Metabolic Support in the Era of Fluid and Electrolyte Shortages

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Disclosures: I have no commercial relationships relevant to the topic being presented.

Presentation Summary: Parenteral nutrition component shortages have resulted in clinicians across the health care continuum scrambling to provide safe and efficacious nutrition support therapy. The intent of this part of the program is to discuss various strategies and techniques for managing fluid and electrolyte shortages, including identifying treatable causes for electrolyte disorders, developing appropriate target goals for the patient, and implementing various treatment strategies including challenges with oral/enteral electrolyte products. The presenters of this session will also serve as facilitators to solicit audience responses and engage attendees into a discussion about their experiences and techniques for metabolic support in this era of parenteral nutrition component shortages.

Learning objectives:
At the conclusion of the presentation, the learner will be able to:

1. Identify the most common electrolyte shortages
2. Describe the clinical relevancy between electrolyte depletion and organ dysfunction
3. Contrast “optimal” and “essential” electrolyte dosing algorithms during shortages
4. Discuss methods for managing electrolyte disorders

Fast Facts:
During electrolyte shortages, one should:

- Use the enteral/oral route if practical or possible
- Identify the “most appropriate” electrolyte target concentration for the patient
- Address the etiology for the electrolyte disorder

Learning Assessment Questions:

1. Which problem has been associated with use of electrolyte sources from outsourcing (503B) facilities?
   a. Electrolyte concentrations may not be the same as conventional sources
   b. Labelling requirements are not required to be in line with USP standards
   c. Packaging of products may be unconventional (e.g., syringes versus vials)
   d. All of the above

2. Why is it difficult to consistently achieve a serum phosphorus concentration ≥ 4 mg/dL in critically ill patients without renal dysfunction?
   a. The renal threshold serum phosphate concentration is ~3 to 3.5 mg/dL
   b. Some critically ill patients exhibit augmented renal clearance
   c. Exaggerated cytokine and catecholamine production suppresses serum phosphate concentration
   d. All of the above

3. During an intravenous calcium gluconate shortage, the hospital has implemented a temporary provision for using intravenous calcium chloride. Which is the correct dosage adjustment to deliver the same amount of elemental calcium?
a. No dosage adjustment is necessary
b. The prescribed calcium chloride dose (in g) should be 3 times higher than calcium gluconate
c. The prescribed calcium chloride dose (in g) should be 1/3 the dose of calcium gluconate
d. Calcium chloride should be administered as a continuous intravenous infusion

4. Why is enteral potassium administration safer than parenteral administration?
   a. The bioavailability is about 60% of the total dose
   b. Blood stream delivery is controlled by rate of absorption and feed-forward regulation
   c. Slow release wax-matrix tablets are preferred for tube fed patients
   d. Gastric and jejunal delivery of KCL liquid are interchangeable

5. Which large volume intravenous fluid would be best as a replacement fluid for a patient with significant small bowel intestinal fluid losses?
   a. Lactated Ringers solution
   b. 0.9% NaCl with 20 mEq KCl/L
   c. 0.9% NaCl with 40 mEq KCl/L
   d. 0.45% NaCl with 20 mEq KCl/L

Learning Assessment Answers:

1. D. All of the above choices have been associated with medication errors when using electrolyte sources from 503B facilities (facilities that compounds sterile products for institutions).
2. D. All of the above factors are reasons why it may be difficult to achieve a serum phosphorus concentration of 4 mg/dL.
3. C. The prescribed calcium chloride dose should be 1/3 the dose of calcium gluconate as 1 g of calcium gluconate provides 4.65 mEq of elemental calcium whereas 1 g of calcium chloride provides 13.6 mEq of elemental calcium.
4. B. A rapid inadvertent pulse dose of potassium cannot be accomplished with oral or enteral administration due to timing of absorption and feed forward regulation of enteral potassium administration unlike intravenous administration. Bioavailability with enteral or oral potassium supplementation is ~95% or better under most circumstances. Wax matrix tablets when crushed will clog the feeding tube and is a poor product choice. Jejunal administration of hypertonic drug solutions like potassium chloride liquid can cause cramping and diarrhea.
5. A. Because of significant sodium, chloride, and bicarbonate content of intestinal fluids, it would be prudent to choose a more “balanced” replacement solution containing lactate (converts to bicarbonate in the liver) to prevent an acidemia particularly if adjustments to the PN solution are limited.

Key References:

Metabolic Support in the Era of Parenteral Nutrition Component Shortages

- Fluid and Electrolytes – Roland Dickerson, PharmD, BCNSP, FASPEN
- Amino Acids, Trace Minerals, and Cysteine – Steven Plogsted, PharmD, BCNSP, CNSC
- Resources for Managing Shortages of PN Components and Multi-Component Products – Beverly Holcombe, PharmD, BCNSP, FASPEN
- Open Discussion Among Session Participants and Speakers

Active Shortages Top 5 Drug Classes

Active Shortages December 31, 2018

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Disclosures

- No conflicts of interest to disclose.

Learning Objectives

- Identify the most common electrolyte shortages
- Describe the clinical relevance between electrolyte depletion and organ dysfunction
- Contrast “optimal” and “essential” electrolyte dosing algorithms for electrolyte disorders during shortages
- Discuss methods for managing electrolyte disorders

Some Common Principles During Intravenous Electrolyte Shortages

(go to www.nutritioncare.org for a more detailed compilation)

- Use the oral/enteral route if practical or possible
- Reserve for patients requiring PN or with a therapeutic need
- Identify the “most appropriate” target goal for the patient
- Reconsider “automatic” use of standardized dosing algorithms
- Address the etiology for the electrolyte disorder
- Consider if use of a commercially available multi-electrolyte product would be acceptable
- Beware of products provided by outsourcing 503B manufacturers
- Think “outside of the box”
Beware of Outsourcing Facilities

- Electrolyte solutions compounded with SWFI from powder sources
- Electrolyte concentrations may not be same as conventional sources
- Labeling requirements are not required to be in line with USP standards for 503B facilities

Think “Outside of the Box”

- Determine the etiology for the electrolyte disorder and treat the etiology if possible (direct example: diarrhea; indirect example: high non-obstructive gastric output with NGT placement)
- Evaluate supplemental IV fluids – could a commercially available large volume IV solution be substituted for the current supplemental fluid? (examples: 0.45% NaCl or 0.9% NaCl with 20 mEq/L or 40 mEq/L of KCl or Lactated Ringers solution)
- Drug substitution: Could a potassium-sparing diuretic be substituted (e.g., in lieu of HCTZ)?

Intracellular Electrolytes

“The Big Questions”

- Is it necessary to keep serum potassium @ 4 mEq/L, phosphorus @ 4 mg/dL, magnesium @ 2 mg/dL, ionized calcium @ ≥ 1.12 mmol/L in all patients?
- Are the etiologies for the electrolyte disorders being adequately addressed?
- Is intravenous treatment of the electrolyte disorder necessary for the patient?

Phosphorus

- Commonly in shortage
- Particularly essential for muscle contractility (cardiac and diaphragmatic), oxygen transport (2,3 DPG)
- Increased demand in patients with traumatic and thermal injuries, undergoing hepatic resection, receiving carbohydrate-based feedings, insulin therapy, or in those with refeeding syndrome

Etiologies for Hypophosphatemia

(most are untreatable short-term)

- Malnourished patients
- Alcoholism
- Refeeding Syndrome
- Drugs (calcium, antacids, phos-binders)
- Hepatic Resection
- Critical Illness/Traumatic and Burn Injury
- Hyperparathyroidism
- Cancer (fibroblast growth factor-23)

Should We Target a Serum Phosphorus Concentration of 4 mg/dL During Intravenous Phosphorus Shortages?

- Serum phosphorus < 2 mg/dL detrimentally influences organ function
- Where did the target of 4 mg/dL come from?
Why do we target a serum phosphorus concentration of 4.0 in ICU patients if the normal range is ~2.5 to 4.5 mg/dL?

Aubier et al. NEJM. 1985;313:420-4

Why it is Difficult to Achieve a Serum Phosphorus Concentration of 4 mg/dL in ICU Patients

• Cytokines/catecholamines
• Increased energy expenditure
• Augmented renal clearance
• Renal phosphate threshold concentration

Dickerson et al. JPEN. 2001;26:153-4.

IV Phosphorus Dosing for Hospitalized Patients

• Serum Phosphorus Concentration (mg/dL)
  • Dosage (mmol/kg)
  General/ICU
  • 2.3 to 3 mg/dL
    • 0.16
    • High needs
  • 1.6 to 2.2 mg/dL
    • 0.32
    • 0.64
  • ≤ 1.5 mg/dL.
    • 0.64
    • 1

Infuse Intravenous Phosphorus at 7.5 mmol/hr
- HALF DOSES FOR PATIENTS WITH KIDNEY IMPAIRMENT!

Sodium Glycerophosphate

• Available for use in the US (due to IV phosphate shortages) from Fresenius Kabi
• Organic form of phosphorus – used extensively in Europe
• Compatible in PN solutions
• 20 ml single use plastic vial (1 mmol/mL of Phosphorus; 2 mEq sodium per mmol of phosphorus)

INTRAVENOUS PHOSPHORUS SOURCES

Potassium Phosphate
- Monobasic
- Dibasic

Sodium Phosphate

Sodium Glycerophosphate

* Only available in single use vials

Enteral Phosphorus Options

• Phos-NaK = 250 mg Phos (8 mmol) + 7.1 mEq K, 7.1 mEq Na.
  Available in powder or capsule. Dissolve 1 packet or open capsule into ~75 mL of water
• Kphos Neutral = Potassium and Sodium Phosphate tablets = 250 mg Phos (8 mmol) + 13 mEq Na + 1.1 mEq K.
  • Practical for significant deficiency?
  • Diarrhea
Should We Target a Serum Phosphorus Concentration of 4 mg/dL During Intravenous Phosphorus Shortages?

Perhaps a target serum phosphorus concentration of ≥ 3 mg/dL is acceptable?

Calcium: Another common IV electrolyte in shortage

- “Normal” values:
  - Total calcium: 8.5 to 10.5 mg/dL
  - Ionized calcium: 1.12 to 1.32 mmol/L
- Modified Orell equation: (0.8 mg/dL decrease in total calcium for every 1 g/dL decrease in serum albumin conc) – not accurate for ICU patients

Hypocalcemia Signs/Symptoms and Etiologies

- Chvostek’s/Trouseau’s
- Cramping/tetany
- Seizures
- CHF, hypotension
- Increased Q-T interval, arrhythmias
- Coagulation disorders
- Metabolic bone disease
- Parathyroidectomy
- Hypomagnesemia
- Malabsorption (?)
- Vitamin D deficiency
- Acute and chronic pancreatitis
- Renal failure
- Hyperphosphatemia

When Should Hypocalcemia Be Treated?

- Significant or symptomatic hypocalcemia or ionized calcium concentration < 1 mmol/L
- Massive blood transfusion with pre-existing myocardial disease
- Calcium channel blocker overdose
- Receiving inotropic agents and/or vaspressors?
- Adjunct to emergent management of severe hyperkalemia
- Coagulopathy or high risk for bleeding?
- Prevention of worsening hypocalcemia???

Calcium Gluconate Dosing Guidelines

Continuous Infusion NOT Necessary!

<table>
<thead>
<tr>
<th>Ca Dose (g)</th>
<th>Ionized Ca</th>
<th>Ionized Ca</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 – 1.12</td>
<td>&lt; 1 mM/L</td>
</tr>
<tr>
<td>(n=29)</td>
<td>(n=8)</td>
<td>(n=8)</td>
</tr>
<tr>
<td>1</td>
<td>8/8 (100%)</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>15/21 (71%)</td>
<td>2/5 (40%)</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>0/2 (0%)</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>1/1 (100%)</td>
</tr>
</tbody>
</table>

20 patients if Ca < 1 mM/L
4 g Calcium Gluconate over 4 hours
if Ca > 0.90 to 1.6 it is 0.11 mM/L
14/20 (70%) corrected over a single 4 g dose
19/20 (95%) > 1 mM/L
2 pts if Ca > 1.34 and 1.38 mM/L after 4 g dose

Dickerson RN et al. JPEN.2007;31:228-233.

Calcium Gluconate Dosing Guidelines for Intravenous Use

<table>
<thead>
<tr>
<th>Ionized Calcium Gluconate (mmol/L)</th>
<th>Calcium Gluconate Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.00 – 1.12</td>
<td>2 g IVPB over 2 hrs</td>
</tr>
<tr>
<td>&lt; 1.00</td>
<td>4 g IVPB over 4 hrs</td>
</tr>
</tbody>
</table>

Dickerson RN et al. JPEN.2007;31:228-233.
Treatment Considerations for Hypocalcemia (for lower risk patients)

• If symptomatic or if the ionized calcium is < 1 mmol/L, treat with calcium and magnesium (if serum magnesium is below normal)
• If asymptomatic/ionized Ca > 1 mmol/L, may just treat with magnesium – iCa should correct within 2 days of therapy with magnesium

Calcium Gluconate vs Calcium Chloride

<table>
<thead>
<tr>
<th></th>
<th>Calcium Gluconate</th>
<th>Calcium Chloride</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Volume</td>
<td>10 mL</td>
<td>10 mL</td>
</tr>
<tr>
<td>g per 10 mL</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>mEq</td>
<td>4.65</td>
<td>13.6</td>
</tr>
</tbody>
</table>

Prescribing:
- 1 g in 50 or 100 mL NS. Infuse over 1 hr
- 2 g in 100 mL NS. Infuse over 2 hrs
- 4 g in 250 mL NS. Infuse over 4 hrs

Oral Calcium Therapy (not suggested for an iCa < 1 mmol/L)

• For more stable, non-critically ill patients
• Calcium carbonate (40% elemental Ca)
• 500 mg to 1 g three to four times daily to achieve an elemental calcium intake of 1200 to 1500 mg/day
• Often taken in conjunction with oral vitamin D

Potassium

• Keep serum K ≥ 4.0 mEq/L?
• “Normal” serum concentration: 3.5 to 5.2 mEq/L
• Hypokalemia (serum K < 3.5 mEq/L) occurs in 21% of hospitalized patients* (may be more frequent in patients receiving nutrition therapy)
• ECG changes not consistent with presence of hypokalemia*
• Most cases of hypokalemia-induced rhythm changes occur in those with underlying heart disease*


Hypokalemia

Etiologies (The “At Risk” Population)

• Decreased intake – rare with oral diet (kidneys adapt)
• Increased requirements due to building of new muscle/tissue (refeeding syndrome) or hypermetabolic states
• Increased gastrointestinal losses
• Hypermagnesemia
• Medications (diuretics, insulin, beta adrenergic agonists, catecholamines, amphotericin B)
• Intracellular shift with alkalosis
• Increased urinary losses (diabetes insipidus)

Hypomagnesemic Hypokalemia

• About 50% of clinically significant hypokalemic patients have hypomagnesemia
• Magnesium is co-factor for Na-K-ATPase pump
• Intracellular magnesium binds Renal Outer Medullary Potassium (ROMK) channels in distal nephron and inhibits K efflux
• If hypomagnesemic, hypokalemia is refractory to potassium therapy alone
• If hypomagnesemic, must treat both!

Empiric IV Dosing Guidelines for Potassium

<table>
<thead>
<tr>
<th>Serum K (mEq/L)</th>
<th>Potassium Dosage (mEq)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.5 – 3.9</td>
<td>40 to 60 mEq X 1 dose</td>
</tr>
<tr>
<td>3.0 – 3.4</td>
<td>40 mEq X 2 doses</td>
</tr>
<tr>
<td>&lt; 3</td>
<td>40 mEq X 3 doses</td>
</tr>
</tbody>
</table>

*Given at 10 mEq/hr. Use half doses for renal impairment; may need to be adjusted based on body size, nutrition therapy, and ongoing losses. Patients with TBI had an attenuated response. Excluded patients with confounding factors. Johnston CT et al. JPEN.2017;41:796-804.

Potassium Therapy and PN

- “Additional” potassium may be added to the PN solution
- Different salt forms available: chloride, acetate, phosphate
- “Standard K” ~ 40 mEq/L or 80 to 100 mEq/d (0.5 to 1.2 mEq/kg/d)
- “Repletion K” ~ 60 to 80 mEq/L or 120 to 160 mEq/d (1.5 to 2 mEq/kg/d)
- Consider using commercially available KCl containing IV solutions (e.g., D5 0.45% NaCl with 20 or 40 mEq of KCl per liter) if necessary

Oral or Enteral Potassium Therapy

- 95% to 100% bioavailable enterally
- “Safer” and often preferred over IV unless contraindicated or severe/symptomatic potassium deficiency
- Slow-release tabs are generally better tolerated or more palatable than effervescent or liquid, but wax-matrix tabs (higher incidence of GI erosions) – Don’t administer via tube!
- KCL liquid can be given via intragastrically (flush tube well if EN)
- Do not administer via the small bowel - diarrhea (osmolality)
- Signs/Symptoms
  - Muscle weakness, cramping, parasthesias
  - Positive Chvostek’s and Trouseau’s signs
  - Tetany
  - QT prolongation: cardiac arrhythmias (PVCs, tach, fibr)
  - Hypocalcemia
  - Hypokalemia
- Etiologies
  - Gastrointestinal losses
  - Septic/critical illness
  - Drugs – brad, laxatives, diuretics, cyclosporin, tacrolimus, foscarnet, amphotericin B, ciprofloxin, carboplatin, ifosfamide, cetuximab, pentamidine
  - Alcohol
  - Pancreatitis
  - Thermal injury

Hypomagnesemia

- Normal serum conc.: 1.8 to 2.4 mg/dL
- When do patients become symptomatic? Serum magnesium < 1.2 to 1.5 mg/dL?*
- Should the target serum magnesium concentration be > 2 mg/dL in patients without heart disease, hypokalemia, hypocalcemia, or symptoms?


Empiric Dosing Guidelines for IV Magnesium Sulfate

<table>
<thead>
<tr>
<th>Serum Magnesium Conc (mg/dL)</th>
<th>Dosage of IV Magnesium Sulfate (g/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.6 – 1.8</td>
<td>0.05</td>
</tr>
<tr>
<td>1 – 1.5</td>
<td>0.1</td>
</tr>
<tr>
<td>&lt; 1</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Half doses for those with renal impairment; Infuse at ~ 1 g/hr

Trauma patients, serum Mag < 1.5 mg/dL (mean, 1.1 mg/dL)
Given IV infusion of 0.125 or 0.19 g/kg

Magnesium Therapy
(during shortage)

- Magnesium therapy generally take 4 to 7 days of therapy to replenish deficit following initial IV loading dosage
- Serum magnesium < 1.5 mg/dL (~1 – 1.5 mEq/kg deficit)
- Serum magnesium < 1mg/dL (~2 mEq/kg deficit)
- Serum magnesium concentrations take 24 to 48 hrs to equilibrate post intravenous dose
- Oral magnesium replenishment may be tried for a serum concentration > 1.2 to 1.5 mg/dL if patient is asymptomatic and if the etiology for the hypomagnesemia is not GI-related (empiric recommendation)

Oral Magnesium Therapy

<table>
<thead>
<tr>
<th>Salt form</th>
<th>Strength</th>
<th>Elemental</th>
<th>Usual Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gluconate</td>
<td>500 mg</td>
<td>2.2 mg/kg</td>
<td>1-2 tabs TID</td>
</tr>
<tr>
<td>Urase</td>
<td>400 mg</td>
<td>140 mg</td>
<td>1-2 tabs TID</td>
</tr>
<tr>
<td>Chloride</td>
<td>tablet</td>
<td>2.6 mg/kg</td>
<td>2 tabs daily</td>
</tr>
</tbody>
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</tr>
<tr>
<td>Chloride</td>
<td>tablet</td>
<td>2.6 mg/kg</td>
<td>2 tabs daily</td>
</tr>
</tbody>
</table>

Multi-Electrolyte Intravenous Solutions

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Plasma Lyte A</th>
<th>Isolyte S</th>
<th>Normosol R</th>
<th>Lactated Ringers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (mEq/L)</td>
<td>140</td>
<td>140</td>
<td>148</td>
<td>140</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Chloride (mEq/L)</td>
<td>98</td>
<td>106</td>
<td>98</td>
<td>109</td>
</tr>
<tr>
<td>Magnesium (mEq/L)</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

Influence of Multi-Chamber Bag PN Solutions upon Electrolyte Needs for (All) PN Patients

<table>
<thead>
<tr>
<th>Electrolyte</th>
<th>Individual PN</th>
<th>Two Chamber MCB-PN</th>
<th>Three Chamber MCB-PN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (mEq/L)</td>
<td>0 – 130</td>
<td>35</td>
<td>32</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>20 – 80</td>
<td>30</td>
<td>24</td>
</tr>
<tr>
<td>Calcium (mEq/L)</td>
<td>5</td>
<td>4.5</td>
<td>4</td>
</tr>
<tr>
<td>Magnesium (mEq/L)</td>
<td>0 – 15</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Phosphorus (mmol/L)</td>
<td>0 – 30</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Acetate (mEq/L)</td>
<td>51 to 80*</td>
<td>59</td>
<td>63</td>
</tr>
<tr>
<td>Chloride (mEq/L)</td>
<td>39</td>
<td>46</td>
<td>50</td>
</tr>
</tbody>
</table>

Target Electrolyte Concentrations: K > 4.0 mEq/L, Phos > 3.0 mg/dL, Magnesium > 2.0 mg/dL

Electrolyte Shortage-Induced Acid-Base Disorders

- Sodium Acetate
- Sodium Chloride
- Potassium Acetate
- Potassium Chloride
- Magnesium Chloride
- Sodium Bicarbonate

*dependent on amino acid concentration


Influence of Multi-Chamber Bag PN Solutions upon KPhos Prescribing for Non-Critically Ill Patients

<table>
<thead>
<tr>
<th>Electrolyte</th>
<th>Individual PN</th>
<th>MCB-PN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (mEq/L)</td>
<td>50</td>
<td>70</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Calcium (mEq/L)</td>
<td>4.5</td>
<td>4.5</td>
</tr>
<tr>
<td>Magnesium (mEq/L)</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Phosphorus (mmol/L)</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>Acetate (mEq/L)</td>
<td>70</td>
<td>80</td>
</tr>
<tr>
<td>Chloride (mEq/L)</td>
<td>39</td>
<td>39</td>
</tr>
</tbody>
</table>

- Previously well-nourished, stable post-op patients with delayed return of bowel function after bowel surgery
- Target Phosphorus Concentration: Phos > 3.0 mg/dL? (not given)
- Given 30 mmol of Phos given daily via MCB-PN (2 L/d), 16,440 mmol of Phos conserved for the year
- Because of a 14 fold increase in cost of KPhos (during shortage period), use of MCB-PN solutions resulted in overall cost savings compared to individualized PN prescriptions.

65 yo male. Prolonged ileus. An average of ~400 mL/d NG suction and ~1600 mL/d jejunostomy drainage (for abd decompression).

PN (1.3 x BEE, 1.8 g/kg/d of protein, and 1.9 L/d of fluid).
Supplemental fluids: 0.9% NaCl ± 0.45% NaCl. Total chloride and acetate intakes from PN and supplemental IV fluids (mEq/d): 430 mEq and 60 mEq. Stable PN for 2 months.

SHORTAGE: No K Acetate; No Na Acetate!

ABG pH 7.28, PCO2 36, HCO3 17: mild non-AG (hyperchloremic) metabolic acidosis

Sodium bicarbonate 50 mEq/day X 3 days

Supplemental fluid changed to Lactated Ringers soln ~ 2 liters/day (provided 56 mEq of lactate and reduced chloride by 90 mEq/day)

ABG: 7.36, PCO2 35, HCO3 30 (vent weaning trials)

**Shortage of Intravenous Fluids**

0.9% NaCl (large volume) shortage
- Initiation of oral rehydration fluid protocol*
- 30% reduction in IV fluid use; 15% reduction in emergency dept*

0.9% NaCl (small volume) shortage
- Repackaging of large volume 0.9% NaCl to piggyback bags
- Purchase pre-mixed medications
- Syringe pumps or small volume infusion devices for medications

Resources for Managing Shortages of Parenteral Nutrition Components and Multi-component Products

Disclosure: I have no commercial relationships to disclose.

Presentation Overview/Summary
Shortages of parenteral nutrition (PN) have been ongoing for almost three decades. Historically, they were intermittent and short-lived. Since 2010, almost every component used in the preparation of PN admixtures has been in short supply and the duration of shortages has been months to years. Providing PN therapy is particularly challenging as multiple ingredients used in the PN may simultaneously be in limited supply and the availability of PN components must be considered during every step of the PN use process from ordering the PN prescription to administering this therapy to a patient. Several federal and healthcare professional organizations have developed resources to assist clinicians in managing shortages. This session will discuss these resources, their features and how to use them in developing institutional efforts and PN product-specific guidance for optimizing patient care and minimizing the potential for adverse health outcomes during shortages.

Learning Objectives
At the conclusion of the presentation, the learner will be able to:
1. explain the role of the FDA in preventing and mitigating medication shortages.
2. identify resources for guidance in selecting appropriate alternative(s) during shortages of PN components and multi-component products.
3. identify resources for developing policy and procedures for managing shortages of PN components and multi-component products.

Key Takeaways/Fast Facts
- Shortages of PN components and multi-component products continue and despite efforts from federal agencies, healthcare providers, group purchasing organizations and pharmaceutical industry no enduring solution(s) to preventing shortages has been identified.
- The American Society for Parenteral and Enteral Nutrition (ASPEN) offers resources for general and component-specific management of shortages of PN components and multi-component products.
- Report any adverse

Learning Assessment Questions
1. The Food and Drug Administration Safety and Innovation Act (FDASIA) gives the FDA Commissioner the authority to require a pharmaceutical manufacturer to make more of a medication.
   A. True
   B. False
2. Which organization publishes conservation and management strategies specifically for managing shortages of PN components and multi-component products?
   A. Institute for Safe Medication Practices (ISMP)
   B. American Hospital Association (AHA)
   C. American Society of Health-System Pharmacists (ASHP)
   D. American Society for Parenteral and Enteral Nutrition (ASPEN)
3. Medication errors or adverse event associated with shortages of PN components and multi-component products should be reported to the Agency for Healthcare Quality and Research (AHRQ).
   A. True
   B. False

4. The best resource for a healthcare system pharmacy developing policies and procedures for identifying and managing shortages of PN components and multi-component PN products is the
   A. American Hospital Association (AHA).
   B. American Pharmacists Association (APhA).
   C. American Society of Health-System Pharmacists (ASHP).
   D. American Society for Parenteral and Enteral Nutrition (ASPEN).

5. The FDA Drug Shortage web site list of medications in short supply includes only medications that are considered medically necessary.
   A. True
   B. False

Learning Assessment Answers:
1. Answer = False; Rationale: FDASIA requires pharmaceutical manufacturers to notify the FDA of a potential shortage or permanent discontinuance or interruption in the production of medications. The FDA cannot require manufacturers to make a drug, produce more of a drug or change how the drug is distributed.

2. Answer = D; Rationale: All organizations, ISMP, ASHP and AHA, provide resources on drug shortages. However, ASPEN is the organization that publishes guidance specific to managing shortages of PN components and multi-component products.

3. Answer = False; Rationale: Medication errors and adverse patient outcomes associated with shortages should be reported to the Institute for Safe Medication Practices Medication Error Reporting Program and the FDA MedWatch. Although AHRQ’s mission is to produce evidence to make health care safer, higher quality, more accessible, equitable, and affordable it does not collect information on medication-related adverse events.

4. Answer = C; Rationale: ASHP provides resources outlining the responsibilities and tasks for pharmacists and pharmacy technicians for each phase of drug shortage management. AHA and APhA have public policy statements regarding drug shortages but not management strategies. ASPEN’s PN component shortage management strategies are specific to PN components but do not guidance for every phase of the management process.

5. Answer = True; Rationale: The FDA’s priority is on medications considered medically necessary, which are those intended to prevent or treat a debilitating disease or condition. The ASHP drug shortage list includes any medication with a supply issue that affects how pharmacies prepare and dispense a product or when prescribers must choose an alternative therapy due to supply issues.

References
Disclosure: I have no commercial relationships to disclose.

Presentation Overview/Summary
Shortages of parenteral nutrition (PN) components pose a great threat to the health of anyone who relies on parenteral therapy. In order for the nutrition specialists to mitigate these threats they first must have an understanding of the normal requirements for their patients. This session will review the recommended intakes for protein, trace elements and cysteine and will discuss alternative products and routes of administration. The session will also briefly some electrolyte replacement strategies.

Learning Objectives
At the conclusion of the presentation, the learner will be able to:
1. Review the protein requirements of the adult and pediatric patient
2. Discuss the micronutrient needs of the adult and pediatric patient
3. Formulate plans for the use of alternative intravenous shortage components
4. Discuss potential safety issues when utilizing alternative strategies to address parenteral component shortages

Key Takeaways/Fast Facts
- Shortages continue to stifle efforts to provide adequate nutrition to our patients. Often we have to employ alternative strategies to provide for the patient’s well-being and in doing so may place the patient’s safety at risk.
- Little formal information is available to help mitigate these risks

Learning Assessment Questions
1. The American Society for Parenteral and Enteral Nutrition (ASPEN) provides guidelines for the safe use of nutritional components.
   A. True
   B. False
2. Multichamber Bag Parenteral Nutrition (MCB-PN) Products are a collection of closed system products that provides full nutrition support to meet the needs of most patients needing parenteral nutrition.
   A. True
   B. False
3. Zinc deficiency in neonates can result in the patient developing
   A. Hypotonia
   B. Anemia
   C. Growth failure
   D. Glucose metabolism
4. What percent of the average adult’s protein content makes up the body cell mass (BCM)
   A. 12.5%
   B. 25%
   C. 80-85%
   D. 50%
5. According to the World Health Organization the safe level for protein intake for a 1 year old is
   A. 2.25 g/kg
Learning Assessment Answers:
1. Answer = True; ASPEN as an organization is dedicated to providing evidence based nutrition support for our patients.
2. Answer = F; Although the products currently available in the marketplace provide a wide range of options in providing nutrition support they don’t meet the needs of a majority of patients, particularly the neonatal and pediatric patient.
3. Answer = C. Zinc plays an important role in linear growth of the neonate. Copper deficiency can result in hypotonia and anemia whereas chromium deficiency can lead to abnormal glucose metabolism.
4. Answer = D. Approximately 50% of the body’s protein makes up the body cell mass. Of the body cell mass skeletal muscle makes up 80-85%
5. Answer = C. According to the World Health Organization the safe level for protein intake for a 1 year old is 1.14 g/kg with the average requirement of only 0.95 g/kg.

References
12. Notes from the Field: Zinc Deficiency Deficiency Dermatitis in Cholestatic Extremely Premature Infants After a Nationwide Shortage of Injectable Zinc — Washington, DC, December 2012
Metabolic Support in the Era of PN Component Shortages: Amino Acids, Trace Elements and Cysteine

Learning Objectives
1. Review the protein requirements of the adult and pediatric patient
2. Discuss the micronutrient needs of the adult and pediatric patient
3. Formulate plans for the use of alternative intravenous shortage components
4. Discuss potential safety issues when utilizing alternative strategies to address parenteral component shortages

ASPEN Recommendations for Conservation of PN Products
Consider oral or enteral administration
Prioritize patients, saving supplies for those most vulnerable patients
Eliminate adding injectable electrolytes/minerals to enteral nutrition products
Minimize the use of additives to daily maintenance IV fluids
Reevaluate replacement algorithms or treatment protocols
Carefully evaluate alternative supplies of individual and multiple electrolyte products that are available, including standardized, commercially available PN products

Protein Needs-Adult

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable Patients</td>
<td>0.8-1 g/kg/d</td>
</tr>
<tr>
<td>Critically Ill</td>
<td>1.5-2 g/kg/d</td>
</tr>
<tr>
<td>Severe malnutrition, acute or chronic kidney injury-with or without renal replacement therapies, hepatic disease, trauma, obese, burns, etc.</td>
<td>See Clinical Guidelines/Scientific literature</td>
</tr>
</tbody>
</table>

Basic Protein Needs-Adult

- Approx 50% of the protein in the body makes up the body cell mass (BCM)
  - Represents ~50% of a healthy male and 40% of a healthy female
- The other 50% of the protein in the body is structural and metabolically inactive
- Skeletal muscle makes up 80-85% of the BCM in normal adults whereas the remaining 15-20% consists of fat free mass of the organs, plasma proteins, blood cells and immunological cells
- Estimated minimum protein requirement of ~0.66 g/kg/day
- Obligatory losses are ~0.3 g/kg/day
**Stressed Protein Needs**

- Generally accepted to be 1.5-2.5 g/kg or greater depending on multiple factors
  - Trauma
  - Sepsis
  - Synthesis of 1 g fibrinogen would require the degradation of 2.6 g muscle protein
  - Burns
  - Open wounds
  - CRRT

**Protein Needs**

<table>
<thead>
<tr>
<th>Age group</th>
<th>Protein needs of the pediatric patient (g/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low birth</td>
<td>2.5-3</td>
</tr>
<tr>
<td>Preterm</td>
<td>2-2.5</td>
</tr>
<tr>
<td>Infant/infants</td>
<td>1.5-2</td>
</tr>
<tr>
<td>Preschool/elementary age</td>
<td>1.5-2</td>
</tr>
<tr>
<td>Adolescent</td>
<td>0.8-1.5</td>
</tr>
</tbody>
</table>

**Basic Protein Needs**

**Basic Protein Needs-Peds**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Maintenance requirement</th>
<th>Growth requirement</th>
<th>Average requirement</th>
<th>Safe level</th>
<th>1989 Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.58</td>
<td>0.86</td>
<td>1.23</td>
<td>1.50</td>
<td>1.65</td>
</tr>
<tr>
<td>2</td>
<td>0.58</td>
<td>0.86</td>
<td>1.73</td>
<td>1.86</td>
<td>1.67</td>
</tr>
<tr>
<td>3</td>
<td>0.58</td>
<td>0.78</td>
<td>1.49</td>
<td>1.24</td>
<td>1.41</td>
</tr>
<tr>
<td>4</td>
<td>0.58</td>
<td>0.78</td>
<td>1.34</td>
<td>1.16</td>
<td>1.30</td>
</tr>
</tbody>
</table>

1. Calculated from maintenance value of 0.50 (balance results with egg and milk). Table 20, plus growth.
2. Growth requirement is derived from population-averaged from Table 21, adjusted for 80% efficiency of maintenance.
3. Calculated from mean value of 1.0 g/kg/day. Bases the 1.5 kg value with that of the 0.50 values for the growth requirement (Table 21, adjusted for 80% efficiency of maintenance and 80% for maintenance and 80% efficiency of maintenance.

**Amino Acid Needs-Neonate**

- If given dextrose alone, infants lose 1-2% endogenous protein stores daily
- 1 g/kg/day achieves protein balance
- 2.5-4 g/kg/day allows accretion (i.e., newborn energy requirement)
- CAN START SOON AFTER BIRTH (within hours)
  - Prevents state of catabolism after birth
Amino Acid Needs-Neonate

• Plasma amino acid profiles of neonates vary with gestational age

• Neonates have immature metabolic systems
  - lack hepatic enzymes needed to convert methionine to cysteine that is
    converted to taurine (conditionally essential amino acids)

• Neonates given "adult/standard" amino acid solutions tend to have
  abnormal amino acid profiles and poor growth

Current Amino Acid Formulations- Pediatric/Neonates

• Trophamine
• Aminosyn PF
• Premasol
  - designed to match plasma amino acid profiles of healthy breast fed infants
  - contain less methionine/glycine/phenylalanine
  - contain conditionally essential amino acids taurine, glutamate, aspartate
  - contain a higher percentage of the branch chain amino acids
    leucine/isoleucine/valine

Current Amino Acid Formulations - "Adult"

• Travasol
• Aminosyn
• Freamine
• Plenamine
• Clinisol
• Prosol
• Procalamine (for peripheral or central)

Multichamber Bag Parenteral Nutrition (MCB-PN) Products

ASPIN Definition
“A standardized parenteral nutrition formulation available from a manufacturer and requiring fewer compounding steps before administration. Examples of these products are concentrated amino acids (with or without electrolytes), concentrated dextrose and with or without intravenous lipid emulsions in multi-chamber bags.

The term “premixed” should be avoided as these products require activation and mixing prior to administration.

ASPIN recommends to consider utilizing in patients depending on needs and resources

ASPIN shortage recommendations- consider one of these products if appropriate
Multichamber Bag Parenteral Nutrition Products

- Advantages
  - Convenient
  - Improved safety

- Disadvantages
  - May not meet the needs of certain patients
  - Cost?

Use in Pediatrics
- Electrolyte imbalances seen
  - 33% Metabolic alkalosis
  - 20% Hyperkalemia
  - 20% Hyperphosphatemia
  - 13% Hypokalemia
  - 7% Hypophosphatemia and hyponatremia
  - 7% Hyperphosphatemia and metabolic alkalosis

Conclusion:
- Appeared to be safe and effective for at least a short period of time
- Patients require close monitoring
- Another option during PN component shortages

When Electrolyte Supplementation Needed
- Clinimix-E
  - Uses inorganic phosphate and calcium gluconate
- Kabiven
  - Uses organic phosphate and calcium chloride

Compatibility Concerns
- Calcium and magnesium
  - Calcium chloride and magnesium sulfate
    - Calcium sulfate (used to make Plaster of Paris)
- Zinc and phosphorus
  - Zinc hypophosphate

Response to component shortage
- 69 patients and 74 courses of therapy
- Age range 1.1 - 18 yrs
- 5.6-7.2 days duration
- 20% discontinuation rate due to lab abnormalities
- 22% required additional fluids
- 38% required change to individualized therapy based on labs results
- 98% of protein goal met
- 67% met calorie goals
### Sodium Salt Substitutes

<table>
<thead>
<tr>
<th>Product</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table salt</td>
<td>~100 mEq/tsp</td>
</tr>
<tr>
<td>Salt tablets</td>
<td>17 mEq/1 gram</td>
</tr>
<tr>
<td>Sodium bicarbonate tablets</td>
<td>7.71 mEq/850 mg</td>
</tr>
<tr>
<td>0.9% NaCl injection</td>
<td>0.154 mEq/mL</td>
</tr>
<tr>
<td>3% NaCl injection</td>
<td>0.5 mEq/mL</td>
</tr>
<tr>
<td>5% NaCl injection</td>
<td>0.85 mEq/mL</td>
</tr>
</tbody>
</table>

### Electrolyte Alternatives

- Potassium
  - 10 mEq/100 mL injection
  - Various oral potassium chloride products
  - Potassium citrate effervescent tab
  - Potassium Salt substitutes

### Additional Oral Salt Substitutes

<table>
<thead>
<tr>
<th>Product</th>
<th>mEq per tsp</th>
<th>mg per tsp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table Salt</td>
<td>102 sodium</td>
<td>2360 sodium</td>
</tr>
<tr>
<td>Morton Lite Salt</td>
<td>50 sodium</td>
<td>35 potassium 1160 sodium 1400 potassium</td>
</tr>
<tr>
<td>Morton’s Salt Sub</td>
<td>62.5 potassium</td>
<td>2440 potassium</td>
</tr>
</tbody>
</table>

### Concentrated Electrolytes-Caution

- Use when only absolutely necessary
- Communicate, communicate, communicate
- Return to standard concentrations as soon as possible then communicate, communicate, communicate
- ISMP Alert-May 24, 2018. Safe Handling of Concentrated Electrolyte Products From Outsourcing Facilities During Critical Shortages
  - Labeling requirements different from medical manufacturers

### Trace Element Requirements

#### Pediatric

- Zinc, mcg/kg/day
  - Preterm infant: 400
  - Term infant: 250
  - Children: 50 (3000 mcg)
- Copper, mcg/kg/day
  - Preterm infant: 20
  - Term infant: 20
  - Children: 20 (100 mcg)
- Chromium, mcg/kg/day
  - Preterm infant: 0.2
  - Term infant: 0.2
  - Children: 0.2 (5 mcg)
- Manganese, mcg/kg/day
  - Preterm infant: 1
  - Term infant: 1
  - Children: 1 (50 mcg)
- Selenium, mcg/kg/day
  - Preterm infant: 2
  - Term infant: 2
  - Children: 2 (20 mcg)

---

*Sources: Sriram 2009, Green 1988*
Trace Element Shortage Zinc

CDC Report
- 3 infants 23-24 wks gestation with cholestasis
- 2 developed biopsy proven dermatitis
- Improvement with oral supplementation

Why is Zinc So Important
- Essential cofactor in approximately 300 enzyme-dependent processes
- Fetal zinc accumulation via placental transport is maximal at 24–34 weeks of gestation
- Inadequate zinc supplementation leads to cutaneous changes, diarrhea, immunologic impairment, growth failure, and poor wound healing

Trace Element Shortage Copper
- Most common features with deficiency include anemia, leucopenia, bone lesions (scorbutic-like bone changes and occipital horn), and vesical diverticula
- In children, some commonly noted findings are hypotonia, psychomotor retardation, and hypothermia
- During shortage copper may not needed in newborns for the first 3 weeks (preemies may need earlier)
- Presence of cholestasis does not ensure adequate copper concentrations

Trace Element Shortage Chromium
- Involved in carbohydrate metabolism
- In very low birth weight newborns chromium deficiency has been associated with increased risk for intraventricular hemorrhage, late-onset bacterial sepsis, necrotizing enterocolitis, and death
- Improved glucose tolerance and carbohydrate delivery demonstrated in very low birth weight newborns supplemented with chromium
- In adults, is there a need to supplement d/t contamination in the PN

Trace Element Shortage Selenium
- Essential nutrient that serves several important functions, including anti-oxidative defense through the actions of glutathione peroxidase as well as thyroid hormone
- Metabolism through the actions of iodothyronine deiodinase
- Deficiency implicated as a cause of cardiomyopathy and death

Trace Element Shortage Selenium
- Do we need to supplement?
  - 5 pediatric patients >1 yr age with intestinal failure
  - Full PN support
  - All 5 developed severe biochemical selenium deficiency
  - No morbidity associated with the deficiency
Trace Element Shortage Selenium

Do we need to supplement?

- 6 infants with selenium deficiency were studied retrospectively
- Onset of selenium deficiency in five patients occurred at <6 mo of age
- All patients had developed growth retardation and alopecia with pseudo-albinism

Trace Element Shortage Treatment Options

- Importation
- Oral products
- Sublingual admin?
  - Zinc sublingual dots
  - Zinc SL solution- 1 mL held under tongue
  - SL Selenium and chromium

L-Cysteine

- Conditionally essential amino acid in neonates
- Improves nitrogen retention
- Normal dose is 40 mg/g of protein
- Improves calcium/phosphate solubility and dosing by decreasing pH

L-Cysteine Other Uses Contributing to Shortage

- Increases chloride load of solution
  - Occasionally used a source of chloride ions when traditional sources can’t be used
    - NaCl, KCl, Arginine
- Used as a catheter clearing agent replacing 0.1N HCL which is problem to compound when following USP <797> guidelines
  - Has approximately the same pH as 0.1N HCL
  - Cheap
  - Already in a sterile ready-to-use vial

L-Cysteine Shortage Considerations

- If there is some product available, restrict L-cysteine supplementation in PN to neonates ≤1 kg or those neonates >1 kg who are at high risk for cysteine deficiency such as neonates who are post-surgical or those with sepsis.
- Normal needs for PN L-cysteine are estimated to be 30-40 mg/g of protein provided. However, studies have documented that as little as 20 mg/g of protein provided is adequate.
- Assess each patient as to the indication for PN and provide nutrition via the oral or enteral route when possible.
- Purchase only as much L-cysteine injections supply as needed. In the interest of fair allocation to all patients nationally, please do not stockpile.
- Reconsider / discourage using L-cysteine as an agent to re-establish intravascular access catheter patency.
- If cysteine is needed strictly to improve calc:phos solubility consider using the imported organic phosphate.
L-Cysteine Shortage Safety Issue

- If cysteine dose is reduced may affect solubility tables
  - Consider not using the cysteine compatibility tables in the ACD

Conclusion

Parenteral nutrition component shortages continue to frustrate the efforts of nutrition support specialists in proving adequate care.

References