Hepatoprotective Therapies for TPN-Associated Cholestasis

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Goals

✓ Review risk factors associated with parenteral nutrition-associated cholestasis (PNAC)
✓ Review evidence for the role of lipid emulsions in PNAC
✓ Review evidence for other nutritional strategies in PNAC
✓ Review evidence for use of medications in PNAC
✓ Review use and outcomes of enteral fish oil
Introduction

• Parenteral nutrition (PN) developed in late 1960s and is life-saving

• PN-associated cholestasis (PNAC) and PN-associated liver disease (PNALD) associated with morbidity and mortality

• How are PNAC and PNALD treated or avoided?
Methods

• Literature review – PubMed, Cochrane Database

• General Topics
  – 1. Non-nutrient risk factors in PNAC
  – 2. PNAC and the role of lipid emulsions
  – 3. Nutritional (non-lipid) considerations
  – 4. Medication use in PNAC

• Specific questions within each topic
Methods

• Studies reviewed and evidence graded

Classes of Evidence

I  Systematic review of RCT’s or RCT with narrow CI
II  Cohort studies, low quality RCT’s, outcomes research
III  Case-control studies
IV  Case series
V  Expert opinion

Grades of Recommendation

A  Consistent Level 1 Studies
B  Consistent Level 2 or 3 studies or extrapolation from Level 1 studies
C  Level 4 studies/extrapolations from Level 2 or 3 studies
D  Level 5 evidence; inconsistent or inconclusive studies
Topic 1 - Non-nutrient Risk Factors in PNAC

• Prematurity/Low Birth Weight
• Role of underlying diagnosis
• Duration of PN therapy
• Sepsis
Non-nutrient Risk Factors in PNAC

• **Question 1 - Does prematurity or low birth weight increase the risk of PNAC?**

  – Multiple case-series published since the 1970s have supported the idea that prematurity is significant risk factor

  – Three recent reports failed to show this same effect

  – **Majority of, but not all, studies support role of prematurity in PNAC (Class II and Class III)**
• **Question 2** – *What underlying diagnoses are most closely associated with PNAC?*
  
  
  
  – Robinson (2008) – Case-control study → NEC
  

• **Necrotizing enterocolitis appears to be a significant risk factor for PNAC (Class II and Class III)**
Non-nutrient Risk Factors in PNAC

• **Question 3 – Does duration of PN impact development of PNAC?**
  - Multiple published studies have shown that longer duration of PN is strongly associated with development of PNAC
  - One surgical study (Beath, et al 1996) failed to show that duration of PN predicted PNAC

• **Majority of data support PN duration as a risk factor for PNAC (Class III)**
Non-nutrient Risk Factors in PNAC

• **Question 4** – *Does the number of septic episodes impact development of PNAC?*
  
  – Association between sepsis and jaundice clear
  
  – Virtually all reviewed studies showed that documented sepsis was closely associated with an increased risk of PNAC

• **Data support sepsis as a risk factor for PNAC (Class III)**
Topic 2 - The role of lipid emulsions in PNAC

- Effect of altering lipid infusion on PNAC
- Effect of non-soybean based lipid administration
- Effect of combination lipids
PNAC and the role of lipid emulsions

• **Question 1** – Does altering the administration schedule or dosing of soybean-based lipid emulsions decrease frequency or severity of PNAC?

  – Several studies (Class III) show that:
    - Restriction of IV fat emulsion (1 g/kg, 2-3 times per week) is safe and does not cause clinically significant fatty acid deficiency
    - Restriction of IV fat emulsion is associated with improved cholestasis in infants and children who have developed PNAC

• Restricting infusion of soybean-based lipid emulsions is indicated for patients at risk for PNAC (Grade B)
PNAC and the role of lipid emulsions

• **Question 2** – *Does use of non-soybean-based lipids decrease the frequency or severity of PNAC?*
  
  – Studies (Class III and IV) on fish oil-based lipids show:
  
  - Safety with low incidence of fatty acid deficiency
  - Ability to ameliorate PNAC that was superior to soy bean-based lipids

• **Fish oil-based lipid emulsions are safe and effective in reversing PNAC in children (Grade B)**
PNAC and the role of lipid emulsions

• Question 3 – Does use of “hybrid” lipids decrease the frequency or severity of PNAC?
  – SMOF – Soybean, MCT, Olive oil, Fish oil (Goulet, et al)
    ➢ Randomized Trial – SMOF effective at lowering bilirubin
  – Olive Oil/Soy bean lipids (80%/20%) – (3 studies)
    ➢ Safe
    ➢ Fatty acid deficiency not reported
    ➢ Effect on PNAC not studied in detail

• “Hybrid” lipid use encouraging but there are insufficient data to recommend use (Grade U)
Topic 3 – Non-lipid strategies in PNAC

- Role of dextrose/protein load
- Role of amino acid formulation
- Role of “conditional” amino acids
- Role of trace elements
- Role of trophic feeding
- Role of cycling
Non-lipid strategies in PNAC

• **Question 1 – Does initial dose/advancement or protein load influence development of PNAC?**
  
  – Early study (Vileisis, 1980)
    
    ➢ Equal incidence of cholestasis, onset sooner, bilirubin higher with higher protein infusion
  
  – Several recent Class I and Class II studies show:
    
    ➢ Initial dose, rate of advancement and protein in PN does not increase risk of developing PNAC
    ➢ Duration of PN and total cumulative amount of PN determine PNAC

• **Initial dose/advancement of PN does not increase risk of PNAC (Class I/II)**
Non-lipid strategies in PNAC

• Question 2 – Which amino acid formulations are associated with development of PNAC?
  – Aminosyn (APF) and TrophAmine (TA)
    ➢ Forchielli (1995) – No difference between APF and TA
    ➢ Wright (2003) – APF, birth weight, duration of PN identified as risk factors for PNAC

• There is little evidence (Class III) that proves a difference between amino acid formulations in development of PNAC
Non-lipid strategies in PNAC

• Question 3 – Can supplementation of PN with “beneficial” amino acids (AA) reduce incidence of PNAC?
  – Taurine – “beneficial” to liver; used to conjugate bilirubin
    ➢ Spencer (2005) – Prospective study; Taurine supplement caused:
      ❖ Decreased direct bilirubin (not statistically significant) – entire cohort
      ❖ Decreased direct bilirubin (significant) – neonates with NEC
  – Glutamine – “hepatoprotective”; trophic to gut
    ➢ Duggan (2004) – Randomized trial; enteral glutamine had no effect on PNAC
    ➢ Wang (2010) – Randomized trial; parenteral glutamine associated with decreased AST and total bilirubin.

• Evidence for AA supplement is weak (Class II-IV, Grade C)
Non-lipid strategies in PNAC

• **Question 4 – What trace elements impact PNAC?**
  
  – Manganese (Mn) and PNAC
    - Mn levels correlated with transaminase & bilirubin levels
    - RCT – higher Mn dose resulted in higher conjugated bilirubin
  
  – Copper (Cu) and PNAC
    - Cu essential, making elimination difficult
    - 50% Cu reduction in setting of PNAC – monitor levels
  
  – Choline and PNAC
    - Choline low in long-term PN
    - Choline supplementation associated with lower ALT/AST but not T bili

• **Evidence weak (Class III/IV, Grade C)**
Non-lipid strategies in PNAC

• Question 5 – *Does trophic feeding, if possible, impact PNAC?*
  
  – Trophic feeding of patients on PN has been shown to:
    • Lower conjugated bilirubin
    • Accelerate enteral autonomy
    • Prevent PNAC
  
  – Studies difficult to control
  
  – Enteral feeding may not be practical in many clinical cases

• Evidence strong (Class II, Grade B) that enteral feeding can reduce incidence and severity of PNAC
Non-lipid strategies in PNAC

• **Question 6** – *Does cycling of PN impact PNAC?*
  
  – Adult study (Hwang 2000) – 65 patients
    
    ⇢ Cycling PN prevented progression of PNAC in mild to moderate cases
    
    ⇢ No effect on severe cases of established PNAC
  
  – Recent pediatric study (Jensen 2009) – Retrospective; 107 patients with gastroschisis (36 cycled, 71 continuous)
    
    ⇢ Cycled group had delayed onset and lower incidence of PNAC
    
    ⇢ Confounding factors affected results

• **Moderately weak evidence (Class IV, Grade C)** that cycling PN decreases PNAC
Topic 4 – Medication use in PNAC

- Role of CCK-octapeptide
- Role of oral supplemental bile acids
- Role of erythromycin
Medications in PNAC

• Question 1 – Is cholecystokinin-octapeptide (CCK-OP) effective in treating PNAC?
  – CCK promotes bile flow
  – Early series showed promise
  – Large, prospective randomized trial (Teitelbaum 2005)
    ➢ 243 infants (124 CCK, 118 Placebo, 1 excluded)
    ➢ No effect on conjugated bilirubin levels, or other secondary outcomes
    ➢ No effect on gallstone formation

• Routine use of CCK-OP not recommended (Class I, Grade A)
Medications in PNAC

• **Question 2** – Are supplemental bile acids (ursodiol) effective in preventing or treating PNAC?
  
  – Effectiveness in sclerosing cholangitis and biliary cirrhosis
  
  – Case series with small numbers showed variable results
  
  – Open label trial (22 treated vs 30 control) – Heubi 2002
    
    ➢ No difference in peak conjugated bilirubin, ALT, etc.
  
  – Randomized controlled trial – Arslanoglu 2008
    
    ➢ Neonates, small numbers
    
    ➢ GTT, ALT, AST decreased in treatment group but not control

• **Supplemental bile acids may result in improvement in PNAC (Class II, III, Grade C)**
Medications in PNAC

• Question 3 – *Is erythromycin effective in preventing or treating PNAC?*
  
  – Increases motility; effective in promoting feeding
  
  – Randomized controlled trial – Ng 2007
    
    ➢ 182 infants (91 erythromycin, 91 placebo)
    
    ➢ Erythromycin associated with lower incidence of PNAC, sooner full enteral nutrition, earlier cessation of PN, lower incidence of sepsis

• A small body of evidence (Class II, Grade C) suggests that erythromycin may prevent PNAC via various effects on enteral tolerance