Not Quite Ready for Prime Time: 
Up and Coming Nutritional Topics in the Neonate!

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The speaker has signed a disclosure form and indicated she 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 examine promising topics in neonatal nutrition that have not yet reached routine practice on a national level. Topics will include designer lipids for the prevention of cholestasis (Omegaven, restricted lipids, etc.), the microbiome and its manipulation (prebiotics), early feeding after gastrointestinal surgery, and others.

References

PNAC


Feeding PDA


**Early Post-Op Feeding**


### Session Outline

See presentation handout on the following pages.
Objectives

- Nutrition and feeding practices vary widely from NICU to NICU. This presentation will consist of short vignettes about some of these practices and why they are not quite ready for “Prime Time”.
  - Cholestasis
  - Feeding during medical treatment for the PDA
  - Early feeding post op
  - Manipulation of the Microbiome

Cholestasis

- PNAC
- PNALD

PNALD

- Pediatric Short Bowel Syndrome (SBS) occurs approx. 24.5/100,000 live births. It may be fatal up to 50% of time.
- The majority of the morbidity and mortality associated with SBS is due to end stage PNALD
- PNALD occurs in up to 67% of children with SBS

Risk Factors for PNAC

- Non nutrient risk factors
- Lipid Emulsions
- Non lipid Considerations
- Supplemental Medications

Children with SBS may progress to irreversible liver failure
The long term outcomes of liver –intestinal transplantation remains poor (50%...2009)
PNAC and Lipids

- Full etiology of PNAC is not clear, multifactorial
- The use of Soybean based Intravenous lipid emulsions (SLEs) is believed to contribute
  - Phytosterols
  - Proinflammatory nature of Omega 6 fatty acids (soybean lipid products rich in omega 6 FA)

Phytosterols

- Plant derived steroid alcohols
  - Naturally occurring in plant cell membranes, cholesterol fills this role in mammals
- May lead to impaired bile drainage and hepatobiliary dysfunction (animal models)

Limiting Lipids

- Causes of PNALD are unclear
- Appears to be multifactorial
  - Loss of epithelial barrier function, passage of enteric organisms into hepatic circulation, release of endotoxins and pro inflammatory cytokines
  - Loss of critical biliary canicular transport proteins (move bile out of hepatocytes and into bile ducts)?
  - Cober and Teitelbaum, (2010)
- Intravenous lipid emulsions
  - Association between lipid administration and PNALD

Restricting Lipids may prevent PNALD

- Lipids restricted to 1 gm/kg/d throughout a patients entire PN course. Only 22% of infants develop PNALD compared 44% in historic controls receiving 3 gm/kg/d (p 0.002).

Reducing Lipids may decrease rate of rise of Direct Bilirubin

- Cober and Teitelbaum decreased lipids to 1 gm/kg/day two times per week in patients who already had a direct bili of at least 2.5mg/kl. Monitored rate of rise of bilirubin and evidence of essential fatty acid deficiency.
- No detriment to growth or development of irreversible essential fatty acid deficiency
- They concluded it could help reverse cholestasis, but diligent screening for EFAD was needed.
- Study prospective with historic controls.

Why is lipid restriction not quite ready for prime time

- In need of further study
- Use of historic controls
- Short term outcomes
- What about myelination and brain growth?
Omegaven

- Fish oil product
- High in Omega 3’s
- Several small case series show resolution of liver disease
- Dose: 1 gm/kg/d
- Cost: ?? $1 per ml or $50-100 per day

Omegaven

- Approved for use in adults in Europe, as a supplement
- In trials has been used as a single agent or in combination with another fat source
- Limits or reverses PNALD
  - Studies have been done with Omegaven as a single agent or as a combo. In all, after about a month direct bilirubins start to fall (takes longer, slower with combination products).

Confounders

- Most studies that use Omegaven have limited lipids to 1 gm/kg/d

So why is it not quite ready for prime time??????

- Not FDA approved
  - Manufactured in Germany
  - The company that makes it has no plans to go through testing needed for FDA approval (Marcus, 2006)
- Does not include all essential fatty acids
  - (low levels of linoleic acid and alpha-linoleic acid)
- Theoretical possible side effects
  - Sensitivity to fish, eggs
  - Bleeding (inhibited platelet aggregation)
  - EFAD Not demonstrated in study of EFAD de Meijer, et al 2010

Currently only available for compassionate use or under study protocol
Review of Current Therapies for PNALD


Non nutrient risk factors

• Prematurity (class II and III data)
  – +/- there may be an association, SGA ? At risk
• Surgical diagnoses (class II and III data)
  – NEC is a significant risk factor
• Duration of parenteral nutrition is a significant risk factor (class II and III data)
• Septic Episodes have an important role (class III)
• Bacterial overgrowth: currently not enough data to support antibiotic use (class III, level I)

Summary of Studies

• Restriction of fat emulsion to 1 gm/kg/d 2-3 x per week may reduce bilirubin without detriment to infant growth (class II, grade B)
• Fish oil based lipid contain sufficient amounts of EFA to prevent deficiency (class IV)
• Therapeutic lipid restriction of soybean based lipid emulsion is indicated for neonates who have PNAC (class III, grade B)

Non Lipid Nutrition and PNAC

• Use of fish oil based lipid emulsions in children with PNAC is safe and effective in reversing PNAC (class II and III; grade C)
• There is insufficient data to recommend the use of hybrid lipids in the treatment of PNAC (2012, Rangel et al)
Non Lipid Nutrition and PNAC

- Weak evidence to support limiting copper and manganese as prophylaxis (have to watch levels)
- Strong evidence that trophic feeding may be helpful (class II, grade B)
- Week evidence that cycling tpn may help

   - 2012, Rangel et al

Supplemental medications and PNAC

- Routine use of CCK-OP (sincalide) is not recommended
- Oral administration of supplemental PNAC may improve some markers of PNAC (class III, grade B)
- Erythromycin promotes motility and may prevent PNAC by facilitating tolerance (class II, grade C)

   - 2012 Rangel, et al

Feeding during Treatment of the PDA

- Audience Poll

Why the concern ???

- Atrophy and impair digestive processes
  - 85% of Neo’s report withholding feeds during treatment (Clyman, et al 2013)
  - NPO as short as 72 hours: atrophy, impaired function and permeability, feeding intol
- The PDA itself.....impaired blood flow
- Current medications used to treat PDA may effect feeding tolerance

Current drugs

- Indocin
  - Decreases intestinal blood flow, inhibits hyperemic response and interferes with mucosal barrier function (Clyman, et al 2013)
- Ibuprofen
  - Does not appear to have same effect on intestinal blood flow, but does effect gastrointestinal permeability (Clyman, et al 2013)

The literature

- Bellander, et al 2003
  - European study, infants routinely fed on indocin, 64 infants, case controls, reported no difference in tolerance of feeds
- Clyman, et al 2013
  - 177 infants, randomized to NPO or trophic feeds (15ml/kg/d). Infants were included that got indomethacin and ibuprofen. Fed infants required fewer days to achieve feedings, no change in incidence of infection, nec, SIP or other morbidity
Literature: Feeding PDA

- Yanowitz, et al 2014
  - 34 infants, randomized to indocin or ibuprofen and then randomized to trophic feeding or NPO. Direct examination of mesenteric blood flow after treatment complete with Doppler ultrasound. Infants who were fed had earlier rises in SMA blood flow (90% of infants got Indomethacin due to shortage).

So....why is this not ready for Prime time?

Other options on the Horizon

- Hammerman
  - 2011: Case reports of oral Paracetamol
    - Also known as: acetaminophen, APAP
  - Working on RCT
  - Hammerman, et al 2011

Manipulation of the Microbiome

- What is the Microbiome?
  - Sum of all microbial life living in and on the human body

Why do we care?

It is the hot topic…….
NEC and feeding intolerance
Growing list of childhood and adult disorders with suspected microbiota component
- Susceptibility to viral and bacte infection, metabolic disorders (obesity and diabetes), inflammatory and autoimmune diseases, neurodevelopmental disorders.

How do we manipulate the Microbiome in the NICU?

- Unintentional
- Intentional
How do we manipulate the microbiome?

- Environment
  - Method of birth
  - NICU environment
- Antibiotics
- Feeding
  - Formula, breast milk
- Pre and Probiotics

NICU environment

Antibiotics

Feeding

Prebiotics

- Will not discuss Probiotics as they are discussed elsewhere at this conference.

Early Post-Op Feeding

- I was asked to present this topic.............I then I went to the literature
- What literature?
Neonatal Studies

  – Turkey: 56 neonates, 33 early feeds. Surgery for anomalies. 12 hours after surgery 3-5 ml BM in tube, clamped for 40 min and then opened to drain. First stool, day of tolerance of full feeding and LOS shorter in fed group. No leakage or dehiscence

  – India: 17 infants. Duodenal atresia, malrotation, jejunal atresia. 3 preterm infants died (all had multiple atresia’s) Post anastomotic tubes placed, feeds started by postoperative day 2 in 14 infants. “well tolerated and preferable to parenteral nutrition”

Pediatric Studies

• Islek, et al 2013
  – Turkey: 69 patients after percutaneous Gtube. Mean age 5 years. Fed at 4 hours or 12 hours post procedure. No difference in tolerance

• Amanollahi & Azizi, 2013
  – Iran: 67 patients, 1 month to 12 years with bowel anastomosis. Early feeding children got clear fluids in 24 hours and progressed to soft diet by 48 hours, late feeders tpn until day 5 and then fed. Early feeders had fewer infections and shorter LOS.

Why is this not ready for Prime time?

• Let us count the ways............

But I just have to ask........

• My area of expertise is feeding........
• Why does almost every other country in the world feed sooner than we do??????

Biography for Microbiome

• Under development

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