Pre-, probiotics and synbiotics in constipation

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Outline of the presentation

- Definition
- Normal flora
- Prebiotics, healthy infants
- Prebiotics, constipation
- Probiotics, constipation
- Synbiotics, constipation
- Dessert
Functional constipation

- Must include one month of at least two of the following in infants, toddlers, children and adolescents:
  - 1. Two or fewer defecations per week
  - 2. History of excessive stool retention
  - 3. History of painful or hard bowel movements
  - 4. History of large diameter stools
  - 5. Presence of a large fecal mass in the rectum

In toilet trained children the following additional criteria may be used

- 6. At least 1 episode/week of incontinence after the acquisition of toileting skills
- 7. History of large diameter stools which may obstruct the toilet

Prevalence of chronic idiopathic constipation according to country

Suaires NC & Ford AC, Am J Gastroenterol 2011
Rationale for the use of prebiotics in constipation

- Nonstarch polysaccharides or other substance supplements poorly digested by human enzymes that nurture probiotic organisms
  - Fructo-oligosaccharides / Inulin / Galacto-, galactosyllactose-, xylo-, isomalto and soya oligosaccharides / Pyrodextrins (glucose oligosaccharides) / Lactulose / Breast milk oligosaccharides

- Promote growth of bifido-and lactobacilli

- Lower colon pH
Rationale for the use of probiotics

- Differences in the intestinal microbiota in healthy and constipated subjects
  - $\downarrow$ bifidobacteria
  - $\uparrow$ non-pathogenic $E\ coli$, bacteroides
  - $\uparrow$ total number of microorganisms
- Improved transit time
  - Several studies involving $B.\ animalis$ DN 173 010

Stool consistency is strongly associated with gut microbiota richness and composition, enterotypes and bacterial growth rates.

$P = \text{Prevotella}, RB = \text{Ruminococcaceae-Bacteroides}$

Safety and efficacy of inulin and oligofructose supplementation in infant formula: Results from a RCT

- 252 formula fed infants were randomized at birth:
- 124 controls, 128 supplementation formula and 131 BF infants; after 4 months 68 controls, 63 supplementation and 57 BF completed the study

Safety and efficacy of inulin and oligofructose supplementation in infant formula: Results from a RCT

<table>
<thead>
<tr>
<th></th>
<th>Control (^a)</th>
<th>SYN1 (^b)</th>
<th>Breastfed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MONTH 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stool frequency (n/day)</td>
<td>2.5 (2.0, 4.0)</td>
<td>4.0 (2.5, 5.1)**</td>
<td>5.0 (2.5, 7.0)</td>
</tr>
<tr>
<td>Stool consistency score (1–7)</td>
<td>6.0 (4.7, 6.0)</td>
<td>6.0 (6.0, 6.0)**</td>
<td>6.3 (6.0, 7.0)</td>
</tr>
<tr>
<td><strong>MONTH 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stool frequency (n/day)</td>
<td>2.0 (1.5, 3.0)</td>
<td>2.5 (2.0, 3.5)**</td>
<td>3.0 (1.5, 5.0)</td>
</tr>
<tr>
<td>Stool consistency score (1–7)</td>
<td>6.0 (4.3, 6.0)</td>
<td>6.0 (6.0, 6.0)**</td>
<td>6.8 (6.0, 7.0)</td>
</tr>
<tr>
<td><strong>MONTH 3</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stool frequency (n/day)</td>
<td>2.0 (1.5, 2.5)</td>
<td>2.5 (1.5, 3.0)**</td>
<td>2.0 (1.0, 4.0)</td>
</tr>
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<td>6.5 (6.0, 7.0)</td>
</tr>
<tr>
<td><strong>MONTH 4</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stool frequency (n/day)</td>
<td>2.0 (1.5, 2.5)</td>
<td>2.5 (1.5, 3.0)**</td>
<td>1.5 (1.0, 3.0)</td>
</tr>
<tr>
<td>Stool consistency score (1–7)</td>
<td>6.0 (4.0, 6.0)</td>
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<td>6.5 (6.0, 7.0)</td>
</tr>
</tbody>
</table>

Effectiveness of inulin intake on indicators of chronic constipation; a meta-analysis of controlled randomized clinical trials


Defecation frequency

Stool consistency

The clinical effect of a new infant formula in term infants with constipation: a double-blind, cross-over trial

- High $\beta$-palmitic acid level
- Non digestible oligosaccharides (GOS and FOS)
- $N = 38$
- Only 24 completed the study

Conventional versus N. Omneo

N = 35

* p<0.05

ns

Conventional versus N. Omneo

Conclusions

• Infant formula containing high proportion of sn-2 palmitic acid and prebiotic oligosaccharides resulted in softer stools, but not in a difference in stool frequency

• Formula transition to this new formula can be considered as initial treatment step in constipated infants with hard stools

Probiotic Supplement Use among Young Children in Taiwan: A Prospective Cohort Study (n = 17,000)

- ~50% received probiotic supplements < of 18 months

- Firstborn children, native mothers, mothers with higher educational levels, higher family income, and parents who lead healthy lifestyles were positively related to probiotic supplement use among children

- Young children who were breastfed, with eczema, or with gastrointestinal tract problems were significantly positively associated with probiotic supplement use

Maternal use of probiotics during pregnancy (N = 2500) and effects on their offspring’s health in an unselected population

- 341 mothers (13.7%) used probiotics during pregnancy

Consumption of probiotics was significantly associated with:

- Use of homeopathic products
- Maternal history of smoking
- Paternal history of smoking
- Common disease symptoms during first year of life in the offspring did not differ between both groups

Prophylactic Use of a Probiotic in the Prevention of colic regurgitation, and Functional Constipation: A RCT

- 589 infants were randomly allocated to receive *L reuteri* DSM 17938 or placebo daily for 90 days

- At 3 months of age,
  - mean duration of crying time (38 vs 71 minutes; \( P < .01 \))
  - mean number of regurgitations per day (2.9 vs 4.6; \( P < .01 \)),
  - mean number of evacuations per day (4.2 vs 3.6; \( P < .01 \))

- Estimated mean savings per patient of $118.71 for the family and an additional $140.30) for the community

Tolerance and safety of *L. paracasei* ssp. *paracasei* in combination with *B. animalis* ssp. *lactis* in an infant formula: a RCT

- 126 new borns

- RCT:
  - Starter formula + *L. paracasei* ssp. Paracasei Lactis (1 x $10^7$ CFU /g) and *B. animalis* ssp. *Lactis* (1 x $10^7$ CFU /g)
  - Starter formula without probiotics

- 3 months

Results

• Normal growths in all infants

• **No difference** between the 2 groups with respect to:
  • gain in weight, length and head circumference

• **No difference** between the 2 groups with respect to:
  • crying and sleeping hours, number of infections, AB use, visits to the general practitioner and number of adverse events

Results

N = 126

Defecation frequency / day

3 months

6 months

p=0.04

p=0.13

Results

N = 126

**Lactobacillus Reuteri and constipation: DBRPCT**

- **44 infants**
- **age 8.2 mnts ± 2.4 SD**

**Graph Details:**
- **L Reu Wk 0**
- **Pl Wk 0**
- **L Reu Wk 2**
- **Pl Wk 2**
- **L Reu Wk 4**
- **Pl Wk 4**
- **L Reu Wk 8**
- **Pl Wk 8**

**Legend:**
- **1-2 BMs/wk**
- **3-4 BMs/wk**
- **5-7 BMs/wk**

**Statistical Significance:**
- **p=.042**
- **p=.008**
- **p=.027**

**Source:**
Lactobacillus Reuteri and constipation: DBRPCT

Consistency of stools

No of subjects

Hard
Normal
Watery

L Reu  PI
Wk 0

L Reu  PI
Wk 2

L Reu  PI
Wk 4

L Reu  PI
Wk 8

0  2  4  6  8  10  12  14  16  18  20
No of subjects
Functional constipation in children
B lactis DN 173010

Functional constipation (Rome III criteria)
Aged 3 to 16 y
N=159

N=79
B lactis DN-173 010
1.2x10^{10} CFU
Orally, for 3 weeks

N=80
Placebo
Orally, for 3 weeks

N=74
ITT analysis

N=74
ITT analysis

**Primary outcome**

The change in stool frequency from baseline to after 3 wk of product consumption

$\text{MD} 0.3 \ (95\% \ CI \ -1.45 \ to \ 0.51)$  
$P=0.35$


- Probiotic group $n=74$
- Control group $n=74$
Secondary outcome
Success rate
≥3 BM per wk and <1 fecal incontinence episodes in 2 wk

RR 1.6 (95% CI 0.97 to 2.7)
P=0.06

# Probiotics for functional constipation

**RCTs in children - summary**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Probiotic</th>
<th>Constipation</th>
<th>N</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Banaszkiewicz &amp; Szajewska 2005</td>
<td>LGG</td>
<td>&lt;3 BM per wk for at least 12 wk</td>
<td>60</td>
<td>NS</td>
</tr>
<tr>
<td>Bu et al. 2007</td>
<td>L casei rhamnosus Lcr35</td>
<td>&lt;3 BM per wk for &gt;2 mo</td>
<td>27</td>
<td>√ (?)</td>
</tr>
<tr>
<td>Coccorullo et al. 2010</td>
<td>L reuteri DSM 17938</td>
<td>Rome III criteria</td>
<td>44</td>
<td>√</td>
</tr>
<tr>
<td>Tabbers et al. 2011</td>
<td>B lactis DN 173010</td>
<td>Rome III criteria</td>
<td>160</td>
<td>NS</td>
</tr>
<tr>
<td>Guerra et al. 2011</td>
<td>B longum</td>
<td>Rome III criteria</td>
<td>59</td>
<td>√</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td>350</td>
<td></td>
</tr>
</tbody>
</table>
Promising foods….

- 20 pts consumed 180 g per day of ordinary artichokes or artichokes enriched with L paracasei IMPC 2.1 for 15 days (daily dose of $2 \times 10^{10}$ CFU)

30 pts fulfilling Rome III criteria for FC and 30 controls were enrolled

Fecal samples were obtained before and after VSL#3 intake (one sachet twice daily for 2 weeks)
- VSL#3 sachet contains 450 billion lyophilized bacteria: *Bifidobacterium* (*B. longum*, *B. infantis* and *B. breve*); *Lactobacillus* (*L. acidophilus*, *L. casei*, *L. bulgaricus*, and *L. plantarum*); and *Streptococcus thermophilus*

Flora examined by quantitative real-time polymerase reaction

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Comparison of fold differences in concentrations of gut flora between functional constipation patients and controls

Fold differences in each bacterial gene expression; healthy controls

- Lactobacillus spp.
  - Quantitative fold difference ($2^{-\Delta\Delta C_t}$)
  - Before vs. After
  - $P = 0.022$

- Bifidobacterium spp.
  - Quantitative fold difference ($2^{-\Delta\Delta C_t}$)
  - Before vs. After
  - $P = 0.018$

- Escherichia coli spp.
  - Quantitative fold difference ($2^{-\Delta\Delta C_t}$)
  - Before vs. After
  - $P = 0.904$

- Clostridium spp.
  - Quantitative fold difference ($2^{-\Delta\Delta C_t}$)
  - Before vs. After
  - $P = 0.126$

- Bacteroides spp.
  - Quantitative fold difference ($2^{-\Delta\Delta C_t}$)
  - Before vs. After
  - $P = 0.076$
Fold differences in each bacterial gene expression; constipated patients

- **Lactobacillus spp.**
  - Quantitative fold difference ($2^{-\Delta\Delta C_T}$)
  - Before: 
  - After: 
  - $P = 0.469$

- **Bifidobacterium spp.**
  - Quantitative fold difference ($2^{-\Delta\Delta C_T}$)
  - Before: 
  - After: 
  - $P = 0.381$

- **Escherichia coli spp.**
  - Quantitative fold difference ($2^{-\Delta\Delta C_T}$)
  - Before: 
  - After: 
  - $P = 0.959$

- **Clostridium spp.**
  - Quantitative fold difference ($2^{-\Delta\Delta C_T}$)
  - Before: 
  - After: 
  - $P = 0.267$

- **Bacteroides spp.**
  - Quantitative fold difference ($2^{-\Delta\Delta C_T}$)
  - Before: 
  - After: 
  - $P = 0.149$
Bristol stool scale and mean complete spontaneous bowel movement before and after VSL#3

After the VSL#3 ingestion period ended

- 50% Return to symptoms of the original severity
- 11% Recurrence
- 39% No recurrence

Role of Synbiotics in the Treatment of Childhood Constipation: A Double-Blind Randomized Placebo Controlled Trial

- 102 children, 4-12 yrs of age, Rome III criteria

- Group A, received 1.5 ml/kg/day oral liquid paraffin + placebo
- Group B, 1 sachet synbiotic/day + placebo
- Group C, 1.5 ml/kg/day oral liquid paraffin + 1 sachet synbiotic/day

- Protexin CO, UK 1x10^9 CFU/1 sachet:
  - Combination of probiotic strains: L. casei, L. rhamnosus, S. thermophilus, B. breve, L. acidophilus, B. infantis and fructooligosaccharide as prebiotic

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Liquid paraffin + Placebo</th>
<th>Synbiotics + Placebo</th>
<th>Liquid paraffin + Synbiotics</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients at randomization (%)</td>
<td>29 (29.9)</td>
<td>31 (32.0)</td>
<td>37 (38.1)</td>
<td>--</td>
</tr>
<tr>
<td>No. of encopresis per week pretreatment (±SD)</td>
<td>2.34 (±4.9)</td>
<td>2.68 (±4.7)</td>
<td>0.92 (±2.9)</td>
<td>0.208</td>
</tr>
<tr>
<td>No. of Encopresis per week after treatment (±SD)</td>
<td>0.24 (±1.3)</td>
<td>0.06 (±0.25)</td>
<td>0.0 (±0.0)</td>
<td>0.317</td>
</tr>
<tr>
<td>No. of patients with abdominal pain pretreatment (%)</td>
<td>17 (58.6)</td>
<td>21 (67.6)</td>
<td>24 (64.9)</td>
<td>0.754</td>
</tr>
<tr>
<td>No. of patients with abdominal pain after treatment (%)</td>
<td>4 (13.8)</td>
<td>2 (6.5)</td>
<td>5 (13.5)</td>
<td>0.582</td>
</tr>
<tr>
<td>No. of patients with side effects (seepage) (%)</td>
<td>18 (62.1)</td>
<td>0 (0)</td>
<td>21 (56.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>No. of patients with successful treatment (%)</td>
<td>24/29 (82.8)</td>
<td>22/31 (71.0)</td>
<td>28/37 (75.7)</td>
<td>0.559</td>
</tr>
</tbody>
</table>

Therapeutic Potential of Fecal Microbiota Transplantation

- Multiple sclerosis
- Chronic fatigue syndrome

- Atherosclerosis
- Idiopathic thrombocytic purpura

- Non-alcoholic fatty liver disease

- Insulin resistance/ type 2 diabetes mellitus

- Obesity

- C difficile infection
  - Irritable bowel syndrome
  - Inflammatory bowel disease

Green: beneficial effect FMT in RCT
Blue: beneficial effect FMT in case series
Black: association between gut microbiota and disease from experimental/observational studies

Smits LP, et al. Gastroenterology 2013
Treatment of Slow Transit Constipation With Fecal Microbiota Transplantation; A Pilot Study

- 20 pts, Rome III-constipation not responsive to conventional treatment including biofeedback training

- Received FMT on 3 consecutive days through nasojejunal tube and followed up for 12 weeks after treatment

## Treatment of Slow Transit Constipation With Fecal Microbiota Transplantation; A Pilot Study

<table>
<thead>
<tr>
<th></th>
<th>Pre-FMT</th>
<th>1 wk</th>
<th>2 wk</th>
<th>4 wk</th>
<th>8 wk</th>
<th>12 wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical remission rate (%)</td>
<td></td>
<td>66.7% (16/24)</td>
<td>62.5% (15/24)</td>
<td>62.5% (15/24)</td>
<td>50% (12/24)</td>
<td>37.5% (9/24)</td>
</tr>
<tr>
<td>Stool consistency score‡</td>
<td>Pre-FMT</td>
<td>2.1 ± 1.7*</td>
<td>3.1 ± 0.6*</td>
<td>3.8 ± 1.1*</td>
<td>3.6 ± 2.1*</td>
<td>3.5 ± 2.3*</td>
</tr>
<tr>
<td>No. bowel movement per week‡</td>
<td>Pre-FMT</td>
<td>1.8 ± 1.3*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Treatment of Slow Transit Constipation With Fecal Microbiota Transplantation; A Pilot Study

- Adverse effects; diarrhea, bloating, abdominal pain

Summary & Conclusions

• Knowledge is lacking regarding the microbiota composition of children with constipation

• The addition of prebiotics/probiotics in infant formula is safe and softens stool

• Inulin seems to be effective in adults with constipation, trials in children with constipation are lacking

• Inconsistent data exist regarding the efficacy of probiotics in children with constipation

• Future studies to determine whether therapeutic strategies aimed at restoration of observed microbial dysbalance are beneficial