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
    - Spencer, et al (2005)
    - Healy, et al (2008)
    - Hsieh, et al (2009)
  - **Majority of, but not all, studies support role of prematurity in PNAC (Class II and Class III)**

Non-nutrient Risk Factors in PNAC

- *Question 2 – What underlying diagnoses are most closely associated with PNAC?*
  - Spencer, et al (2005) – Prospective trial → NEC
  - Christensen, et al (2007) – Case series → NEC, gastroschisis, intestinal atresia
  - Robinson (2008) – Case-control study → NEC
  - Healy et al (2008) – Fluconazole prophylaxis → 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**