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Key Parenteral Solution Shortages, Alternatives & the Role of Commercially Available Parenteral Nutrition

Joseph Ybarra, PharmD, BCNSP, FASPEN

Sr. Clinical Director, Corporate Clinical Pharmacy, Steward Health Care

Disclosures / Potential Conflicts of Interest

- Joseph Ybarra has a vested interest in or an affiliation with Baxter Healthcare – speaker and consultant; Fresenius Kabi – speaker and consultant; Rockwell Therapeutics – consultant

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Learning Objectives

At the end of this session, participants should be able to:

1. Identify the impact of large volume parenteral (LVP) solutions and parenteral nutrition (PN) shortages on patient care populations in the acute care, critical care and ambulatory care settings
2. Recall the appropriateness of alternative LVP solutions and commercially prepared multichambered PN in all patient care settings
3. Recognize evidence-based interventions required to maintain the highest level of patient care while mitigating the negative impact of shortages on patients receiving LVP solutions and PN therapies

Introduction

Background

- Drug shortages have affected components of PN since 2010
- Drug shortages of the past
 - 2010 → 178 (132 sterile injectable products)
 - 2011 → 251 (183 sterile injectable products)
 - 2012 → 117 (84 sterile injectable products)
 - 2013 → 44 (35 sterile injectable products)
 - 2014 → 44 (30 sterile injectable products)
 - 2015 → 26 (15 sterile injectable products)
 - 2016 → 23 (17 sterile injectable products)
 - 2017 → 35 (26 sterile injectable products)
 - 2018 → 50 (24 sterile injectable products)
- All PN products have been in short supply



| Why

- Manufacturing / quality control issues
- Loss of manufacturing site (e.g., hurricanes, pandemics)
- Increased demand
- Delays in procuring raw materials
- Availability of components (e.g., vials)
- Companies no longer producing



What do we have??? What do we not have???

This week or next week or

Shortages → We Are the Gatekeepers





LVP Solution & PN Shortages

Impact on LVP Solutions

Fluid	Na (mEq/L)	Cl (mEq/L)	K (mEq/L)	Ca (mEq/L)	Mg (mEq/L)	Dextrose (g/L)	Buffer (mEq/L)	pH	Osmol. (mosm/L)
Plasma	140	103	4	5	2	Variable	Bicarb. (25)	7.4	290
D5W/D10W	-	-	-	-	-	50 / 100	-	4.7 / 4.6	250 / 505
0.45% NaCl	77	77	-	-	-	-	-	5.6	154
LR	130	109	4	3	-	-	Lactate (28)	6.4	273
0.9% NaCl	154	154	-	-	-	-	-	5.7	308
Plasmalyte-A	140	98	5	-	3	-	Acetate (27) + Gluconate (23)	7.4	294
3% NaCl	513	513	-	-	-	-	-	5.8	1030

D5W – dextrose 5% solution in water, D10W – dextrose 10% solution in water, NaCl – sodium chloride, LR – Lactated Ringer’s solution

| Impact on LVP Solutions

Crystalloid LVP Solutions

- Acute care / hospitalization
- Home health setting
- Ambulatory care centers / surgery centers



Impact on LVP Solutions

Body Fluid	Na (mEq/L)	K (mEq/L)	HCO ₃ (mEq/L)	H (mEq/L)	Cl (mEq/L)	pH	Volume per 24 hr
Sweat	30-50	5	-	-	45-55	-	0.5
Saliva	45	20	60	-	44	7	0.5-1.5
Gastric	40-65	10	-	90	100-140	2	2-4
Pancreas	135-155	5	70-90	-	55-75	8	1
Bile	135-155	5	35-50	-	80-110	7	1.5
Jejunum/ileum	100-120	10	50-70	-	50-60	7	1.8
Diarrhea	25-50	35-60	30-45	-	20-40	-	-
Normal stool	5	10	-	-	10	-	0.1

Assessment Question: #1

Which electrolyte is lost through excessive nasogastric tube (NGT) losses?

- a. Magnesium
- b. Phosphate
- c. Potassium
- d. Bicarbonate (HCO_3)

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| Impact on Parenteral Nutrition

- Macronutrients
- Electrolytes
- Micronutrients
- Containers / supplies



| Impact on Parenteral Nutrition

- ISMP Survey → November–December 2013
- 234 practitioners (81% pharmacists)
 - 3-28% errors from shortages
 - 1 in every 4 to 5 responders → preventable adverse outcomes
 - Majority of errors → concentration issues, dosing adult with pediatric formulations, mix-up of electrolyte salts
 - 68% responders → used imported products



| Impact on Patients

- Davis, et al. (2014) → Selenium deficiency in pediatric patients with intestinal failure
- Franck (2014) → Zinc deficiency attributed to trace element shortages
- Palm and Dodtson (2014) → Zinc and copper deficiency in long-term PN with trace element shortages
- Ruktanonchai, et al. (2014) → Zinc deficiency-associated dermatitis in infants attributed to zinc shortages
- Brown, et al. (2018) → Non-anion gap metabolic acidosis seen with shortage of potassium acetate and sodium acetate



Managing Shortages

| Managing IVP Solution Shortages

- Emergency departments / primary care → evaluate the need for oral rehydration solutions (ORS) +/- antiemetics
 - Acute gastroenteritis
 - Pregnancy-related nausea / vomiting
 - Mild viral upper respiratory infection / pharyngitis
- Assess interchangeability between isotonic fluids
 - Normal saline (NaCl 0.9%), Lactated Ringers (LR), Plasmalyte-A



Impact on LVP Solutions

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Source: Adapted from Marino PL. The ICU Book. 2nd ed. 2007. pp. 235.

| Interchangeability of NS & LR

- Friederich, et al. (2018) → Emergency Department (ED) use of LR in place of NS had no difference in recovery or return to ED (after discharge)
- Yule, et al. (2020) → Women with preeclampsia requiring magnesium sulfate prophylaxis received NS in place of LR had no difference in renal function



| Managing LVP Solution & PN Shortages

- Conservation (e.g., evidence-based guidelines)
- Alternative agents (e.g., injectable to oral multivitamin, pre-mixed PN)
- Trade and borrowing with other institutions
- Extended beyond use dating (BUD) → check with manufacturer or FDA
- Foreign products
- “Gray Market”



| Managing PN Shortages

Macronutrients

- Amino acids (protein)
 - ✓ Utilizing different volumes
 - ✓ Alternative products (8%, 8.5%, 10%, 15%, 20%)
 - ✓ Pre-mixed PN
- IV lipid emulsions
 - ✓ Pay special attention to the brand name of the IV lipid product
 - Intralipid / Nutrilipid → intermittent dosing allowed
 - All others → daily dosing recommended, to prevent essential fatty acid deficiency
 - ✓ In adults → consider holding lipids up to 1–2 weeks
 - ✓ Drawing down large volumes into smaller volumes



Managing PN Shortages

Lipid Product	Contents	Recommended Dosing	Intermittent Dosing Allowed?
Intralipid	100% soybean oil	Critically ill: < 1 g/kg/d	Yes, achieve a minimum of 100g per week (e.g. 50g twice weekly)
Nutrilipid		Stable: 1 g/kg/d	
SMOF	30% soybean oil, 30% MCT oil, 25% olive oil, 15% fish oil	1-2 g/kg/d	No, must be dosed daily
Clinolipid	80% olive oil, 20% soybean oil	1-1.5 g/kg/d	No, must be dosed daily
Omegaven	100% fish oil	1 g/kg/d (pediatrics only)	No, must be dosed daily

Assessment Question #2

Which lipid can be given intermittently during a shortage?

- a. Intralipid
- b. SMOF
- c. Omegaven
- d. Clinolipid

Assessment Question #2

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- a. **Intralipid**
- b. SMOF
- c. Omegaven
- d. Clinolipid

| Managing PN Shortages

Electrolytes

- When appropriate, utilize other salt forms
- Commercial electrolyte products
- Imported products
- Evidence-based guidelines
- Some alternatives have limited or no solubility data



| Shortages – Electrolytes in PN

- Potassium and Sodium
 - Y-site LVP solutions (e.g. PN at 50 mL/hr + 0.9% NaCl at 50 mL/hr)
 - Chloride vs. Acetate
 - Oral products → caution for GI intolerance
 - Correct magnesium imbalances (potassium)
 - Correct fluid imbalances (sodium)
- Magnesium (sulfate)
 - Magnesium chloride???
 - Oral magnesium → caution for GI intolerance
 - Repletion doses → evidence-based literature
- Calcium (gluconate)
 - Reduce protein content in long-term/home PN patients
 - Calcium chloride???
 - Oral calcium → consider
 - Omit from peripheral parenteral nutrition
 - Monitor ionized calcium levels



| Shortages – Electrolyte Repletion

Magnesium

- Utilize premixed IV magnesium
- Increase duration of IV magnesium infusions
- Oral magnesium → issues with diarrhea

Calcium

- 3 grams calcium gluconate = 1 gram calcium chloride
- Avoid calcium chloride in PN
- Calcium chloride → central line
- Oral calcium should be considered

Shortages – Electrolyte Repletion, continued

Potassium

- IV potassium acetate
 - Utilize potassium chloride
 - ✓ Chloride provided by potassium chloride will not significantly affect acidosis
- PO potassium
 - Oral solutions → diarrhea, bad taste, GI discomfort
 - Oral SR tablets or effervescent tablets
- Correct magnesium imbalances

Phosphate (phosphorus)

- Potassium phosphate and sodium phosphate
 - Utilize oral/enteral routes
- Repletion bolus < 1 mg/dL
- Consider imported products → sodium glycerophosphate (Glycophos)
- Reserve for pediatric/neonates
- IV fat emulsions
 - Source → egg phospholipids
 - Amount → 15 mmol/L

Oral Phosphate Repletion

	PO4 (mmol)	Na (mEq)	K (mEq)
K Phos Neutral tab.	8	13	1.1
Neutra Phos cap.	8	7.1	7.1
Skim milk (per 8 oz.)	8	3	5
Fleet's Phospho Soda (per mL)	4.15	4.82	-

Shortages – Trace Elements

- Multiple Trace Elements (MTE)

- [Adult] Tralement → contains Zinc, copper, manganese, selenium
- [Neonatal] Multrys → contains Zinc, copper, manganese, selenium

- Management

- Reserve Zn and Se for pediatrics/neonates!!!
 - ✓ Se deficiency rare in the adult population
 - ✓ Se supplementation might be required in the critically ill population
- Change to Q Monday and Thursday dosing of MTE
 - ✓ Daily Zn dosing for wound healing
- Consider imported products



| Shortages – Multivitamins

Adult Multivitamin Injection (MVI)

- Intermittent or reduced dosing in PN
- Remove from “banana bags”
- Oral multivitamin w/ trace elements (daily or twice daily)
 - Chewable multivitamins → patients with impaired absorption (i.e., SBS)
- Individualized dosing → thiamine, folate, pyridoxine, ascorbic acid, cyanocobalamin, vitamin K
- Reserve for profoundly malnourished patients



| The Role of Multichambered Bag (or Premixed PN) ???

- Commercially available products in predetermined volumes
 - Premixed can also mean outsourced PN
- Fixed doses of amino acids and dextrose in separate chambers
 - Double-chambered products (Clinimix)
 - ✓ Lipids delivered at y-site or added to admixture
 - ✓ With or without standard electrolytes
 - Triple-chambered products (Kabiven/Perikabiven)
 - ✓ Lipids included (soybean oil-based)
 - ✓ Only provided with standard electrolytes
- Available ports for adding insulin, multivitamin, trace elements, additional IV lipids
- Available for peripheral (PPN) or central PN



Multichambered Bag (PN)

Pros

- Institutions with low PN census
 - Potential cost-savings
 - Compounder not needed
- Safe form of parenteral nutrition
 - Avoids compounding confusion
 - Inexperienced clinicians
 - ✓ Rate of $X \text{ ml/hr}$ → $Y \text{ kcal/day}$
- Pontes-Arruda A, et al. Clin Nutr. 2012. 31(5):728-34.
 - Lower ICU and hospital LOS
 - Compounded PN associated with 19% higher bloodstream infections

Cons

- Fixed electrolyte dosing
 - Additional electrolytes → y-siting IV boluses or add to premixed bag
- Fixed macronutrient dosing
 - Protein → 27.5-80 g/L
 - Dextrose → 50-250 g/L
 - Additional protein → provided at y-site or add to premixed bag
- Hypervolemia + hyponatremia
 - Improved in products with higher protein concentrations
- Calcium-phosphate solubility
 - Calcium chloride
 - Cannot add additional phosphate or calcium to premixed bags

| Assessment Question #3

An undesired side effect of commercially prepared multichambered PN bags may consist of:

- a. Auditory hallucinations
- b. Hypoglycemia
- c. Electrolyte abnormalities
- d. Thrombocytopenia

Assessment Question #3

An undesired side effect of commercially prepared multichambered PN bags may consist of:

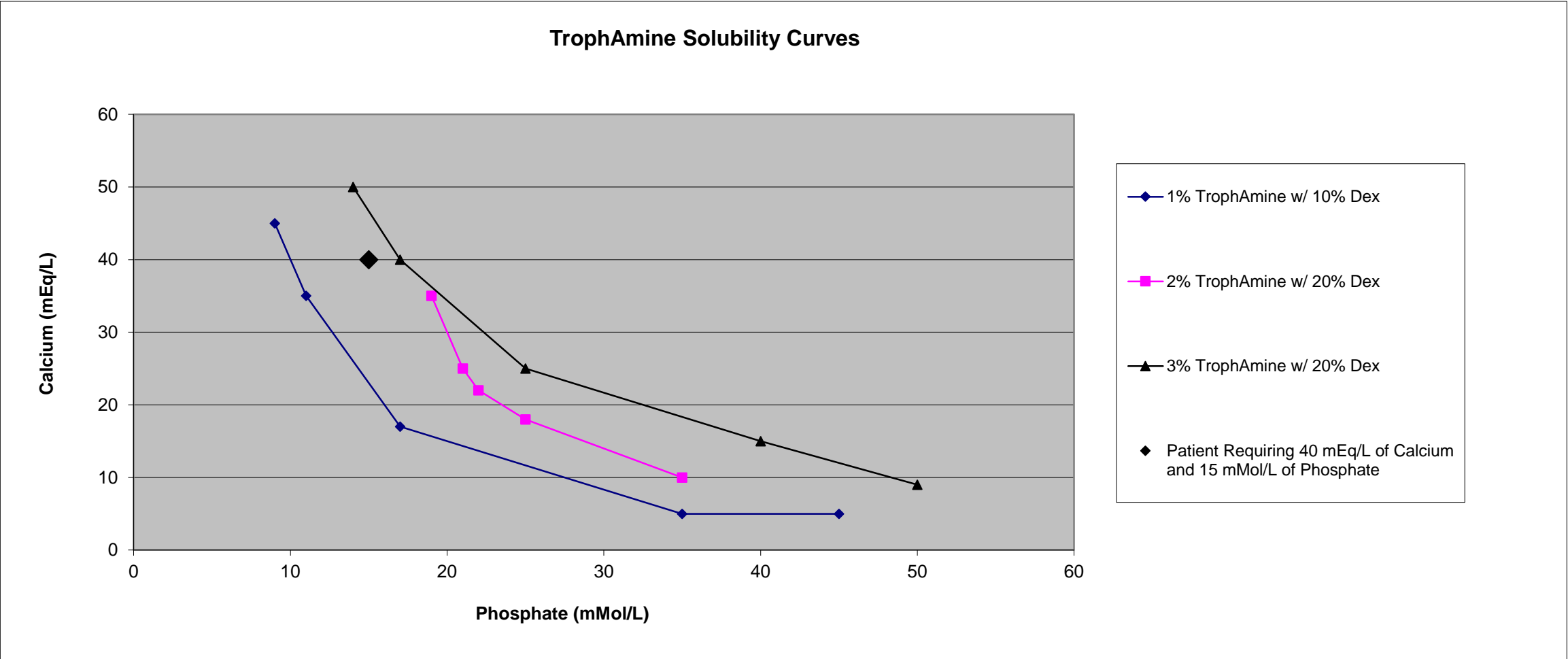
- a. Auditory hallucinations
- b. Hypoglycemia
- c. Electrolyte abnormalities**
- d. Thrombocytopenia

PN Shortages – Pediatric Considerations

- Amino acids
- Lipids
 - Utilizing syringes?
 - Draw-down method of individualized dosing
 - Using 3-in-1 admixtures (only if > 30 kg)
- L-carnitine
- Electrolytes
 - Adhere to guidelines / dosing recommendations
 - Calcium and phosphate → biggest problems
- Multivitamins / trace elements
 - Individualized dosing
 - Oral products, if possible
- Cysteine
 - Calcium-phosphate restrictions
 - Use solubility curves

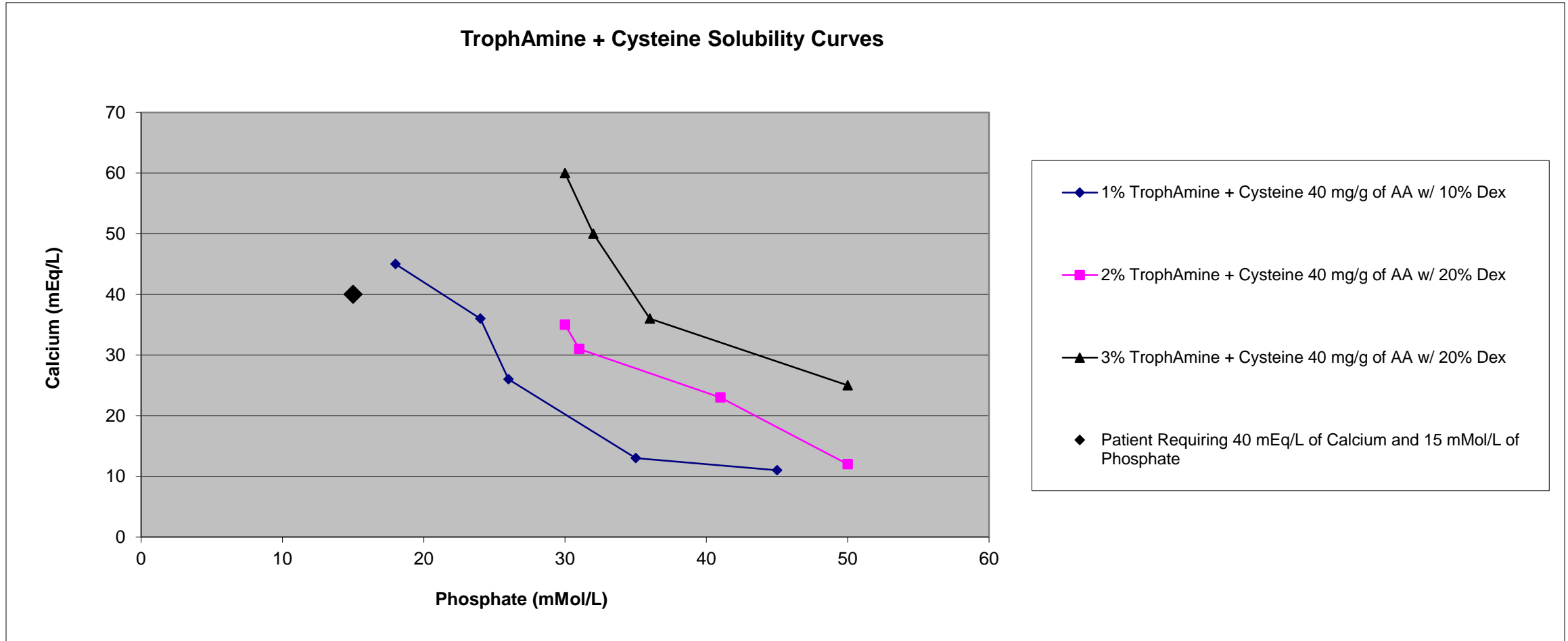


PN Shortages – Pediatric Considerations



Source: J Pediatr Pharmacol Ther. 2019;24(1):45-52.

PN Shortages – Pediatric Considerations



LVP Solutions and PN Shortages

IN CONCLUSION

- Causes of drug shortages are multifactorial
- Impact on patient management
 - Adverse events reported
 - Solubility data?
 - Right patients receiving the right dose?
- Management varies
 - Utilizing smaller / larger volumes
 - Conservation / rationing
 - Alternative formulations
 - Evidence-based protocols
 - Imported products
 - “Gray market” → \$\$\$



Online Resources

- American Society for Parenteral and Enteral Nutrition (ASPEN)
 - Published “Product Shortage Considerations”
 - ✓ Trace elements
 - ✓ Amino acids
 - ✓ Cysteine
 - ✓ PO₄, Na, Mg, K
 - ✓ IV lipids
 - ✓ Multivitamins
 - Found at → <http://www.nutritioncare.org/>
- U.S. Food & Drug Administration
 - Current shortage list
 - Information on extended use dates (go beyond original beyond use date)



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Thank you...

Joseph Ybarra | joseph.ybarra@steward.org