Food for Thought:
Balancing Parenteral Nutrition Compounding Challenges

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Disclosures

Speaker Bureau: Fresenius Kabi

Any brand names utilized are for educational purposes only

Objectives

- Define the types of parenteral nutrition preparations and the typical components they are comprised of
- Identify some of the challenges that present when compounding parenteral nutrition orders
- List potential solutions to overcome compounding challenges to optimize both nutrition and safety
- Recognize potential safety concerns when preparing a parenteral nutrition order

INTRODUCTION TO PARENTERAL NUTRITION

Parenteral Nutrition (PN) Overview

Macronutrients

- Protein
- Carbohydrates
- Lipids

Micronutrients

- Sodium
- Potassium
- Calcium
- Magnesium
- Acetate
- Chloride
- Phosphate

Additives

- Multivitamins
- Trace Elements
- Medications
  - Heparin
  - Insulin
- Others
  - Levocarnitine
  - L-Cysteine

Mueller, C.M. (Ed.). The ASPEN Adult Nutrition Support Core Curriculum, 3rd Edition. 2017. Silver Spring, MD: ASPEN.

Types of Parenteral Nutrition

2-in-1

- 2 Bag System
  - Amino Acids + Dextrose + Electrolytes
  - Lipids run separately
- Components are y-sited together before infusing in the patient
- Filtered through a 0.2 micron filter
- ***More equipment and set-up time required***
- ***Greater contamination risk***

3-in-1

- 1 Bag System
  - Lipids included in the PN bag
- Less equipment and set-up time required
  - Better option for home PN patients
- ***Filtered through a 1.2 micron filter***
  - *Cannot filter bacteria*
- ***Increased stability concerns***
  - *Not recommended for Neonates*

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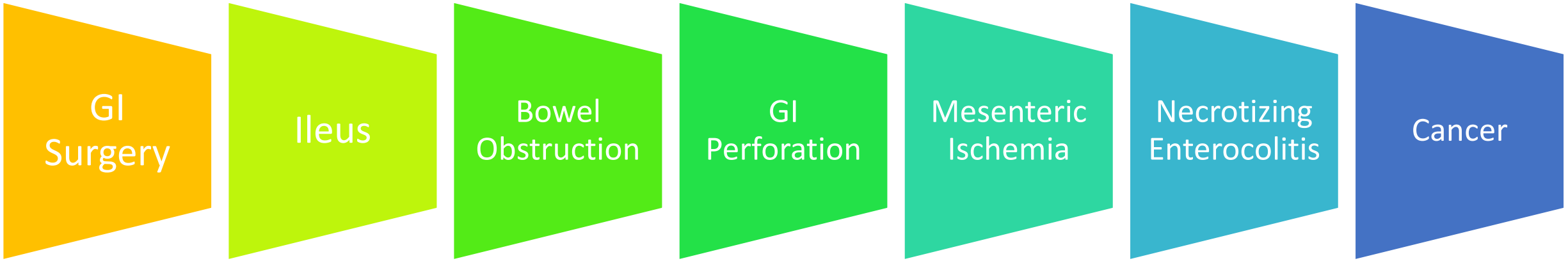
Mueller, C.M. (Ed.). The ASPEN Adult Nutrition Support Core Curriculum, 3rd Edition. 2017. Silver Spring, MD: ASPEN.
Mundi, M.S. et al. Management of Parenteral Nutrition in Hospitalized Adult Patients. 2017. JPEN, 41: 535-549.

Indications for Parenteral Nutrition

- The only true "diagnosis" that is associated with PN is Malnutrition
  - Patient must have also failed enteral feedings **OR**
  - The patient is not expected to feed enterally for at least 5-7 days*

- Some common disease states seen with PN include:



Worthington, P., et al. (2017), When Is Parenteral Nutrition Appropriate?. 2017. JPEN, 41: 324-377.

Warning Signs for Malnutriton

Adults

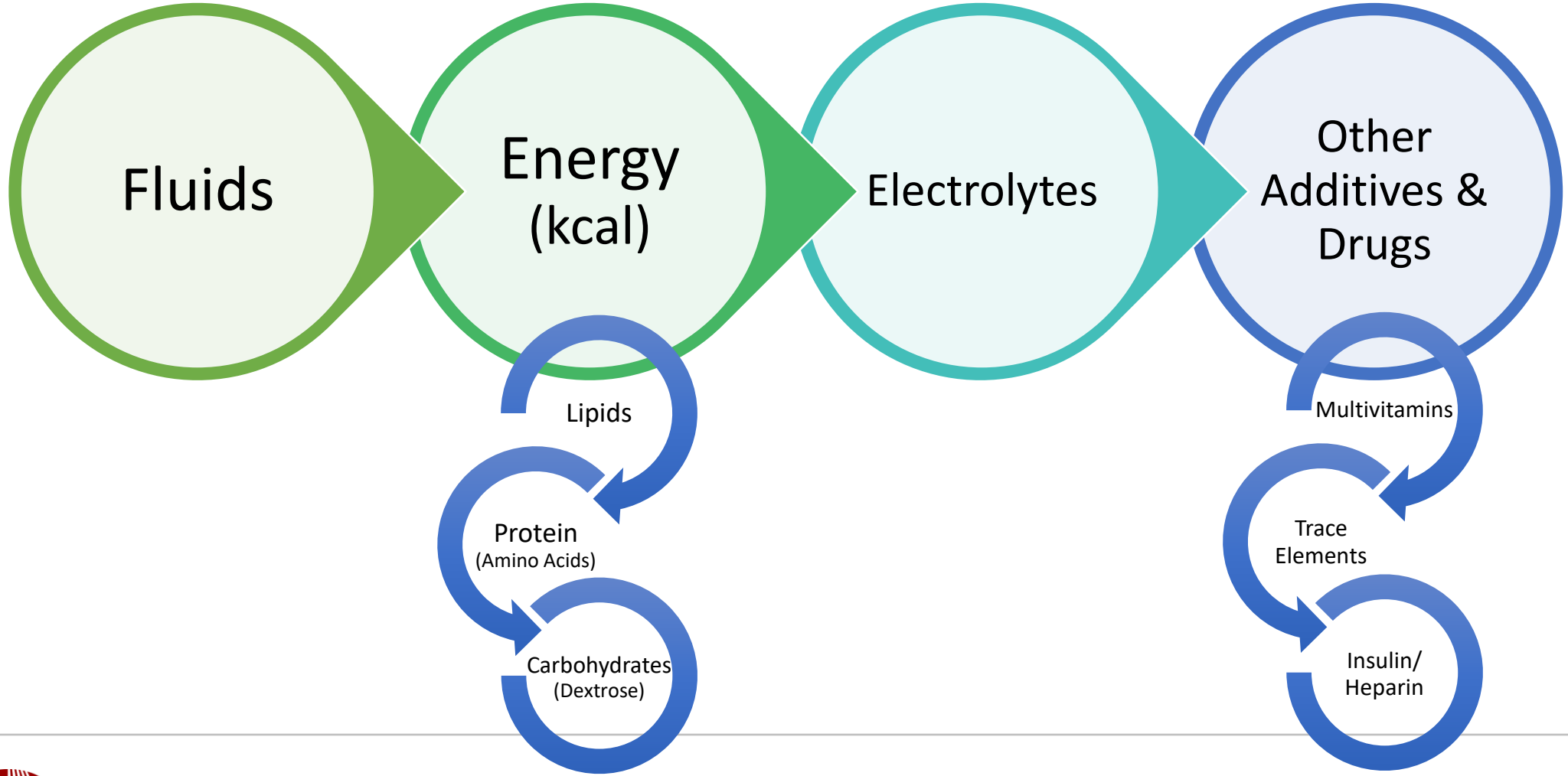
- Involuntary weight loss
  - 10% within 6 months
  - 5% within 1 month
  - 10lb within 6 months
- Body mass index (BMI) <18.5 kg/m^2
- Increased metabolic requirements
- Altered diets or diet schedules
- Inadequate nutrition intake
  - No nutrition for >7 days

Children

- Weight for length, height, or sex less than 10th percentile
- BMI for age or sex less than 5th percentile
- Increased metabolic requirements
- Impaired ability to tolerate oral feeding
- Inadequate provision of nutrients
- Inadequate weight gain or a significant decrease in usual growth percentile

Worthington, P., et al. (2017), When Is Parenteral Nutrition Appropriate?. 2017. JPEN, 41: 324-377.

Creating a PN Order



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COMPOUNDING PARENTERAL NUTRITION


Baxa
Windows
Embedded
WARNING

PN Compounding Fundamentals

Manual Compounding

- Ingredients are individually added by hand or by gravimetric compounder
- Good for institutions with low or inconsistent PN usage

Automated Compounding

- Utilization of technology to streamline the compounding process by sequentially adding ingredients into a bag automatically
- Ability to conduct volumetric & gravimetric checks
- More expensive, but cost must be weighed with overall utilization

Ayers P, et al. ASPEN Parenteral Nutrition Handbook, 3rd Edition. 2020. Silver Spring, MD: ASPEN.

PN Compounding Fundamentals

- PN is considered a **Medium Risk** sterile preparation
  - Based upon the risk of microbial contamination
  - Sterile compounding area must meet the requirements outlined by USP <797>
- Proper aseptic technique and use of laminar flow hoods are essential to maintain sterility throughout the compounding process

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USP <797> (2008) – Pharmaceutical Compounding – Sterile Preparations
Buchanan, E. C., Schneider, P. J., & Forrey, R. A. (Eds.). (2017). "Appendix A: ASHP Guidelines on Compounding Sterile Preparations". In Compounding Sterile Preparations. Bethesda MD, USA: American Society of Health-System Pharmacists.

PN Compounding Fundamentals

Compatibility

- Physical and Chemical coexistence of components within the bag

Examples of incompatibility include:

- Precipitate formation
- Color change
- pH changes

Stability

- Maintenance of chemical and physical integrity of the ingredients and the entire preparation

Examples of instability include:

- Ingredient degradation
- Lipid destabilization/separation

Mays A, et al. Safety in parenteral nutrition compounding. Nutr Clin Prac. 2023;38:1253-1262.

Compounding Challenges

Volume Required of Raw Ingredients

Pump Restrictions

Salt Availability

Stability of the Bag

- Calcium/Phosphorous solubility
- Lipid complications
- Other additives

Important Definitions

- **Total Volume:** the volume you ***intend*** to administer to the patient
  - All nutrients will be added based on this volume

- **Overfill:** ***extra*** volume included in a bag
  - Contains additional nutritional content in proportion to the total volume contents
  - Not counted as part of the total ordered volume

1. Volume of Raw Ingredients

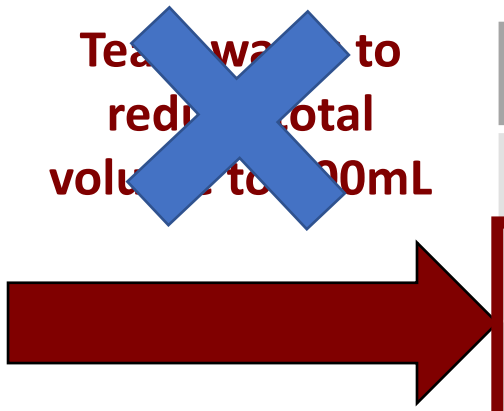
- When you are trying to create a volume restricted bag, there is a limit to how low the total volume can go

- Each ingredient requires a specific volume, when added up it cannot exceed the total volume

Overfill will NOT help you in this case

1. Volume of Raw Ingredients

PN Order	Dose
Total Volume	210mL
Protein	4 g
Dextrose	10%
Sodium	1 mEq
Potassium	1 mEq
Magnesium	0.3 mEq
Calcium	2 mEq
Phosphate	1 mmol



Pump Formula	Dose
Sterile Water	QS 111.7mL
Trophamine 10%	**69.6 mL**
Dextrose 70%	**33.6 mL**
Sodium phosphate	0.26 mL
Potassium phosphate	0.4 mL
Magnesium sulfate	0.13 mL
Calcium gluconate	7.5 mL
Multivitamins	3.5 mL

1. Volume of Raw Ingredients

Daily Requirements

Electrolyte	Preterm Neonates	Infants/Children	Adolescents & Children > 50 kg	Adults
Protein	3-4 g/kg	2-3 g/kg	1-1.5 g/kg	0.8-1.5 g/kg
Sodium	2-5 mEq/kg	2-5 mEq/kg	1-2 mEq/kg	1-2 mEq/kg
Potassium	2-4 mEq/kg	2-4 mEq/kg	1-2 mEq/kg	1-2 mEq/kg
Calcium	2-4 mEq/kg	0.5-4 mEq/kg	10-20 mEq	10-15 mEq
Phosphorus	1-2 mmol/kg	0.5-2 mmol/kg	10-40 mmol	20-40 mmol
Magnesium	0.3-0.5 mEq/kg	0.3-0.5 mEq/kg	10-30 mEq	8-20 mEq

Mueller, C.M. (Ed.). The ASPEN Adult Nutrition Support Core Curriculum, 3rd Edition. 2017. Silver Spring, MD: ASPEN.

2. Pump Restrictions

- Automated compounders have certain limitations and rules in order to accurately mix all ingredients into a final formula

- These rules are manufacturer-specific

2. Pump Restrictions

- Universal ingredient:
  60mL or higher
  - Water or Dextrose 70%
  - Used to flush the line
  - Combined total of 100mL also needed
- Minimum volume to pump:
  0.2mL
  - Otherwise manual addition needed

Adding overfill to the PN bag often helps correct these issues!

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3. Salt Availability

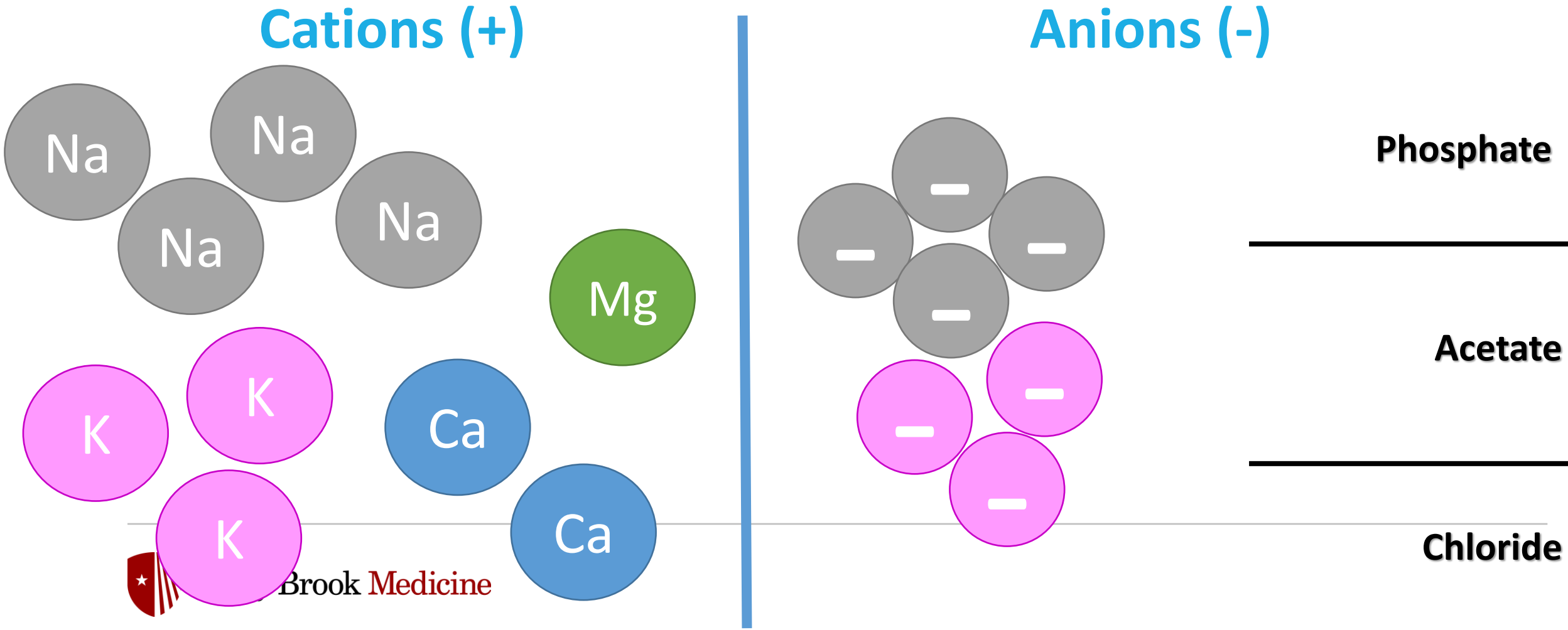
- Agents used for compounding are interrelated
- Limitations on one particular electrolyte may prevent optimization of other electrolytes due to salt pairing

Sodium	Phosphate Acetate Chloride
Potassium	Phosphate Acetate Chloride

Cations **Anions**

3. Salt Availability

PN Order:
- 4 mEq/kg Na
- 3 mEq/kg K
- 0.3 mEq/kg Mg
- 2mEq/kg Ca



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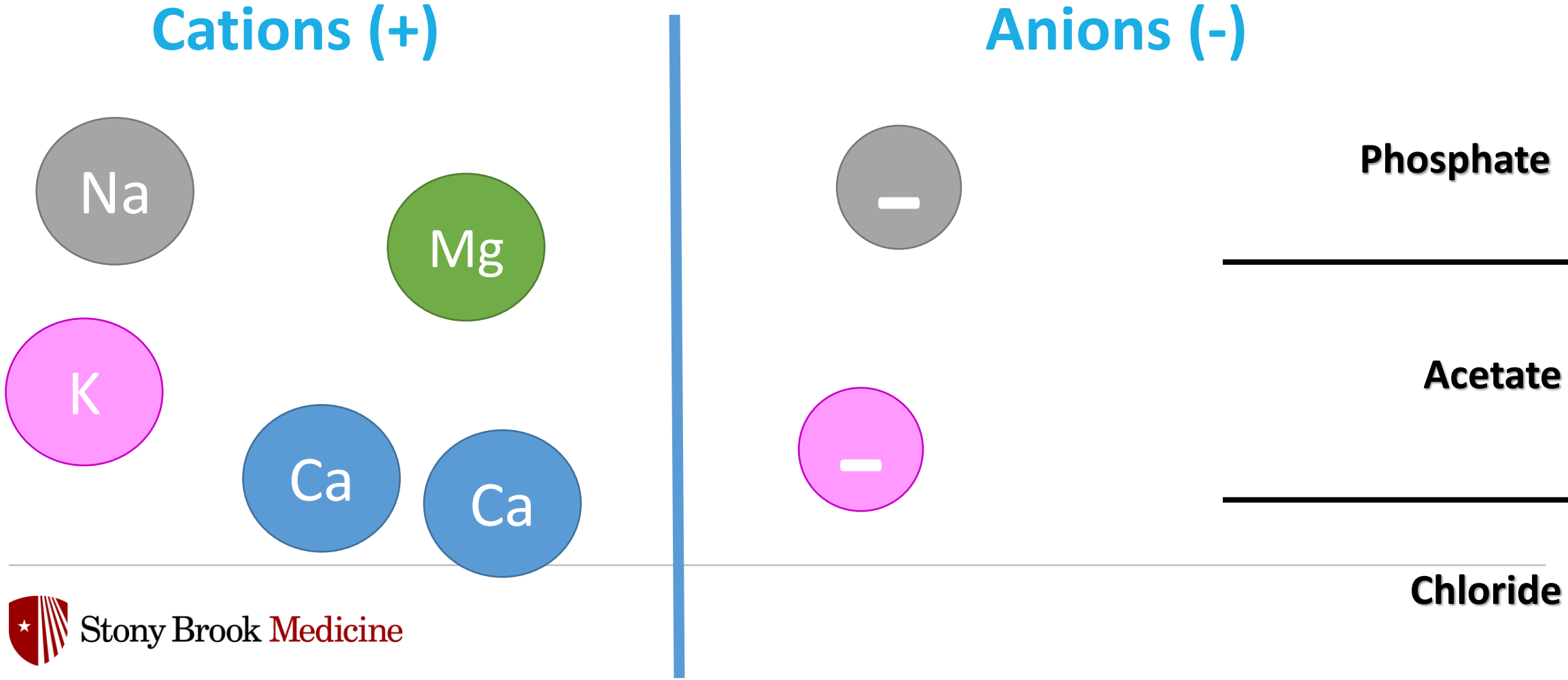
3. Salt Availability

PN Order:
- 1 mEq/kg Na
- 1 mEq/kg K
- 0.3 mEq/kg Mg
- 2mEq/kg Ca



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4. Stability of the Bag

Calcium/Phosphorous Solubility

- Calcium and Phosphorous tend to form an insoluble precipitate when exposed in their ionic forms
  - Calcium phosphate formation is a sign of PN instability
  - Appears as a while solid
- Dangerous as it can cause thrombosis & IV line occlusion
  - Higher risk in warm environments***

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Klang, M.G. (2015), PFAT5 and the Evolution of Lipid Admixture Stability. Journal of Parenteral and Enteral Nutrition, 39: 67S-71S.

4. Stability of the Bag

Calcium/Phosphorous Solubility

- Factors Affecting Solubility:

Total volume of PN	Doses of Ca + Phos • Inverse relationship	pH of formula • More acidic = better solubility	Type of Calcium Salt • Gluconate > chloride
2-in-1 formulas preferred	Type of Amino Acid • Trophamine for Pediatrics	Concentration of Amino Acids & Dextrose	Temperature (keep cool)

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Mays A, Ayers P, Monczka J, Cober MP. Safety in parenteral nutrition compounding. Nutr Clin Pract. 2023; 38: 1253-1262.

4. Stability of the Bag

Calcium/Phosphorous Solubility

- Implement Additive Sequencing when compounding
  - Ingredients are added in a specific order to minimize stability issues
    - Calcium is the last electrolyte added after most large volume components
  - Built into the programming of automated compounders
  - For manual compounding, use the following sequence:

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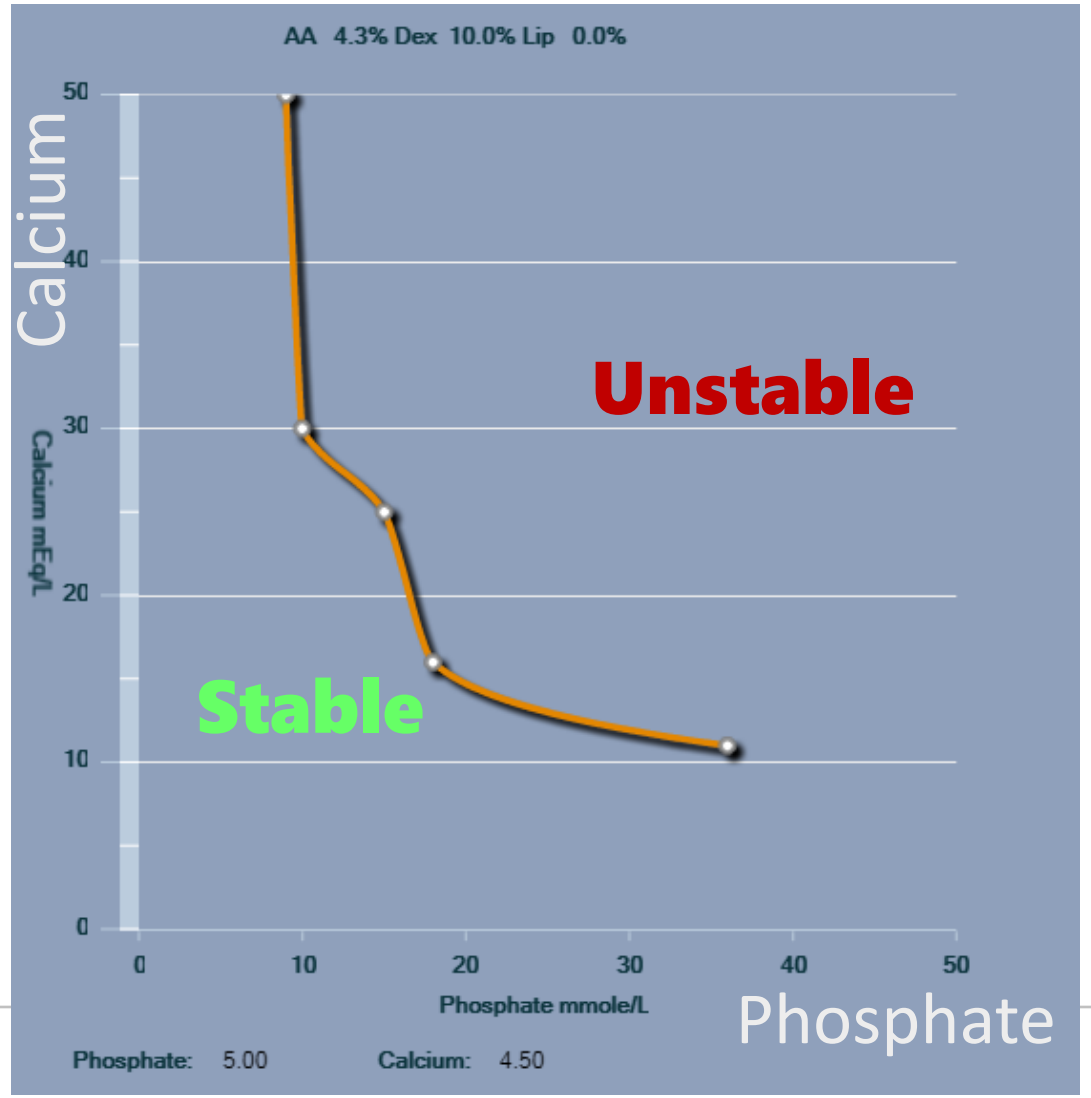
4. Stability of the Bag

- Solubility curves help to visualize and determine PN stability
  - Helps evaluate potential for precipitate formation
    - Total Volume
    - Calcium
    - Phosphate
    - Dextrose
    - Amino Acids



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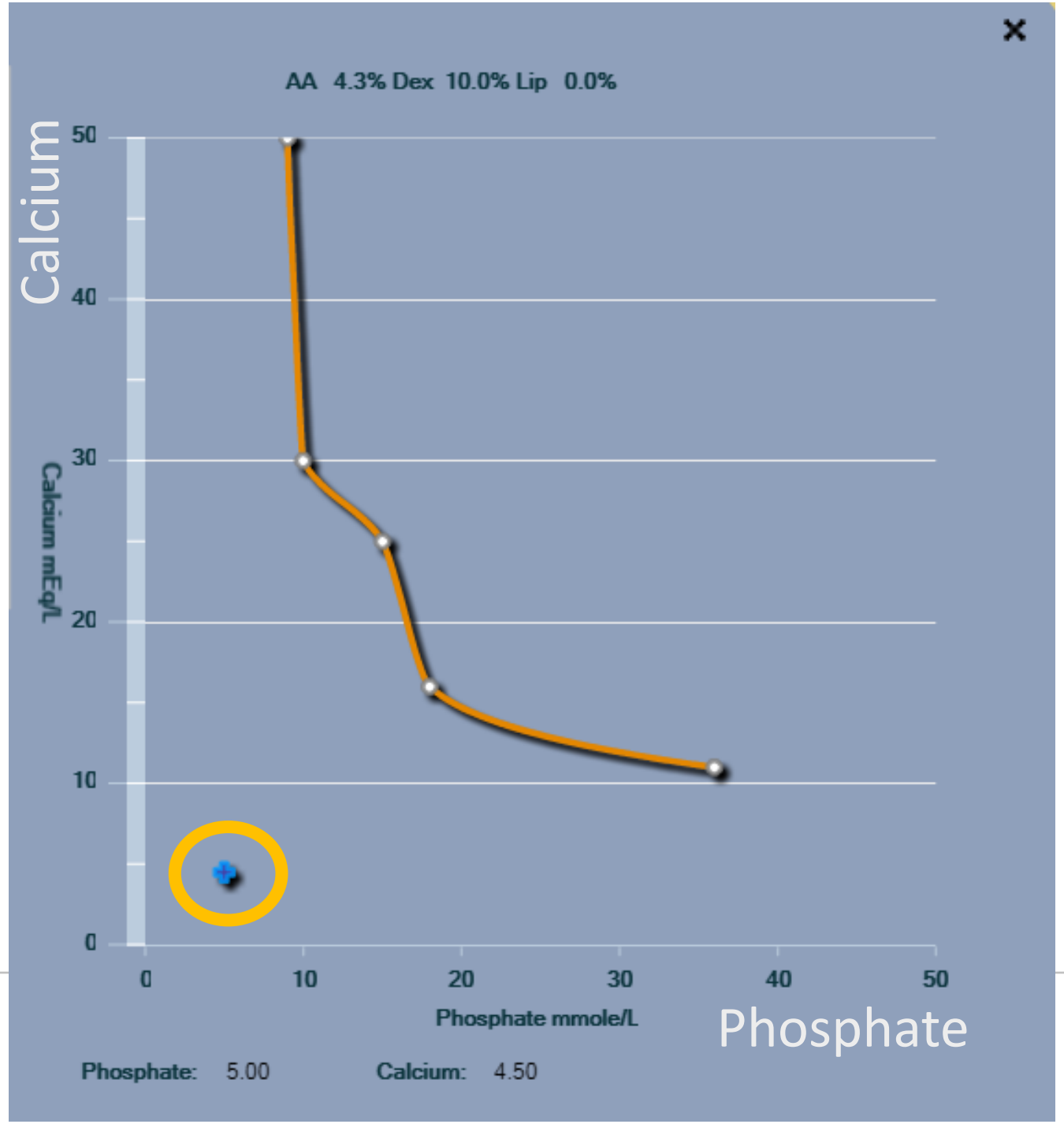
Solubility Curves



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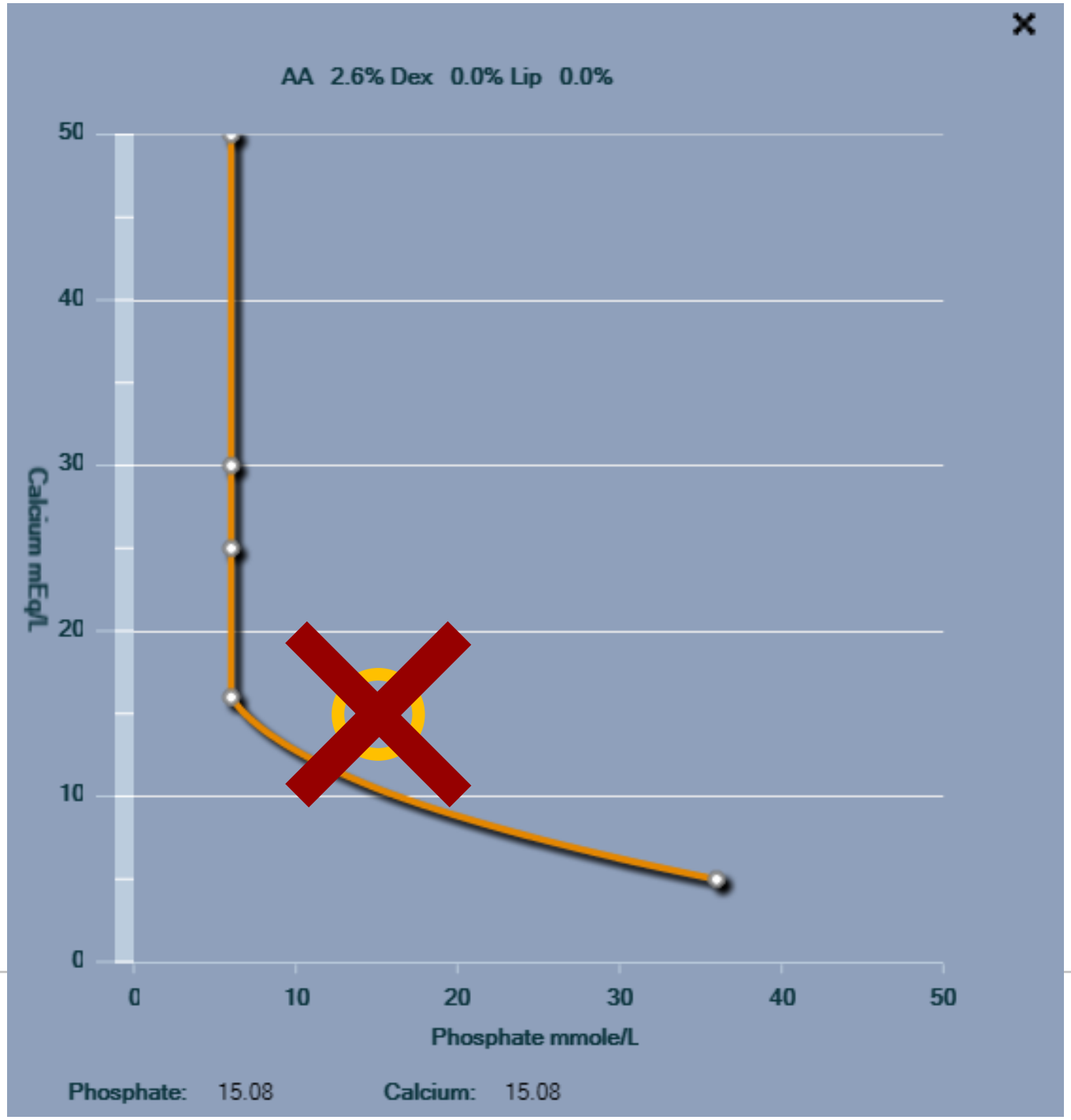
Solubility Curves



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4. Stability of the Bag

How Can We Fix an Insoluble Bag?

Increase the total volume

Dosage Adjustments

- ↓ Calcium
- ↓ Phosphate
- Dextrose*
- Amino Acids*

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4. Stability of the Bag

How Can We Fix an Insoluble Bag?

- There is no one answer!
- Every bag/patient has different needs
- **Try to limit aggressive changes**
  - May need to discuss with the team what their priorities are
  - Best interventions are to trim a little bit off of everything
  - *Interdisciplinary discussions are essential to maximize outcomes!*
- <u>Example:</u>

A slight increase in total volume of 10mL **+** a drop in Calcium by 0.5mEq/kg **=**
Phosphate dose falls by only -1mmol instead of -3mmol

4. Stability of the Bag
Lipid Stability

- Intravenous lipid emulsions (ILE) are specially formulated to isolate small oil molecules within an external hydrophilic phase
  - Maintains small molecule size
  - Relies on a negative polar charge (zeta potential) to repel other lipid particles
- The polarity between lipid particles may be disrupted based on
  - Low pH (less than 6)
  - Addition of electrolytes (too much Ca^{++} or Mg^{++})
  - Other additives (i.e. L-cysteine, iron)

Ayers P, et al. ASPEN Parenteral Nutrition Handbook, 3rd Edition. 2020. Silver Spring, MD: ASPEN.
Pertkiewicz M, et al. Basics in clinical nutrition: stability of parenteral nutrition admixtures. *e-SPEN*. 2009: e117-e119.
Klang, M.G. (2015), PFAT5 and the Evolution of Lipid Admixture Stability. Journal of Parenteral and Enteral Nutrition, 39: 67S-71S.

4. Stability of the Bag

Lipid Stability

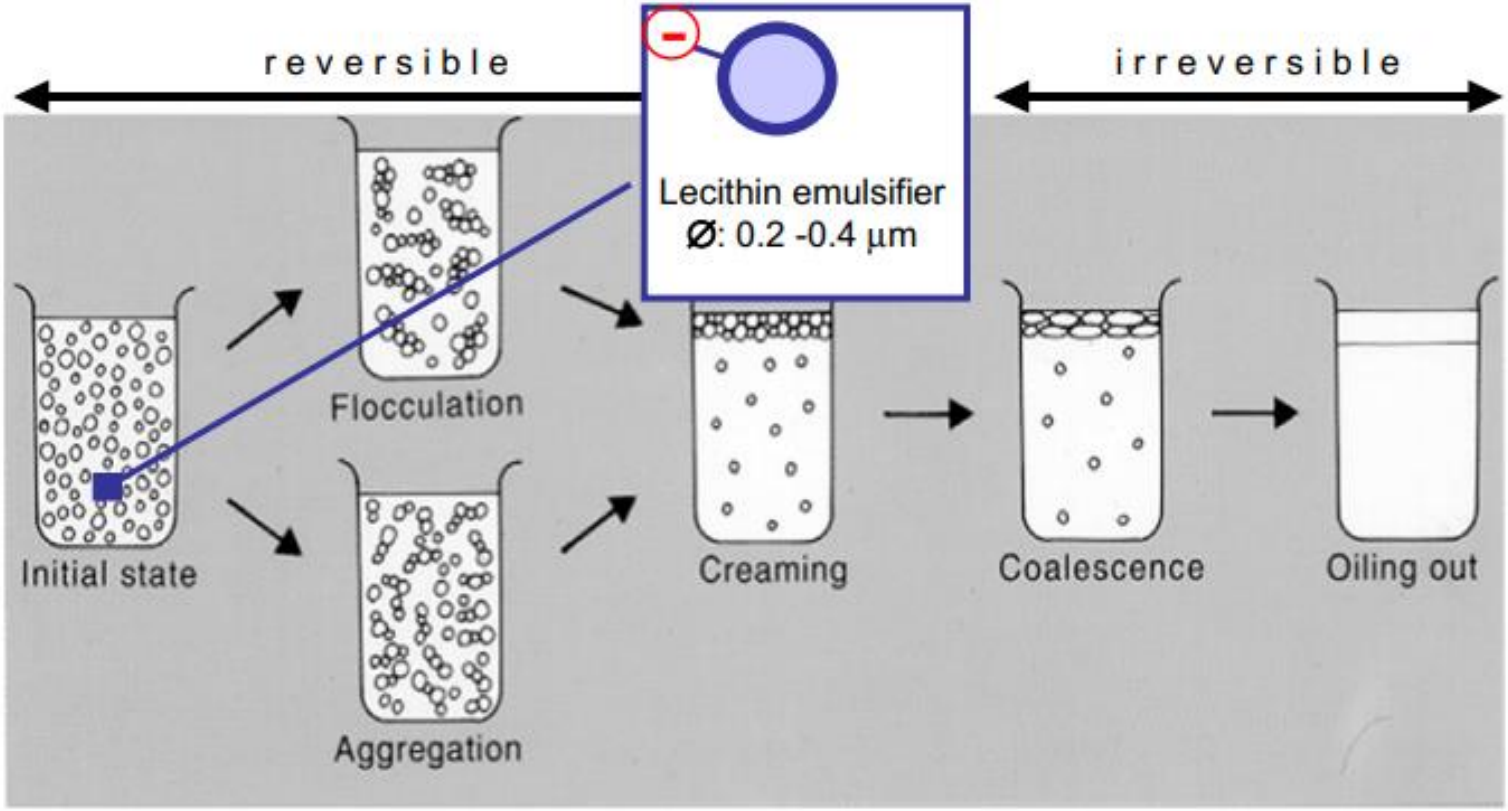

Fig. 1. Phases of lipid emulsion instability.

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Pertkiewicz M, et al. Basics in clinical nutrition: stability of parenteral nutrition admixtures. *e-SPEN*. 2009: e117-e119.
ASPEN. Parenteral Nutrition Preparation. 2013. Available at: https://www.nutritioncare.org/uploadedFiles/Documents/CNW/PN%20Preparation%20Slide%20Handouts.pdf [accessed March 1, 2023].

4. Stability of the Bag
Other Additives

- Addition of medications into PN should be limited
  - Must consider medication stability **AND** chemical compatibility with **ALL** components of the bag

- Must have supporting literature to support its addition in PN
  - Insulin
  - H_2 Receptor Antagonists
  - Heparin*

**Not compatible with 3-in-1 parenteral nutrition formulations*

Boullata JI, et al. ASPEN clinical guidelines: parenteral nutrition ordering, order review, compounding, labeling, and dispensing. *JPEN. 2014.*

OTHER SAFETY CONSIDERATIONS

Osmolarity

- Definition: the concentration of a solution, expressed as the total number of solute particles per liter of solution
- The osmolarity determines how a PN formula can be administered
  - Peripheral v. Central line
  - Increases risk of thrombophlebitis
- The most commonly accepted cut-off is **900 mOsm/L** for central administration
  - There are different limits in the literature (600-1200 mOsm/L), and are typically an institution-based standard

Boullata, JI, et al. "A.S.P.E.N. Clinical Guidelines." JPEN. 2014, 38(3): 334-377.

Osmolarity

- **Carbohydrates & Amino Acids are the largest contributors to osmolarity**

Dextrose

5% = 253mOsm/L

10% = 505mOsm/L

15% = 758mOsm/L

Amino Acids

Trophamine 10% = 875mOsm/L

➢8.75mOsm/1g protein

Plenamine 15% = 1383mOsm/L

➢9.2mOsm/1g protein

Trophamine [package insert]. Bethlehem, PA: B. Braun Medical Inc.; 2020.
Plenamine [package insert]. Bethlehem, PA: B. Braun Medical Inc.; 2018.

Osmolarity of Electrolytes

Electrolyte	Osmolarity per 1mEq (mOsm)
Sodium chloride	2
Sodium acetate	2
Sodium phosphate	3
Potassium chloride	2
Potassium acetate	2
Potassium phosphate	1.7
Calcium gluconate	1.5
Magnesium sulfate	12.6
MultiTrace-4	5 (mOsm/1mL)
Multivitamin	4.1 (mOsm/1mL)

Adjusting the Osmolarity

Increase the Volume

- Good for small adjustments
- May be required for large adjustments
- Risk of over-diluting

Reduce Macronutrients

- Required for large adjustments
- Try to trim both dextrose and protein to conserve nutrition

Reduce Micronutrients

- Good for small adjustments

Always try to preserve the nutritional content as much as possible! Don't forget to try different combinations!

Maximum Dose Restrictions
(Preventing Additive Risks)

- Its easy to lose track of dosing proportions when your total volumes are not an even number (i.e. 1000mL, 2000mL)
- Be aware of high risk medications!
  - Sodium chloride
    - Do not exceed the equivalent of normal saline
    - 154mEq/ 1000mL
  - Potassium
    - Do not exceed your institution's policy for large parenteral volumes
    - 60mEq/ 1000mL

Drug Shortages

- Unfortunate reality of PN compounding in recent years
  - Most due to manufacturing delays
- Reduces the flexibility to optimize nutrition & electrolyte goals
- Balances are required to benefit **ALL** patients
  - Dose restrictions
  - Age restrictions
  - Product allocation

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PN Component Shortages

- Shortages over the past 2 years, per the FDA
  - Amino acids
  - Calcium gluconate
  - Lipids (multiple products)
  - Multivitamins (adult & pediatric)
  - Potassium acetate
  - Potassium chloride
  - Sodium chloride 23.4%
  - Sodium phosphates
  - Sterile water for injection
  - Lipid Filters (1.2 micron)
  - PN filters (0.2 micron)
  - Empty bags
  - Compounder tubing

Parenteral Nutrition Product Shortages. ASPEN. Available at: https://www.nutritioncare.org/Guidelines_and_Clinical_Resources/Parenteral_Nutrition_Product_Shortages/ [accessed 3/2/2023].

Drug Shortages

Multivitamin Shortage, March 2023

- **Adults** - 5 mL (half dose) Adult MVI daily
- **Neonates –** Pediatric MVI dose restrictions, as follows:
  - No vitamins will be added to any NICU Standard TPNs
  - Patients < 1 kg can get 2 mL/kg (normal dose)
  - Patients > 1 kg can get 1 mL/kg (half dose)
  - Patients > 36 weeks - no MVI
- **Pediatrics –** Product selection based on age, with dose restrictions
  - Patients < 12 years old - 2.5 mL (half dose) Pediatric MVI daily
  - Patients 12 years of age and older - 5 mL (half dose) Adult MVI daily

Consider oral supplementation for any patients tolerating >50% of their caloric needs enterally

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Parenteral Nutrition Product Shortages. ASPEN. Available at: https://www.nutritioncare.org/Guidelines_and_Clinical_Resources/Parenteral_Nutrition_Product_Shortages/ [accessed 3/2/2023].

Drug Shortages

Staying Up To Date

- ASHP Drug Shortages Database
- FDA Drug Shortages Database
  - Provides shortage reasons, product availability, & estimated duration
- ASPEN (American Society for Parenteral & Enteral Nutrition)
  - Parenteral Nutrition Product Shortages Webpage
    - Provides clinical guidance on how to best allocate limited resources & manufacturer updates
  - Adult/Pediatric Nutrition Support Core Curriculum and/or Handbook
    - Provides general guidance based on minimum dosing requirements

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ASHP Drug Shortages Database. Available at: https://www.ashp.org/drug-shortages/current-shortages [accessed 3/2/2023].
FDA Drug Shortages Database. Available at: https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm [accessed 3/2/2023].
Parenteral Nutrition Product Shortages. ASPEN. Available at: https://www.nutritioncare.org/Guidelines_and_Clinical_Resources/Parenteral_Nutrition_Product_Shortages/ [accessed 3/2/2023].
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Assuring Safe Preparation

- A visual check should always be completed after compounding is complete to check for precipitate formation
  - Filters should be provided with tubing for administration
- Standardized Systems and Double Checks should be implemented during all steps of the PN preparation process
  - Verification (Pharmaceutical & Clinical)
  - Compounding
  - Administration

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Conclusion

- Parenteral Nutrition compounding is a complex process
- Pharmacists are responsible for a significant amount of safety checks
  - Dosing
  - Compounding Restrictions
  - Patient-Specific Needs
- Understanding how PN components influence each other will help solve potential issues, while still optimizing patients' needs
  - Interdisciplinary collaboration is essential
- Standardized systems for order verification, preparation, & administration are essential to assure safe patient care

Food for Thought:
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