The Short of Short Bowel Syndrome: Management of PNAC, PNALD, and Pharmacologic Approaches to Advancing Feeds

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The speaker has signed a disclosure form and indicated he has no significant financial interest or relationship with the companies or the manufacturer(s) of any commercial product and/or service that will be discussed as part of this presentation.

Session Summary

This presentation will focus on evidence- and practice-based management and monitoring of parental nutrition-associated cholestasis (PNAC) and parenteral nutrition-associated liver disease (PNALD) in the setting of short bowel syndrome. Upon completion of this presentation, the attendee will be able to successfully manage parenteral nutrition in the setting of PNAC and PNALD and select pharmacologic therapy to assist advancing feeds in patients’ refractory to traditional management.

Session Objectives

Upon completion of this presentation, the participant will be able to:

- discuss parenteral nutrition-associated cholestasis (PNAC), parenteral nutrition associated liver disease (PNALD), and short bowel syndrome (SBS);
- identify PN and pharmacologic methods to minimize or reverse progression of PNAC and PNALD;
- implement pharmacologic modalities to facilitate advancing feeds.

References


The Short of Short Bowel Syndrome:
Management of PNAC, PNALD, and pharmacologic approaches to advancing feeds
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Patient Case
GC is a 37/4 week PMA neonate born with jejunal atresia
- Day of life (DOL) 1 had surgical correction with tapering jejunostomy and anastomosis
- DOL 10 ex-lap performed with approximately ¾ of residual bowel necrotic, requiring immediate removal
- Undocumented amount of jejunum remaining
- DOL 17 pertinent labs
  - Albumin – 3.4
  - Direct bilirubin – 6.7
  - ALT/AST – 208/155

What is the Definition of PNAC?
American Society of Parenteral and Enteral Nutrition (ASPEN)
- Conjugated bilirubin (D. Bili) ≥ 2 mg/dL in association with prolonged (≥ 14 days) of parenteral nutrition
- D. Bili ≥ 2 an arbitrary number
- Severe PNAC – D. Bili >5 mg/dL
Can have cholestasis in conjunction with PN that is not PNAC

PNAC:
- ~ 50% prevalence in infants on prolonged PN
- Up to 85% prevalence in patients on PN for SBS or intestinal failure
- Can lead to end stage liver disease

Lauriti G et al J Parenter Enteral Nutr 2013

Question 1
Based on our patient’s presentation, our patient can be diagnosed with PNAC and PNALD at this time.
True
False

What is PNALD?

Short Bowel Syndrome
Complex disease resulting from physical and functional loss of portions of the small intestines
- 25/100,000 live births
- ~40% mortality rate
Intestinal failure:
- Seen in more severe SBS mainly as result of large resection
Management goals:
1. Maintain proper fluid balances
2. Maintaining electrolyte balances
3. Promoting growth
4. Optimizing quality of life for the entire family


FANNP 27th National NNP Symposium: Clinical Update and Review
Intestinal Failure-Associated Liver Disease

Intestinal failure → PN → PNAC → IFALD

Infections and inability to advance feeds

PNAC Risk Factors

Prematurity
Low birth weight
Prolonged PN administration
Infection/sepsis
Inability to advance feedings

Others:
- Intralipid emulsion (ILE) therapy > 1g/kg/day
- Increased GIR
- Fluconazole prophylaxis

Methods to Minimize PNAC and PNALD

PN administration techniques:
- PN cycling
- Intravenous lipid emulsion (ILE):
  - Reduce dose
  - Utilize different formulation
- Carbohydrates:
  - Reduce glucose infusion rate (GIR)
- Trace elements and electrolytes:
  - Dose adjustment and monitoring of trace
  - Reducing aluminum content of PN
- Medications:
  - Ursodiol
  - Cholecystokinin
  - Phenobarbital

Question 1

Based on our patient’s presentation, our patient can be diagnosed with PNAC and PNALD at this time.

True
False

Question 2

Based on the previous case, which of the following methods is most likely to prevent further worsening of PNAC and PNALD?

1. Cycling of TPN
2. Reduction of ILE to 1 gram/kg/day
3. Reduction of GIR to 6 mg/kg/min
4. Initiation of ursodiol or phenobarbital
5. Two of the above

PN Cycling in Gastrochisis

May reduce time to onset and incidence of cholestasis

Jensen A. et al.
- Retrospectively evaluated 107 patients with cholestasis
  - 36 received cycled
  - 71 received continuous PN
- No significant differences in patient characteristics
  - Only exception was length of stay
  - 60 days in cycled group vs. 41 days in continuous group (p<0.011)
- No differences in infection rates

PN Cycling in Gastroscisis

27 Patients developed PNAC
- 22 (81%) in continuous PN group
- 5 (14%) in cycled PN group
3 times more likely to develop PNAC on continuous PN
- After adjusting for uncol, cholestatis, feedings, and alrease

Weaknesses:
- Decision for cyclic PN?
- Disproportionate sample size
- Not all factors accounted for
- Lab monitoring not addressed


How to: PN Cycling

Factors to consider:
- PN at least 38-40 weeks
- Glucose stability on continuous PN
- Nutritional status
- Small for gestational age?
- What, how much, and how are feeds being administered

Monitoring during cycle:
- Blood glucose prior to new PN
- Blood glucose 30 minutes after initial drop in rate

Administration consideration:
- Can hang and prime KVO fluids if needed with new PN

How to: 20 hour PN Cycle

1. Run PN over 22 hours. Dextrose 10% for ½ GIR last 2 hours.

2. Run PN over 20 hours. Dextrose 10% at ½ GIR for 2 hours, ½ GIR the last 2 hours.

3. Run PN over 20 hours. At hour 18, ½ the TPN rate. At hour 19, ¼ the TPN rate. Run dextrose 10% at ½ GIR for 2 hours. For 2 hours.

4. Run PN over 20 hours. At hour 18, ½ the rate and hour 19, ¼ the rate.

Hours 20-24 off PNL.

Lipid Reduction for Prevention of PNAC

No difference in incidence of cholestasis between groups
- 15/29 (52%) in 1 g/kg/d group vs. 14/32 (44%) in 2-3 g/kg/d group (p=0.61)


Lipid Reduction for Prevention of PNAC

No difference in time to ELE therapy, 50% enteral feeds, operative procedures, or bloodstream infections


Lipid Reduction for PNAC Patients

AS PEN recommendation:
- Decreasing lipids to 1 g/kg/d in patients with parenteral nutrition associated liver disease (PNALD)
- Low strength recommendation with very low quality evidence to support t

Cober at al. evaluated reducing lipids to 1 g/kg twice weekly, however, mild essential fatty acid deficiency was observed in the treatment group
- Prospective matched cohort study
- Evaluated change in total bilirubin
- Essential fatty acid deficiency (EFAD)
- Weight gain
- Allowed for increase in GIR up to 16 mg/kg/min

Cobet M, et al. JPNLD. 2012
Lipid Reduction for PNAC Patients

Cober et al. Intravenous fat emulsions reduction for patients with parenteral nutrition-associated liver disease.

Results
- Baseline demographics
  - More biliary sludging in reduced lipid group
  - Did not ultrasound all patients
  - More patients in reduced lipid group received gut decontamination therapy (7 (23%) vs 0, p=0.016)
  - Longer duration of PN in reduced lipid group
  - 96 vs 61 days, p=0.033
  - Total bilirubin change (see figures)
  - Weight gain similar between groups
  - ~13.55 vs. 13.25 gm/day, p= 0.937
  - IFALD (triglyceride/solvent ratios)
  - 13 of 31 patients (42%) in study group

Study
- No definite recommendation per 2015 IFALD position paper
- No definitive recommendation per 2016 ILE position paper

Lipid Formulation and PNAC

Lipid Dosing Recommendations

ASCPN recommendations:
- Reduce to 1 g/kg/day

ESPGHAN recommendations:
- No definitive recommendation per 2015 IFALD position paper
- No definitive recommendation per 2016 ILE position paper

Florida Hospital for Children Short Bowel Guidelines:
- Reduce ILE to 2 g/kg/day
- Will decrease to 1 g/kg/day
- LFT abnormalities
- GGT elevations

Carbohydrate Dosing in PNAC

Higher g/kg/day have been possibly correlated with increased rates of cholestasis

Jolin-Dahel et al.
- Retrospective chart review of 87 neonates admitted to NICU at Children’s Hospital Eastern Ontario
- Received PN for > 14 days
- Baseline characteristics similar between groups with exception of gender
- Results of interest:

<table>
<thead>
<tr>
<th>Control (UR)</th>
<th>Cholestasis (N=18)</th>
<th>P value</th>
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<tbody>
<tr>
<td>Dextrose g/kg/day, median (IQR)</td>
<td>Dextrose of PN, days, median (IQR)</td>
<td></td>
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<tr>
<td>12.5 (10-13.2)</td>
<td>12.5 (10-13.2)</td>
<td>0.003</td>
</tr>
<tr>
<td>16.4 (12.5-16.2)</td>
<td>39 (26-51)</td>
<td>0.001</td>
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Trace Elements in PN

Copper:
- Powerful antioxidant: Essential for organ function and metabolism. Promotes RBC production.
- Accumulates in cholestasis and can lead to hepatic cirrhosis and kidney damage

Manganese:
- Deficient for multiple enzymes. High doses can cause or worsen TPN-induced cholestasis. Can accumulate in cholestasis and cause CNS catecholamine depletion due to displacement.

Selenium:
- Powerful antioxidant: Helps promote proper thyroid function

Zinc:
- Defector for enzymatic function. Important for growth and metabolism

Chromium:
- Important for macronutrient metabolism and helps improve insulin sensitivity
Trace Elements in PNAC

**Copper:**
- ASPEN recommended daily intake in infants = 20 mcg/kg/day
- Intrauterine accretion rate = 63 mcg/kg/day
- 80% biliary excretion

**Manganese:**
- ASPEN recommendation for PN supplementation = 1 mcg/kg/day
- No reports of manganese deficiency in neonates
- Third trimester intratranine accretion = 9 mcg/kg/day
- 90% biliary excretion

Electrolytes and Cholestasis?

All products contained within PN contaminated with aluminum

Aluminum can lead to the following:
- Liver disease/cholestasis
- Neurologic dysfunction
- Metabolic bone disease

FDA recommends limit of < 5 mcg/kg/day in neonates
- Using the least contaminated products, Poole R, et al averaged 10 mcg/kg/day

<table>
<thead>
<tr>
<th>Calcium gluconate</th>
<th>Sodium Phosphate (American Regent)</th>
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<tr>
<td>Potassium Phosphate</td>
<td>Potassium Chloride (American Regent)</td>
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Trace Element Products

Pediatric no longer available in the United States

**Multitrace 4 neonatal**
- Zinc = 300 mcg/kg/d
- Copper = 10 mcg/kg/d
- Chromium = 0.85 mcg/kg/d
- Manganese = 5 mcg/kg/d
- Selenium = None

**PNAC dosing recommendation:**
- Individually dose trace elements
- Reduce copper to 3 mcg/kg/day
- Remove manganese from PN

**Choloretics**

**Cholecystokinin (CCK)**
- Synthetic analog of cholecystokinin
- No reported benefit in prevention or resolution of PNAC

**Phenobarbital:** (4-5 mg/kg/day)
- No compelling literature to advocate its use
- Theorized to induce enzymatic activity and promote biliary excretion
- Known negative effects on neurologic outcomes

**Ursodiol:** (20-30 mg/kg/day in BID or TID dosing)
- Ursodeoxycholic acid displaces biliary salts within biliary tract and promotes excretion of bile
- Variable low-quality evidence to support its use

**What did we do for our patient?**

Cycled TPN to 20 hours

Administered 1 g/kg/day ILE
- Given over 12 hours

Trace Elements:
- Removed copper
- Remove manganese

Average GFR of 14 mg/kg/min

Total kcal/kg/day = 88 kcal/kg/day

Prior to reanastomosis:
- 4 mL Q 3 hours (~10 mL/kg/day)
Our Patient’s Direct Bilirubin

Week 1 Week 2 Week 3 Week 4 Week 5 Week 6 Week 7

Removal of Necrotic Bowel
ILE of 1 g/kg/day and reduced trace elements

Began to PN cycling

Question 2
Based on the previous case, which of the following methods is most likely to prevent further worsening of PNAC and PNALD?

1. Cycling of TPN
2. Reduction of ILE to 1 gram/kg/day
3. Reduction of GIR to 6 mg/kg/min
4. Initiation of ursodiol or phenobarbital
5. Two of the above

Question 3
Our patient is now approaching 75% enteral feeds and is beginning to experience loose, watery stools in excess of 40 mL/kg/day. The stools are characterized as watery and normal in color. Electrolytes are low normal. Her ileocecal valve is intact and her stools do not appear greasy. Which of the following therapeutic options would our patient most likely benefit from?

1. Loperamide 0.2 mg/kg/day PO in twice daily dosing
2. Atropine/Diphenoxylate – Do Not Use
3. Cholestyramine 240 mg/kg/day PO in three times daily dosing
4. Creon – 1,000 units of lipase/kg/dose with feedings
5. Gentamicin 2.5 mg/kg/dose PO in twice daily dosing

Diarrhea in SBS

Diagnoses:
- Increased intestinal motility
- Increased GI secretions
- Bacterial overgrowth
- Malabsorption of fats and bile salts

Increased Intestinal Motility

Treatments:
- Loperamide – 1st Line
  - Peripherally acting u-opioid receptor agonist
  - No CNS effects
  - Effective in patients with ileostomy
  - Administer 30-60 minutes before feeds due to gastroscolic reflex
- Atropine/Diphenoxylate – Do Not Use
  - Peripherally and centrally acting u-opioid receptor
  - CNS effects, abuse deferred by atropine
  - Similar efficacy as loperamide
  - Not recommended < 2 years of age due to risk of atropine toxicity

Kumpf V. J Parenter Enteral Nutr. 2014

Kumpf V. J Parenter Enteral Nutr. 2014
Gastric Acid Hypersecretion

Many patients following resection will have increased acid secretion

- Most often transient
- Resolves after several weeks

Treatment of gastric hypersecretion can lead to:

- Worsening of diarrhea
- Decreased efficacy of pancreatic enzymes
- Bacterial overgrowth

Treatment options:

1. Proton pump inhibitors (PPIs) – omeprazole or lanoseprazole
   - These treatments can lead to osteoporosis, fractures, and B12 deficiency
2. H2 receptor antagonists – famotidine or ranitidine
   - Not considered to be as efficacious as PPIs
   - Both of these can lead to GI bacterial overgrowth
3. Octreotide
   - Inhibits gastrin and prolongs intestinal transit time
   - Expensive, continuous infusion or subcutaneous infusion
   - Cholestasis and hyperglycemia

Cholestatic Diarrhea

Bile acids primarily absorbed in distal jejunum:

- In patients with ileal resections, bile acids can dump into colon
- Colonic bacteria conjugate salts into free bile acids
- Can lead of movement of chloride and water into the colon

Treatment options:

1. Cholestyramine (240 mg/kg/day PO in TID dosing)
   - Binds free bile acids and forms insoluble complex
   - Not recommended per ASPEN 2010 Core Curriculum
   - Can worsen steatorrhea
   - Dosing difficult for parents
2. Water soluble A, D, E, K

Pancreatic Insufficiency

Gastric acid hypersecretion:

- Especially around period of surgery
- Lower GI pH denatures pancreatic enzymes -> fat malabsorption
- Fat malabsorption presents as steatorrhea

Pancreatic enzyme replacement therapy:

- Not well studied in SBS
- Dosing: 500-1,000 units lipase/kg/feeding
- Dosing extrapolated from cystic fibrosis patients
- Concerns:
  - Fibrosis colonicopathy
  - Stool impaction
  - Administration concerns; g-tubes, sodium bicarbonate, dosing

Small Bowel Bacterial Overgrowth (SBBO)

Occurs in patients with preserved colon

Overgrowth of colonic bacteria in small intestine:

- Degradation fermentable carbohydrates into D-lactate
- D-lactic acidosis causes large anion gap

Treatment of SBBO:

- Trial other modalities first
- Measure D-lactate level (positive if > 1 mg/dL)

Management of SBS Diarrhea

Adapted from Kumpf V. JPEN. 2014
Question 3

Our patient is now approaching 75% enteral feeds and is beginning to experience loose, watery stools in excess of 30 mL/kg/day. The stools are characterized as water and normal in color. Electrolytes are low normal. Her ileocecal valve is intact and her stools do not appear greasy. Which of the following therapeutic options would our patient most likely benefit from?

1. Loperamide 0.2 mg/kg/day PO in twice daily dosing
2. Famotidine 0.5 mg/kg/day PO once daily
3. Cholestyramine 240 mg/kg/day PO in three times daily dosing
4. Creon - 1,000 units of lipase/kg/dose with feedings
5. Gentamicin 2.5 mg/kg/dose PO in twice daily dosing

Conclusions

PNAC and IFALD are consequences of short bowel syndrome due to prolonged need for PN along with known risk factors.

Preventing and reversing cholestasis in SBS is not a one-trick pony. A multifaceted approach must be applied to all patients to promote growth and limit progression of PNAC into PNALD.

Pharmacologic options available to facilitated advancing feeds and promoting growth in the setting of SBS diarrhea. However, perceived benefits must outweigh risks of administration.

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