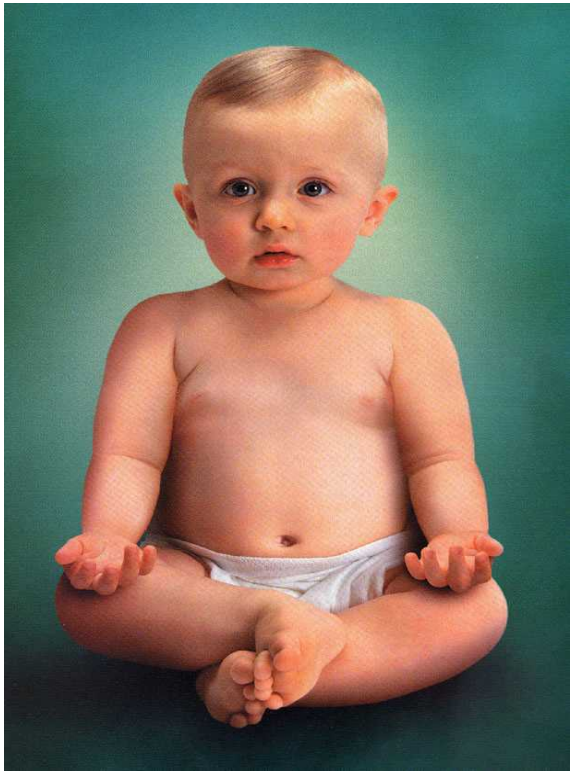
Probiotics and Pediatric Health



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Probiotics Pre-Conference Seminar
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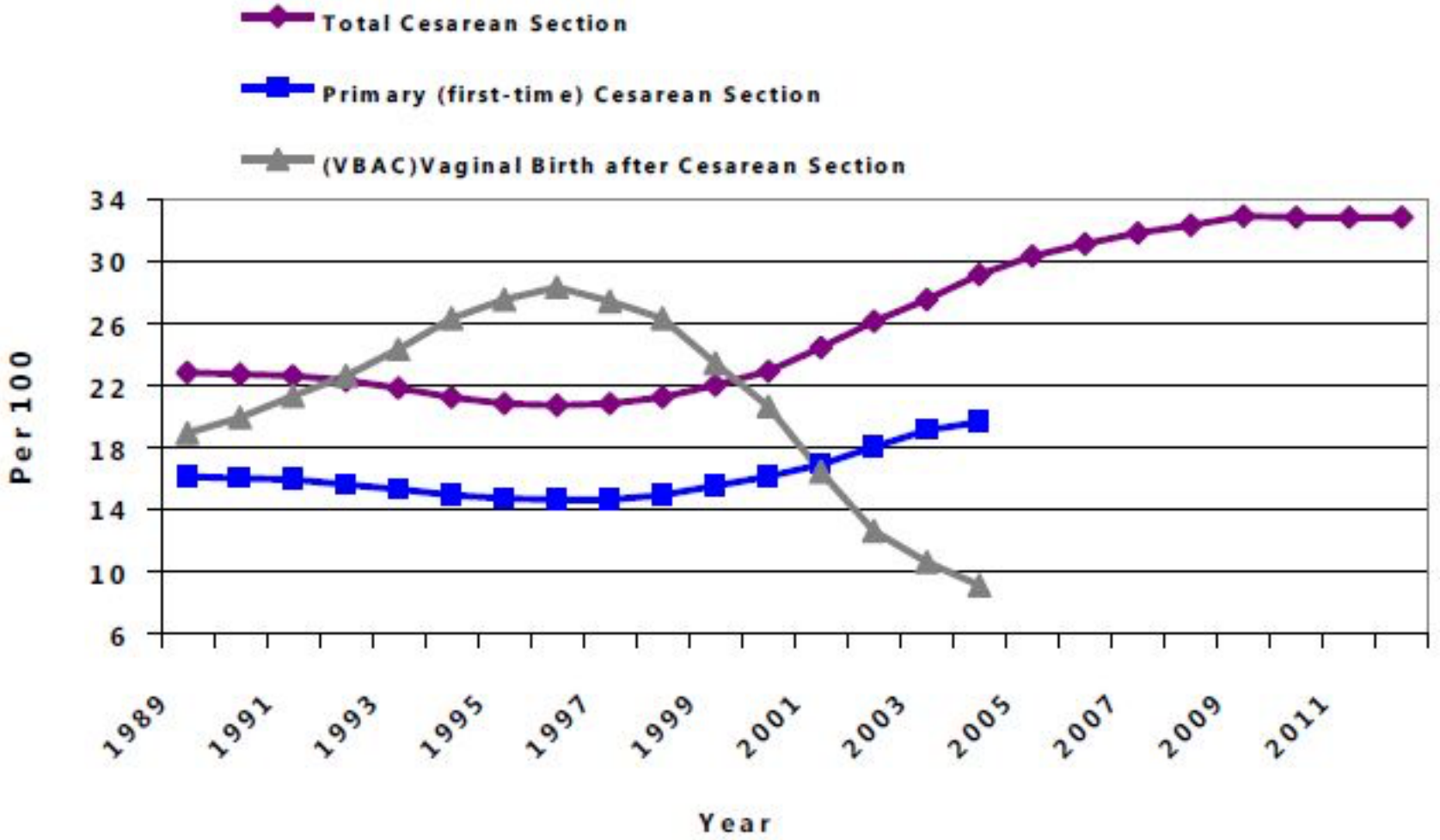
Human Microbiome
"Richness" and Metabolic Markers

- Human gut microbial composition was studied in 292 Danish adults
- Individuals with "low bacterial richness" (23% of the population studied) were characterized by more:
  - Overall adiposity
  - Insulin resistance
  - Dyslipidemia
  - A more pronounced inflammatory phenotype

Nature 2013;500:541-6.

Cesarean Births in the U.S.



Cesarean Births in the U.S.

- U.S. cesarean section rate was 4.5% in 1965
- After steeply increasing over more than a decade it "leveled" off at 32.8% in 2010 and 2011
- So, about one mother in three now gives birth by cesarean section in the U.S.

Development of Gut Microflora

- The infant gut is thought to be sterile at birth, although some new research characterizing the placental microbiome may be challenging this. Microbial colonization occurs at birth when the infant swallows microflora from the vaginal fluid at delivery.
- Development of GALT begins shortly after birth
- The infant gut microbiota is characterized by a high degree of instability, reaching a state similar to adults by 2-3 years of age (consistent with a varied solid food diet)
- Factors influencing the gut flora of an infant include:
  - Mode of delivery – vaginal vs. cesarean
  - Breast fed vs. Formula fed

Development of Gut Microflora

- Canadian study compared gut flora in infants 4 months after birth:
  - The profiles were generally dominated by Actinobacteria (mainly the genus Bifidobacterium) and Firmicutes (with diverse representation from numerous genera).
  - Infants born by cesarean delivery had particularly low bacterial richness and diversity.
  - Compared with breastfed infants, formula-fed infants had decreased richness of species, with over-representation of *Clostridium difficile*.

CMAJ 2013.DOI:10.1503/cmaj.121189.

Development of Gut Microflora
Breast-fed vs. Formula-fed Infants

- The flora of breast-fed infants contains more Actinobacteria – primarily *Bifidobacterium* species.
- IgA and lysozyme in breast milk prevent the growth of some bacteria and breast milk appears to have prebiotic properties.
- The feces of breast fed infants mainly contain lactic and acetic acid compared to acetic and proprionic acid in formula-fed infants who also have higher fecal ammonia and potentially harmful bacterial products.

Immunomodulatory Effects

- Some probiotic strains have been shown *in vitro* induce Th1 production and downregulate some proinflammatory cytokines and Th2-mediated allergic responses (IgE). Implications for allergic rhinitis, atopic dermatitis and ulcerative colitis?

Probiotic Supplementation
Cesarean Born or Formula-Fed Children

- RDBPCT study using a combination of 4 probiotic strains in mothers with infants at risk of atopic disease for the last month of pregnancy and their infants to continue until 6 months of age (along with GOS or placebo) found a significantly reduced incidence of IgE-associated disease (eczema, food allergy, allergic rhinitis, asthma) in cesarean-delivered children only. (*J Allergy Clin Immunol* 2009;123:335-41)
- RDBPCT - formula-fed infants supplemented with *B. lactis* (BB12; 10^6 cfu per day) showed increase sIgA levels. Cesarean-delivered children also showed heightened immune response as measured by anti-rotavirus-specific IgA increase. (*J Parenter Enteral Nutr* 2012; 36:106S-117S).

Gastrointestinal Indications

- Necrotizing Enterocolitis
- Antibiotic Associated Diarrhea
- Acute/Infectious Diarrhea
- Irritable Bowel Syndrome/Functional Abdominal Pain
- Ulcerative Colitis
- Functional Constipation
- Colic

Necrotizing Enterocolitis
Prevention with Probiotics

- 11 eligible randomized studies with 2,176 preterm infants <37 weeks gestational age and <1500 g birth weigh
- Enteral probiotics supplementation significantly reduced the incidence of NEC and mortality by approximately 30%.
- The included trials found no increase in sepsis in infants taking probiotics.

Pediatrics 2010;125:921-30.

However, caution is needed……

- A 29-week old premature infant in Connecticut was treated with ABC Dophilus powder (B. lactis, S. thermophilus, l. rhamnsosus) in the hospital for 4 days.
- The infant died of gastrointestinal mucormycosis.
- Tests of the product by the CDC found *Rhizopus oryzae,* a known cause of mucormycosis.

Antibiotic Associated Diarrhea

- The estimates of prevalence vary greatly - one source says 25% of adults and 11% of children (higher in very young children). One says it is infrequent in outpatient settings (< 0.1%).
- It is a benign, self-limited diarrhea following the use of antibiotics (usually 2-8 weeks after exposure) – most commonly those that have enterohepatic circulation. Most patients respond to supportive measures and discontinuation of antibiotics.
- Causes include:
  - Decrease in anaerobes reduces the metabolism of carbohydrates and a resultant osmotic diarrhea
  - Change in gut microflora results in overgrowth of potentially pathogenic organisms such *C. difficile, Salmonella, C. perfringens* type A, *S. aureus, C. albicans.*

Pediatric AAD
Probiotics for Prevention

- Meta-analysis includes 16 studies with 3,342 children.
- The incidence of AAD in the probiotic group was 9% compared to 18% in the control group but ITT analysis was non-significant overall
- An *a priori* analysis suggests that higher doses of probiotics (> 5 billion cfu/day) is more effective than lower doses (< 5 billion cfu/day) [p = 0.010]. In the high dose group, the NNT to prevent one case of diarrhea is seven.
- Reviewers call for greater attention to drop-out rates and subjects lost to follow-up in future studies as well as greater standardization of organisms used.

Cochrane Database Syst Rev 2011;11:CD004827.

Acute Infectious Diarrhea
Probiotics Shorten Duration

- In a DBPCT, 87 children (2 mths - 6 years old) with infectious diarrhea were rehydrated orally or intravenously and then realimentation was initiated. Children were then randomized to receive either 1.2 x 10^{10} CFU of a freeze-dried mixture of three *L. rhamnosus* strains or placebo b.i.d. for 5 days.
- Etiology of diarrhea was identified in 53 of 87 children: 39 had rotavirus infection, 5 had adenovirus gastroenteritis, and 9 showed the presence of bacterial organisms (e.g., *Salmonella enteritidis, E. coli*).

Acute Infectious Diarrhea
Probiotics Shorten Duration, cont.

- Considering all cases combined, the duration of diarrhea was not significantly shorter than those in the control group.
- However, the duration of diarrhea in children with rotavirus infection taking probiotics was significantly shorter than those receiving placebo ($p = 0.03$). In patients below the age of 12 mths with rotavirus infection, those treated with probiotics had a significant reduction in the duration of diarrhea compared to controls ($p = 0.001$).
- When the intervention started before the 72nd hour of diarrhea, probiotic-treated children had a significantly shorter duration of illness than controls. If after, then there was no difference.

Aliment Pharmacol Ther 2006;23:247–53.

Irritable Bowel Syndrome (IBS)

- RDBPCT with 59 children (ages 4 to 18 years) with IBS. After a run-in period, children received either VSL#3* (450 billion cfu per day for 4-11 year olds and 450 billion cfu bid for 12-18 year olds) for 6 weeks.
- VSL#3 was found to be reduce overall symptoms significantly compared to placebo ($p < 0.05$) and 3 of 5 secondary endpoints – abdominal pain/discomfort ($p < 0.05$), abdominal bloating/gassiness ($p < 0.05$), and family assessment of life disruption ($p < 0.01$). No change was found in stool pattern. No significinat adverse events were reported.

VSL#3 is a combination of: *Bifidobacterium breve, B longum, B infantis, Lactobacillus acidophilus, L plantarum, L casei, L bulgaris, and Streptococcus thermophilus.*

JPGN 2010;51:24-30

IBS/Functional Abdominal Pain (FAP)

- A 20-week RDBPCT study with 136 children (ages 5-14 years) with a diagnosis of IBS (n = 80) or FAP (n = 56) were randomized to receive (following a 4-week run-in) *LGG* (3 x 10^9 cfu/day) or placebo for 8 weeks. This was followed by an 8-week follow-up phase. Intestinal permeability was also tested in 55 children.
- In the children with IBS, the number of episodes of pain during the run-in was 3.4 ± 2.3 in the LGG group and 4.0 ± 3.5 in the placebo group. At the end of the 8-week treatment period, the number of painful episodes was 1.6 ± 0.8 and 3.2 ± 1.9, respectively ($p < 0.001$). At the end of the 8-week follow-up, the number of episodes was 0.9 ± 0.2 and 1.6 ± 0.9, respectively ($p < 0.001$).

IBS/FAP, cont.

- The severity of pain at baseline was 4.4 ± 2.1 for the LGG group and 4.6 ± 2.8 for the placebo group. After the treatment period, severity of pain was 2.5 ± 1.2 and 3.6 ± 2.2, respectively ($p < 0.001$). At the end of the follow-up, severity of pain was 1.8 ± 0.3 compared to 3.3 ± 1.5 ($p < 0.001$). At the end of the 8-week treatment period, treatment success was achieved in 82% of the children in the LGG group compared to 45% in the placebo group ($p < 0.01$).
- Children with a diagnosis of FAP did not show significant changes in either measure compared to placebo.
- The treatment was well tolerated with no significant adverse events.

Pediatrics 2010;126:e1445-e1452.

Ulcerative Colitis

- Small RDBPCT with 29 children (mean age 9 years) with newly diagnosed UC were randomized to receive placebo (n = 15) or VSL#3 (n = 14; weight based dose range: 450-1,800 billion cfu/day) for one year. All were also treated with steroid induction therapy for 4 week as well as oral mesalamine maintenance treatment (50 mg/kg/day).
- Remission was achieved in 13 children in the VSL#3 group compared to 4 in the placebo group ($p < 0.001$). Overall, 3 of 14 children in the VSL#3 group and 11 of 15 in the placebo group relapsed within 1 year of follow-up ($p = 0.014$). At 6 months, 12 months, or at time of relapse endoscopic and histological scores were significantly lower in the VSL#3 group ($p < 0.05$).

Am J Gastroenterol 2009;104:437-43.

Atopic Diseases
Prevention, Treatment, or Both?

- Atopic Dermatitis
- Asthma/Wheeze

Probiotics – Prenatal and Postnatal
Atopy and Asthma

- Meta-analysis of 25 studies with a total of 4,031 participants.[1]
  - Probiotics were effective in reducing total IgE and the reduction was more pronounced with longer follow-up.
  - Probiotics significantly reduced risk of atopic sensitization when administered prenatally and postnatally.
  - Probiotics did not significantly reduce asthma/wheeze
- Another meta-analysis from Canada found no evidence to support a protective association between perinatal use of probiotics and asthma or wheeze.[2]

1. *Pediatrics* 2013 Sep;132(3):e666-76.
2. *BMJ* 2013 Dec 4;347:f6471. doi: 10.1136/bmj.f6471.

Atopic Dermatitis
Prevention with Probiotics

- 159 pregnant women (or their partner) with at least one first-degree relative with a history of atopic dermatitis, allergic rhinitis, or asthma (this included mother, father, or older sibling) and their infants postnatally.
- 132 women and their infants completed the study at the end of the two years. *Lactobacillus GG*— two capsules daily for 2 to 4 weeks before expected delivery. After delivery, breastfeeding mothers continued to take the capsules; otherwise, infants were given the contents of the capsules mixed with water. The duration of postnatal supplementation was six months.

Atopic Dermatitis
Prevention with Probiotics, cont.

- Two Year Follow-up
  - Frequency of AD was 46% in the placebo group compared to 23% in the probiotic group *(Lancet* 2001;357:1076-9.).
- Four Year Follow-up
  - Frequency of AD was 46% in the placebo group compared to 26% in the probiotic group (*Lancet* 2003;361:1869-71).
- Seven Year Follow-up
  - Cumulative risk of developing AD was significantly lower in the probiotic group (42.6%) compared to the placebo group (66.1%) (*J Allergy Clin Immunol* 2007;119:1019-21).

Atopic Dermatitis
Prevention with Probiotics

- DB, PC trial with 474 infants. Mothers took either *L. rhamnosus* HN001 (6 x 10^9cfu/day), *B. lactis* HN019 (9 x 10^9cfu/day), or placebo from 35 weeks gestation until 6 months if breastfeeding or the same dose to the infant if weaned. Infants in the *L. rhamnosus* group had a significantly ($p = 0.01$) reduced incidence of AD at 24 months but not the *B. lactis* group. (*J Allergy Clin Immunol* 2008;122:788-94). Reduced incidence persisted to 2 and 4 years old. (*Clin Exp Allergy* 2012;42:1071-9.
- Follow-up at 6 years found that *L. rhamnosus* HN001 continued to be associated with a significantly lower prevalence of AD, SCORAD ≥ 10, and atopic sensitization (measured by skin prick test and total and specific IgE). There was no effect on incidence of wheeze or asthma. (*Clin Exper Allergy* 2013;43:1048-57)

Pediatric Atopic Dermatitis
Treatment with Probiotics

- Double-blind, placebo-controlled crossover trial using *L. reuteri* and *L. rhamnosus* for children with moderate to severe atopic dermatitis. Marked decrease in gastrointestinal symptoms and decreased gastrointestinal permeability with probiotic therapy (*J Pediatr* 2004;145:612-6).
- An earlier pediatric study found that eczema improves with combination of *L. reuteri* and *L. rhamnosus (J Allergy Clin Immunol* 2003;11:389–95).
- Infants with AD (3-12 months) treated with *L.* GG or placebo for 12 weeks. No therapeutic effect for the probiotic treatment (*Allergy* 2007;62:1270-6).

Pediatric Atopic Dermatitis
Probiotics Reduce Symptoms in IgE-sensitized Infants

- 230 infants (ages 1.4-11.9 months) with symptoms that suggested cow's milk allergy (CMA), one of which had to be atopic eczema/dermatitis syndrome (AEDS) – received either *L. GG* (5 x 10^9 CFU) mixed with food b.i.d; a MIX group, which were treated with *L.GG*, *L. rhamnosus* LC705 (5 x 10^9 CFU), *B. breve shermanii JS* (2 x 10^9 CFU) b.i.d; or placebo.
- *L. GG* reduced mean SCORAD significantly greater than placebo in a subgroup of infants with IgE-associated AEDS (-26.1 vs. -19.8, respectively; p = 0.036). The MIX group showed no difference compared to placebo in this subgroup.

Allergy 2005;60:494-500.

Probiotics and Prevention of URTIs

URTIs in Children
Prevention with Probiotics

- 326 children (3-5 years of age) were randomized to receive either *L. acidophilus* (1 x 10^{10} cfu/day; n = 110), *L. acidophilus NCFM* combined with *B. animalis subsp lactis* Bi07 (1 x 10^{10} cfu/day; n = 112), or placebo (n = 104) for 6 months.
- Compared to the placebo group, the following was found:
  - Reduced fever incidence – single probiotic (53%; p = 0.0085); combination (72.7%; p = 0.0009)
  - Reduced coughing incidence – single (41.4%; p = .027); combination (62.1%; p = 0.005)
  - Reduced rhinorrhea – single (28.2%; p = 0.68) combination (58.8%; p = 0.03)
  - Fever, coughing, and rhinorrhea duration was decreased significantly by 32% in the single strain group (p = 0.0023) and 48% in the combination (p < 0.001)

URTIs in Children
Prevention with Probiotics, cont.

- Incidence of antibiotic use was reduced by 68.4% in the single strain group ($p = 0.0002$) and 84.2% in the combination group ($p < 0.0001$)
- There was a significant reduction in absences from day care in both probiotic groups compared to the placebo group—31.8% in the single strain group ($p = 0.002$) and 27.7% in the combination group ($p < 0.001$)

Pediatrics 2009;124:e172-e179.

URTIs in Children

- RDBPCT, 109 one-month old newborns were randomized to receive either BB-12 (10 billion cfu) or placebo until the age of 8 months. Infants receiving BB-12 experienced less respiratory infections than the placebo group (65 vs. 94%; RR 0.69; 95% CI 0.53-0.89; p = 0.014). (*Br J Nutr* 2010; doi: 10.1017/S0007114510003685).
- RDBPCT - 281children (mean age 53 months) in day care centers were randomized to recieve *LGG* (10^9 cfu/day) or placebo for 3 months. Children in the LGG group had a significantly reduced risk of UTRIs (RR 0.66, 95% CI 0.52 to 0.82, NNT 5, 95% CI 4 to 10), a reduced risk of UTRIs lasting longer than 3 days (RR 0.57, 95% CI 0.41 to 0.78, NNT 5, 95% CI 4 to 11) and a significantly lower number of days with respiratory symptoms (p < 0.001). (*Clin Nutr* 2010;29:312-6).

Probiotic Strains
Checklist

- Important issues in strain selection
  - Viability (including stomach acid and bile resistance)
  - Intestinal adherence
  - No translocation
  - No transferable antibiotic resistance
  - Clinical evidence of safety and efficacy
  - Commercial – stability and shelf-life - potency to time of the expiration date!!