Vitamin and Mineral Supplementation in Enteral and Parenteral Nutrition

Department of Pediatrics
Dell Medical School
The University of Texas at Austin
sabrams@austin.utexas.edu
Objectives

- Interpret literature related to mineral requirements in IV nutrition
- Identify issues related to trace minerals provided in IV nutrition
Case: Extreme malnutrition in neonate

- 23 week, 506 g infant
- Transferred at 10 weeks of age from hospital in Texas due to inability to feed and inability to place/maintain CVL
- Ventilated, minimal oxygen
- Rickets and long-bone fracture
- Transferred with minimal history, PIV only
Labs on admission

- Conj bili 4.9 mg/dL
- Albumin 1.7 g/dL
- Phosphorus 2.5 mg/dL
- Alk phos 323 IU/L
- Zinc 68 microg/dL (low normal)
- Serum copper 14 microg/dL (normal 75-153)

Begun on Omegaven, TPN with CVL 4 g/kg/d protein, supplemental copper, continue trace minerals daily.
Diagnoses

- Severe protein-energy malnutrition. Prealbumin < 5, very low BUN
- Profound copper deficiency
- Rickets
- Liver disease, likely inflammatory-mediated due to TPN, malnutrition, recurrent infections
- All of these diagnoses could be avoided with good nutritional management and use of novel lipid products
Hypocalcemia: Definition

- No absolute definitions. Usual values are:
  - Babies ≥ 1500 g
    - Total calcium (Ca) < 8.0 mg/100 mL (2mM) – don’t measure total Ca in first week of life.
    - Ionized calcium (iCa) < 4.4 mg/dl = 1.1 mM
    - Usually no symptoms unless < 1.0 mM
  - VLBW infants (< 1500 g)
    - Total Ca < 7.0 mg/100 mL (1.75 mM)
    - iCa < 4 mg/100 mL (1.0 mM)
    - Usually no symptoms unless < 0.8 mM
TPN: Minerals and Micronutrients

- Minerals
  - Increase Ca/Phos **slowly** to up to 1.75-2.0 mmol/dL over 5-10 days. Caution in babies < 1000 g birth weight (BW).
  - Begin phos 1:1 With Ca by 24-30 hours of age. It is acceptable to begin within first 6 hours of life.
  - We usually limit to 1-1.2 mmol/kg/d each of Ca and Phos in infants < 1000-1250 for first 4-5 days to prevent hypercalcemia
  - Make minimal changes in the Ca/Phos ratio in most infants.
  - Hypocalcemia is uncommonly a problem in VLBW infants, Accept iCa > 0.80 mmol/L in most cases and rarely if ever should calcium be given by bolus to VLBW infants.
Early hypocalcemia (first 3-4 days of life)

- Prematurity
  - Impaired PTH function, etiology unknown
  - Infants of diabetic mothers: 10-20% or more
    - Excess calcitonin and inadequate PTH function
- Cardio-respiratory depression at birth
  - Increased phosphate load from tissue catabolism
  - We are seeing with fluid restriction in cooled infants
- Intrauterine growth retardation (IUGR)
  - Decreased transplacental Ca and phosphorus transfer
- Maternal long-term magnesium sulfate therapy (rare)
- Severe maternal vitamin D deficiency (rare in US)
- Hyperventilation, exchange transfusion
Interventions

- Prevention via early TPN in high-risk populations
  - Early TPN. No benefit to separate infusion.
- Symptomatic
  - Boluses of Ca should be followed by a continuous infusion in almost every case
  - Hypomagnesemia ($\leq 1.5 \text{ mg/100 mL}$): Suppresses PTH
    - Magnesium sulfate 25 mg/kg/dose (0.2 mEq/kg/dose) q12 hours IV over 2 hours. Usually 2 doses.
Does vitamin D deficiency cause symptomatic hypocalcemia?

- Maternal vitamin D deficiency can cause symptomatic neonatal hypocalcemia.
  - Probably rare in US but limited data.
  - Recent case series of 19 babies in Qatar*.
  - Symptomatic hypocalcemia (13 seizures, 5 jittery, 1 stridor), mean age about 9 days.
  - Serum 25-OHD mean of 9 ng/mL (range 3 to 18 ng/mL), in mothers was 6 ng/mL (range 4 to 12 ng/mL).

Case: Itsy bitsy baby with hypercalcemia

- Asked to see infant at 72 hours of age due to ionized calcium of 1.84 mmol/L (mM)

- History:
  - Born at 580 g and 24 3/7 weeks gestation
  - Started on TPN at 2 hours of age providing 1.2 mmol/dL Ca, no P. IV rate = 100 mL/kg/d
  - At 60 hours of age, 1.2 mmol/dL phosphorus (P) added
  - Serum P = 3.1 mg/dL, serum Mg = 1.8 mg/dL
  - Infant is asymptomatic, remains on ventilator
Etiology/symptoms

- Probably a combination of low usage of Ca for bone formation, limited renal calcium excretion
- May also have high P utilization
- Not usually primarily related to vitamin D or PTH
- Most commonly seen in ELBW infants. Very common < 750 g birthweight
- Extremely high iCa seen on DOL 3-5: iCa may exceed 2.0 mmol/L – values that are life-threatening in older children
Etiology/Symptoms (cont.)

- Relatively common to have mild hypercalcemia (total Ca 11-12 mg/dL or iCa 1.45-1.6 mM). Probably a non-disease.

- Hypercalcemic neonates do not have symptoms, but serious concern for peripheral or CNS calcification.

- Also seen in cardiac babies given calcium infusions.

- Can occur if KPhos and KCl are stopped for > 48 hours due to concern of K excess in any infant.
Hypercalcemia: Therapy

- Start P within 24 hours of life in most cases in VLBW infants to prevent hypercalcemia. Usually 1:1 mmol:mmol with Ca.*
- Mild-moderate hypercalcemia (iCa 1.4-1.7 mM) – decrease TPN Ca infusion to < 1 mmol/dL
- Some infants only tolerate 0.3-0.5 mmol/dL Ca in TPN with increase of 0.1-0.2 mmol/dL daily.
- If severe (iCa > 1.7-1.8 mM), stop all TPN calcium and recheck in 12-24 hours.
- Can persist in smallest infants for several weeks.

*Ca is 40 mg = 1 mmol and P is 31 mg = 1 mmol
Case: Rickets in ELBW infant

- Asked to see an infant due to an incidental finding on a chest X-ray of two rib fractures with subsequent measurement of serum alk phos of 1480 IU/L
  - History: Former 25 2/7 week, 760 g male with history of BPD, sepsis, medical NEC not requiring surgery
  - Now 53 days old and weight 1560 g. Tolerating feeds of 120 mL/kg/day of a specialized formula with high MCT. TPN stopped DOL #51
  - Continues on mechanical ventilation. Medications include low-dose IV hydrocortisone and furosemide
Factors contributing to rickets

- **Major:**
  - ELBW (< 1000 g birth weight)
  - Long-term TPN
    - Although full TPN has enough Ca and P to avoid rickets, often have fluid restriction or mineral intake limitation in long-term TPN.
  - Steroids
    - Often a major etiology. Steroids block Ca absorption, increase renal losses and demineralize bone directly.
Other factors

- Use of non-preterm formula
  - Low Ca and P content relative to needs.
  - May have inhibitors of Ca absorption (e.g. soy protein)
- Fluid restriction
  - Critical unrecognized factor.
- Nutrient malabsorption secondary to bowel injury?
Less likely to be involved

- Immobility
- Loop diuretics
  - Usually use furosemide which causes approximate doubling of urinary Ca. Smaller factor in rickets than intake decreases.
- Vitamin D deficiency
  - Rarely principal factor in VLBW infants.
X-ray findings in infants with rickets

Abnormalities of metaphyses
Fraying and cupping
Dense line (healing)
Findings similar to older infants with rickets
More information

- Further lab evaluation to include:
  - Serum P, conjugated bilirubin/other liver function tests.
  - Serum 25-OHD (not 1,25-OH\(_2\)D), PTH, fractionated (bone-specific) alkaline phosphatase activity may be considered, but difficult to identify normal values.
- Needs X-rays of at least one wrist or knee.
# Recommendations

## Table 4. Recommendations for Enteral Nutrition for VLBW Infants

<table>
<thead>
<tr>
<th></th>
<th>Calcium mg/kg/day</th>
<th>Phosphorus mg/kg/day</th>
<th>Vitamin D IU/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tsang et al (2005)³²</td>
<td>100-220</td>
<td>60-140</td>
<td>150-400*</td>
</tr>
<tr>
<td>Klein (2002)³³</td>
<td>150-220</td>
<td>100-130</td>
<td>135-338†</td>
</tr>
<tr>
<td>Agostoni (2010)⁶</td>
<td>120-140</td>
<td>65-90</td>
<td>800-1000</td>
</tr>
<tr>
<td>This AAP clinical report</td>
<td>150-220</td>
<td>75-140</td>
<td>200-400</td>
</tr>
</tbody>
</table>

* Text says “aim to deliver 400 IU/daily.”
† 90-125 IU/kg (total amount shown is for 1.5-kg infant).
Some details of AAP recommendations for preterm infants

- When infants reach a body weight >1500 g and tolerate full enteral feeds, vitamin D intake should generally be approximately 400 IU/day, up to a maximum of 1000 IU/day.
- Serum APA >800 to 1000 IU/L or clinical evidence of fractures should lead to a radiographic evaluation for rickets and management focusing on maximizing calcium and phosphorus intake and minimizing factors leading to bone mineral loss.
- A persistent serum P concentration < about 4.0 mg/dL should be followed, and consideration should be given for P supplementation.

Abrams SA and Committee on Nutrition, AAP, Pediatrics, May 2013
Vitamin D in high risk infants

- Dietary requirements have on-going research and controversy.
- **Routine** assessment of vitamin D status in all preterms is not part of IOM/AAP recommendations. We do not recommend it.
  - Also not recommended in all older children (AAP Oct. 2014)
- Screening may be considered with rickets, bowel or liver disease, poor nutritional status or some chronic illnesses such as renal failure.
  - Target 25-OHD ≥ 20 ng/mL
Hypercaldemia

- Monitor iCa – should usually be between 0.8 and 1.45 mmol/L in VLBW and 1.0 and 1.45 mmol/L > 1500 g BW.
  - Mild hypercalcemia (1.45-1.6 mmol/L) – Usually do nothing. If increasing rapidly, decrease Ca and usually Phos (typically to 0.5 mmol/mL each).
  - Do not remove all of the calcium unless iCa > 1.8 mmol/L.
- DO NOT leave magnesium or phosphorus out of TPN beyond about 24-36 hours of age unless lab tests show markedly elevated values.
## Calcium Gluconate

#### Guidelines to Conserve Calcium (and Phosphorus)

<table>
<thead>
<tr>
<th>Neonatal Patients</th>
<th>&lt;1500 grams</th>
<th>&gt;1500 grams</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Calcium Gluconate</strong></td>
<td>1.5 mmol/100 mL</td>
<td>0.6 mmol/100 mL</td>
</tr>
<tr>
<td><strong>Phosphorous</strong></td>
<td>1.5 mmol/100 mL</td>
<td>0.6 mmol/100 mL</td>
</tr>
</tbody>
</table>
| **Exceptions** | • Fluid restriction  
• Increase alkaline phosphatase | • Rickets  
• Severe fluid restriction (<80 mL/kg/day)  
• Dialysis patients |
Calcium Supplementation

- Calcium bolus
  - Non-physiologic
  - Potentially harmful
  - Should not be a standard way to administer maintenance calcium to a neonate

- Calcium Chloride
  - Use for all separate IV infusions and boluses
  - Consider removing calcium gluconate and continue phosphorus supplementation in TPN
  - Not recommended to be added to TPN or with phosphate-containing solutions
  - Extravasations could occur – central line access preferred
Potassium Phosphate

- Restricted for patients who require intravenous phosphorus supplementation and cannot be managed with sodium phosphate and potassium chloride.
- Patients must meet one of the following indications:
  - Serum sodium greater than 150 mmol/mL
  - Serum potassium less than 3 mmol/L and chloride greater than 110 mmol/L
Sodium Glycerophosphate

FDA approved a temporary importation of Glycophos® to alleviate the shortage

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Potassium Phosphate</th>
<th>Sodium Phosphate</th>
<th>Sodium Glycerophosphate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphate Concentration</td>
<td>3 mmol/mL</td>
<td>3 mmol/mL</td>
<td>1 mmol/mL</td>
</tr>
<tr>
<td>Type of Phosphate</td>
<td>Inorganic</td>
<td>Inorganic</td>
<td>Organic</td>
</tr>
<tr>
<td>Sodium</td>
<td>X</td>
<td>1.3 mEq/mL</td>
<td>2 mEq/mL</td>
</tr>
<tr>
<td>Potassium</td>
<td>1.4 mEq/mL</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
Sodium and Potassium Acetate

- Restricted for neonatal patients who require an intravenous alkalinizing agent and cannot be managed with sodium bicarbonate

- Patients must meet one of the following indications
  - Birth weight less than 1,250 grams due to renal bicarbonate wasting
  - pH less than 7.25, acid base excess greater than 8 mmol/L and lactate less than 3 mmol/L
Sodium and Potassium Acetate

Consider adjusting NaCl or KCl when adding either NaAcetate or KAcetate

<table>
<thead>
<tr>
<th></th>
<th>TPN #1 (mEq/100 mL)</th>
<th>TPN #2 (mEq/100 mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaCl</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>KCl</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>NaAcetate</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>KAcetate</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Cysteine

- Conditionally-essential amino acid
- Decreases the pH of TPN solution to allow increased calcium and phosphorus solubility
- Evaluate solubility curves to optimize standard concentrations of calcium and phosphorous without cysteine
- Some do not use it in babies < 1 kg due to concern about acidosis
Cysteine

- Minimum amino acids 2%
  - Safely provides a standard amount of calcium and phosphorus 1.2 mmol/100 mL

- If infant requires less protein or more calcium or phosphorus
  - Discuss with prescriber to determine true need
    - Rickets, renal failure or metabolic?
  - Check solubility curve
    - Remember to refer to the curve without cysteine
Solubility Curve

Minimum amino acids 2%

- Safely provides a standard amount of calcium and phosphorus 1.2 mmol/100 mL

Texas Children’s Hospital Formulary with Permission of B. Brown Medical Inc, Irvine
Estimated Iron Requirement

- Birth: ≈ 75 mg
- 1 year: ≈ 360 mg
- Increment: = 290 mg/ yr
  \( \div 365 \) ≈ 0.8 mg/d
- Assume absorption: ≈ 10%
- Requirement: ≈ 8 mg/d
  ≈ 2 mg/kg/d

After Oski et al
IV iron

- Usually no transfusions in 2 weeks
- Serum ferritin not markedly elevated
- No ongoing bacterial infection
- Unlikely to be able to tolerate oral iron for 3-4 weeks or poor absorption is likely
- Likely to be inpatient for 2 weeks after start
- Physician isn’t too afraid to use it (anaphylaxis risk)
  - Current safety profile is excellent.
  - Issue is the anion it is with, not the Fe itself
  - “Only Thing We Have to Fear Is Fear Itself” (FDR)
Box 2
Sample protocol for iron dextran administration to TPN-dependent infants

Order anaphylaxis medications (diphenhydramine, hydrocortisone, and epinephrine) to bedside to be administered only per physician’s orders; physician must be present during test dose administration

Day 1: test dose: 0.2 mg IV once over 5 minutes
Day 2 of test dose: give iron dextran 0.5 mg IV once over 5 minutes
Day 3 of test dose: give iron dextran 0.8 mg IV once over 5 minutes
Monitor blood pressure during and after administration
Then start: iron dextran 1 mg IV every Monday, Wednesday, and Friday
Copper requirements

- **Parenteral**
  - 20 mcg/kg/day
  - Do not stop with cholestasis

- **Enteral**
  - AAP 108 mcg/kg/d
  - ESPGAN 117-156 mcg/kg/d
  - Formulas 100-250 mcg/100kcal
Neonatal copper deficiency

- Microcystic anemia, neutropenia, thrombocytopenia
- Hypothermia, hypotonia
- Apnea
- Depigmentation of skin, hair, prominent superficial veins
- Brittle “kinky” hair, pili torti
- Boney changes
  - Osteoporosis, fractures, metaphyseal cupping/spurs
  - Hepatosplenomegaly, conj hyperbilirubinemia
- Lethargy
- Recurrent infections
- Vascular rupture
- Death
Neonatal copper deficiency

- Biochemical
  - Low serum Copper - usually increases with age
    - We are especially concerned if < 50 microg/dL
  - Low ceruloplasmin (copper carrying protein)
  - Low eSOD (superoxide dismutase activity in erythrocytes)
Copper deficiency radiographs: Osteopenia and the symmetrical appearance of sickle-shaped metaphyseal cupping and spurs
Zinc Deficiency - Diagnosis

- Clinical signs esp. diaper rash
- Low alkaline phosphatase
- Low plasma Zn
  - Normal 60-100 µg/dL (prefer > 80)
  - Deficiency < 60 µg/dL
  - Severe deficiency < 40 µg/dL
- Hair/ RBC/ WBC/ Monocyte zinc
- RBC metallothionein
- Trial of therapy
Recommended zinc Intakes

- Preterm infants (enteral)
  - AAP: 600 mcg/kg/d
  - ESPGAN: 720 - 1440 mcg/kg/d
  - CPS: 1000 mcg/kg/d
  - Consensus: 1000 mcg/kg/d

- Parenteral
  - AAP/ESPGAN/CPS
    - 400-500 mcg/kg/d
Trace mineral packages

Table 3. Preterm Infant Parenteral Trace Element Recommendations and Product Comparison Table.\(^3,10,11,12,13,14\)

| Trace Element | ASCN Preterm Recommended Dosage,\(^{10}\) mcg/kg/d | A.S.P.E.N. Preterm Recommended Dosage,\(^{1}\) mcg/kg/d | ESPGHAN Preterm Recommended Dosage,\(^{11,12}\) mcg/kg/d | Multitrace-4 Neonatal (American Regent), per mL\(^{13}\) | Multitrace-4 Neonatal Dosing\(^\text{a}\) (0.2 mL/kg/d), mcg/kg/d | Peditrace (Fresenius-Kabi),\(^{14}\) European, per mL
|----------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------
| Zinc           | 400                                           | 450–500                                       | 450–500                                       | 1.5 mg (1500 mcg) (as zinc sulfate)           | 300                                           | 0.25 mg (250 mcg) (as zinc chloride)
| Copper         | 20                                            | 29                                            | 20 (infant)                                   | 0.1 mg (100 mcg) (as cupric sulfate)         | 20                                            | 0.02 mg (20 mcg) (as copper chloride)
| Chromium       | 0.2                                           | 0.05–0.3                                      | Recommendation to add none                    | 0.85 mcg (as chromic chloride)               | 0.17                                          | None                                          
| Manganese      | 1                                             | 1 (infant)                                    | 1 (infant)                                    | 0.025 mg (25 mcg) (as manganese sulfate)     | 5                                             | 0.001 mg (1 mcg) (as manganese chloride)    
| Selenium       | 2                                             | 1.5–4.5                                       | 2–3                                           | None                                          | NA                                            | 2 mcg (as sodium selenite)                  
| Iodide         | 1                                             | 1 mcg/d (infant)                              | 1                                             | None                                          | NA                                            | 1 mcg (as potassium iodide)                 
| Molybdenum     | 0.25                                          | 1 (not currently added to PN in the United States) | 1 (LBW infant)                               | None                                          | NA                                            | None                                          
| Iron           | 100–200 (not currently added to PN in the United States) | 200                                           | 50–100 (infant)                               | None                                          | NA                                            | None                                          
| Fluoride       | No recommendation                             | No recommendation                             | No recommendation                             | None                                          | NA                                            | 57 mcg (as sodium fluoride)                 

\(^{a}\)Dosing recommendations per package inserts: Multitrace-4 Neonatal: Recommendations for preterm infants up to 3 kg—zinc, 300 mcg/kg/d; copper, 20 mcg/kg/d; manganese, 2–10 mcg/kg/d; chromium, 0.14–0.2 mcg/kg/d\(^3\) (dosing of 0.2 mL/kg/d provides these amounts). Peditrace: General pediatric dosing recommendations—1 mL/kg/d should be adequate to meet the baseline trace mineral needs of pediatric patients.\(^{14}\)

\(^{\text{a}}\)Available for use in United States.
Summary

- Micronutrients are key part of nutritional intake in high-risk infants
- Interactions, shortages and medical management remain problems for providing adequate intakes
- Intravenous use of iron, supplementation with zinc and copper need more consideration in special circumstances