Probiotics to prevent NEC: what is the evidence?  
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Learning objectives  
1. Provide an update on the composition of the gut microbiota in early life.  
2. Consider the impacts of an altered microbiota.  
3. Critically assess the evidence for using probiotics to prevent necrotizing enterocolitis.  

Case presentation  
Case #1. 5-day-old M born by C-section @ 32 weeks, 1,000 g about to start on enteral formula feedings post r/o sepsis & course of IV antibiotics.  

How can one reduce the risk of necrotizing enterocolitis?:  
a) Probiotics  
b) Oral antibiotics  
c) Prebiotics  
d) Gradual introduction of enteral feedings, breast milk, donor milk  
e) Fecal microbial transplant  

Pathogenesis of necrotizing enterocolitis (NEC)  

Differing levels of analyses of the gut microbiome  

Disclosures  
I have the following financial relationships to disclose:  
*Lallemand Human Nutrition  
(research contract)  
*Abbott Nutrition (honorarium)  
*Mead Johnson Nutrition (honorarium)  
*Nestlé Nutrition (honorarium)  
*Procter & Gamble (honorarium)  
Antibe Therapeutics (stockholder)  

* Products or services produced by this company are relevant to my presentation.
Development of the gut microbiota

- Fetal intestine: “sterile”
- Initial colonization determined by:
  - Delivery mode (caesarian section vs. vaginal)
  - Diet (breast feeding vs. formula feedings)
  - Hygiene (exposure to pathogens)
  - Medication (antibiotics)
- Temporal changes over the first years of life


Antibiotic use in preterm infants

- Present in all parts of the intestinal tract
- Increase from esophagus to colon
  - acid production
  - bile
  - motility
  - ileocecal valve
- Surface-lumen axis: more anaerobes in the outer mucus
- FISH: bacteria are not in direct contact with the mucosa
  - at least, in healthy subjects (vs. Crohn disease)

Impact of the gut microbiota on human health.

Reduced bacterial diversity (dysbiosis): an emerging theme across diseases

- Microbiota affected by:
  - Infections
  - Antibiotics
  - Xenobiotics
  - Diabetes mellitus
  - Obesity
  - Cancers: gastric, colonic
  - Inflammatory bowel diseases
  - Irritable bowel syndrome
  - Necrotizing enterocolitis


How does one increase diversity?

Scientific American
June 2012


Nature’s First Functional Food

WHAT’S IN HUMAN MILK

Milk

Macronutrients

Micro- and Macronutrients

HMOs

Prebiotics


Definition & examples of a probiotic

Is: S is not:

Examples:

Microbes

Synonymous with “commensal”

Bifidobacterium (longum, bifidum)

Alive

Synonymous with “live, active culture”

Streptococcus thermophilus

Defined and properly named

Live vaccine

Lactobacillus (GG, acidophilus, rhamnosus, casei, plantarium)

Safe

Fecal enema

Lactobacillus (fictis, cremoris)

Regulatory categories

- Food
- Dietary supplement
- Drug
- Designer/genetically modified
- Direct fed (animal uses)

E. coli

Saccharomyces (boulardii, cerevisiae)


Meta-analyses of probiotics to prevent NEC

Study design:

- Birth weight: includes <1,500 g (VLBW infants)
- Randomized
- Double-blinded with placebo:
  - only in 2 (and both were negative trials!)
- Dose: 0.5-5 x 10⁹ bacteria/day
- Treatment duration: started on day 1-7 & stopped at 4 weeks of age or hospital discharge
- Probiotic strains: different strains/combinations in all trials, but two (LGG, both were negative!)
- Breast milk exclusive: none (poorly described)


Necrotizing enterocolitis

Incidence: 2% probiotics vs. 6% placebo (p<0.001)
Number needed to treat: 25

Mortality

Incidence: 3.5% probiotics vs. 8% placebo (p<0.001)
Number needed to treat: 20
Use probiotics to prevent NEC?

“Evidence that probiotics reduce mortality is as conclusive as that for surfactant for RDS.”


“Great reason to be hopeful . . . However, meta-analyses and multiple small trials have led us astray before”


“We suggest that the effect of probiotics on the incidence of NEC is still controversial.”


“The efficacy of probiotics is no longer questionable. They are more firmly established than almost any other therapy in Neonatology.”

KJ Barrington, J Pediatr 2014;165:417-418

ProPrem trial

• 10 NICU’s in Australia + New Zealand
• 1,099 VLBW infants (<1500g, <32 wk gai)
• Double-blinded, placebo-controlled
  B. infantis DSM 96579 +
  B. animalis subspecies lactis DSM 15954 +
  S. thermophilus DSM 15957
  (1 X 10^9/d)
• Repeat of a previous design (Bin-Nun A, J Pediatr. 2005;147:192-6.)
• 97% received breast milk - due to donor milk bank
• Low background incidence of NEC (4-5%)  


Results of ProPrem trial

<table>
<thead>
<tr>
<th>Probiotics</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=548)</td>
<td>(n=551)</td>
</tr>
<tr>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>NEC:</td>
<td></td>
</tr>
<tr>
<td>&gt;1000g</td>
<td>11 (2.0)</td>
</tr>
<tr>
<td>&lt;1000g</td>
<td>10 (4.3)</td>
</tr>
<tr>
<td>Sepsis:</td>
<td>62 (13.1)</td>
</tr>
<tr>
<td>Mortality:</td>
<td>27 (4.9)</td>
</tr>
</tbody>
</table>

German Neonatal Observational Network: Decreased NEC and mortality, but not sepsis

N=n. 351


Current view on probiotics to prevent NEC

Need studies of sufficient power in the ELBW (<1,000 g)
Confirm results of effective probiotic strain(s)
Double-blinded, as well as placebo-controlled
North American & western European context
Manufacturing process very important=quality!


Challenges related to probiotic use

• Stability of formulations
• Dosage and timing of delivery
• Single versus combination strains
• Distraction from mother & donor milk access
• Safety concerns:
  - for highly atopic subjects, cow’s milk protein in some commercial probiotic preparations
  - bacteremia and fungemia with short gut s. & central line
  - mesenteric ischemia with severe illness, high dose, and multiple probiotic agents (in adults with acute pancreatitis)
  - severe immunodeficiency
  - extreme prematurity


Case presentation revisited

Case #1. 5-day-old born by C-section @ 32 weeks, 1,000 g
who is about to start on enteral formula feedings post r/o sepsis.

How can one reduce the risk of necrotizing enterocolitis?

a) Probiotics - in Asia-Pacific and parts of Europe
b) Oral antibiotics
c) Prebiotics - require further study . . .
d) Gradual introduction of GI feeding [mother’s milk, milk bank [Pasteurized]] - in USA and Western Europe
e) Fecal microbial transplant
Take home messages in 2014:

Gut microbiota is increasingly recognized to play a role in promoting health.

Intestinal dysbiosis appears to play a role in various disease states, including NEC.

Probiotics: comparative efficacy and relative safety profiles are needed.

“Physicians should advocate for further research to define which strains and dose of probiotics should be used in specific conditions.”


Thank you for your attention!

Questions, comments, feedback . . .