
<td></td>
<td>Considered safe</td>
</tr>
<tr>
<td>Charon et al.</td>
<td>2003</td>
<td>0.40-0.65</td>
<td>30 mmol</td>
<td>15 mmol/h</td>
<td>Equally effective</td>
<td>Mild hyperphosphatemia and mild hyperkalemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;0.40</td>
<td>30 mmol</td>
<td>7.5 mmol/h</td>
<td></td>
<td>Considered safe</td>
</tr>
<tr>
<td></td>
<td></td>
<td>45 mmol</td>
<td>15 mmol/h</td>
<td></td>
<td>Equally effective</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>45 mmol</td>
<td>7.5 mmol/h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perreault et al.</td>
<td>1997</td>
<td>0.40-0.80</td>
<td>15 mmol</td>
<td>5 mmol/h</td>
<td>IP normalized in 81.5%</td>
<td>Considered safe</td>
</tr>
<tr>
<td>Rosen et al.</td>
<td>1995</td>
<td>&lt;0.40</td>
<td>30 mmol</td>
<td>10 mmol/h</td>
<td>IP normalized in 30%</td>
<td>Considered safe</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15 mmol</td>
<td>7.5 mmol/h</td>
<td>IP normalized in 100%</td>
<td></td>
<td>Considered safe</td>
</tr>
<tr>
<td>Bollaert et al.</td>
<td>1995</td>
<td>&lt;0.05</td>
<td>20 mmol</td>
<td>20 mmol/h</td>
<td>IP normalized in 80%</td>
<td>Considered safe Mild hypercalcemia</td>
</tr>
<tr>
<td>Kruse et al.</td>
<td>1992</td>
<td>&lt;0.80</td>
<td>20-40 mmol</td>
<td>20 mmol/h</td>
<td>mean IP rose from 0.65 to 1.0 mmol/L</td>
<td>considered safe Mild hypercalcemia</td>
</tr>
</tbody>
</table>

There’s no consensus about the dose or rate to administer IV phosphate. (IP = inorganic phosphate).

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**oral phosphate**

- Used if there isn’t an indication for IV phosphate (listed above).
- High bioavailability, but tends to cause diarrhea.
- Available in increments of 8 mM phosphate. One of the following options may be chosen, depending on the patient’s potassium level:
  - (a) PHOS-NAK packet (8 mM phosphate, 7 mEq potassium, 7 mEq sodium)
  - (b) Oral sodium phosphate liquid
  - (c) Oral potassium phosphate liquid
- Dosing depends roughly on patient’s phosphate level, for example:
  - Phosphate <1.5 mg/dL (\(<0.48 \text{ mM}\)) \(\Rightarrow\) 16 mM q6hr
  - Phosphate >1.5 mg/dL (\(<0.48 \text{ mM}\)) \(\Rightarrow\) 8 mM q8hr
- For patients with active refeeding syndrome, consider using higher doses than would otherwise be indicated based solely on the phosphate level.
Hypophosphatemia - EMCrit Project

**Treatment of hypophosphatemia**

Significant hypophosphatemia (phosphate level <2 mg/dL or <0.65 mM)

<table>
<thead>
<tr>
<th>Moderate/severe renal failure?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
</tr>
</tbody>
</table>

Abnormal calcium level?

| Yes | No |

Indication for IV phosphate?

- Phosphate <1 mg/dL (<0.32 mM)
- Symptoms
- Lack of enteral access
- Severe malabsorption

<table>
<thead>
<tr>
<th>IV phosphate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Either K-Phos or Na-Phos (depending on potassium level)</td>
</tr>
<tr>
<td>Initial dose:</td>
</tr>
<tr>
<td>Phosphate &gt;1.5 mg/dL or &gt;0.48 mmol/L: 15 mmol over 4 hr</td>
</tr>
<tr>
<td>Phosphate &gt;1.5 mg/dL or &lt;0.48 mmol/L: 30 mmol over 4 hr</td>
</tr>
<tr>
<td>Repeat electrolytes &amp; re-dose PTH (if severe may require several doses)</td>
</tr>
</tbody>
</table>

Oral phosphate

- Choose formulation (dosed in terms of elemental phosphate equivalents, generally in increments of 8 mmol phosphate)
- Potassium-containing formulation, e.g. PHOS-NAK packets (8 mmol phosphate, 7 mmol potassium, 7 mmol sodium)
- Sodium phosphate oral solution
- Dosing depends roughly on phosphate level (but consider higher doses in active refeeding syndrome)
- Phosphate < 1.5 mg/dL (<0.48 mmol/L): 16 mmol phosphate q6hr x 24 hours for a total dose of 64 mmol phosphate > 1.5 mg/dL (<0.48 mmol/L): 8 mmol phosphate q6hr-q8hr x 24 hours for total dose of 24-32 mmol phosphate

Follow & dose-titrte

- Follow electrolytes (including Ca/Mg/Phos)
- Re-dose phosphate depending on levels & dynamic renal function (decrease doses if worsening renal function)

[Image](https://emcrit.org/wp-content/uploads/2019/04/phosdosingprep.png)

**podcast**


**The Podcast Episode**

Want to Download the Episode?

[Right Click Here and Choose Save-As](http://traffic.libsyn.com/ibccpodcast/IBCC_EP_36_-_All_things_phosphate.mp3)

**questions & discussion**

To keep this page small and fast, questions & discussion about this post can be found on another page [here](https://emcrit.org/pulmcrit/phos/).

- Patients with alcoholism, diabetes, or malnutrition may initially have a normal phosphate level, but develop hypophosphatemia later on during their hospital course (following administration of carbohydrate and/or insulin).
Don't overlook the possibility of refeeding syndrome in patients with hypophosphatemia after initiation of nutrition. In this situation, other electrolytes and thiamine may be needed.

In severe hypophosphatemia treated with IV repletion, several doses may be required. Don't assume that a single dose will be effective.

**Going further:**

- [Hypophosphatemia](https://litfl.com/hypophosphataemia/) (Chris Nickson, LITFL)

**References**
