Microbiota and probiotics in pediatric IBS

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Outline

1. Definition and subtypes of IBS

2. Pathogenesis of IBS

3. Probiotics and IBS
H2b. Diagnostic Criteria* for Irritable Bowel Syndrome

Must include *all* of the following:

1. Abdominal discomfort (an uncomfortable sensation not described as pain) or pain associated with *2 or more* of the following at least 25% of the time:
   a. Improved with defecation
   b. Onset associated with a change in frequency of stool
   c. Onset associated with a change in form (appearance) of stool
2. No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject’s symptoms

*Criteria fulfilled at least once per week for at least 2 months before diagnosis

In adults, the Rome III committee recommends a subclassification into different subtypes based on the predominant bowel habit (constipation-IBS [C-IBS] or diarrhea-IBS [D-IBS]).

Different authors consider that patients with symptoms of both constipation and diarrhea should constitute an alternating-IBS (A-IBS) or a mixed-IBS subtype.

A recent study in adults showed that the distribution of IBS subtypes is stable over time in most of the patients, although 30%-40% of patients with IBS changed intestinal pattern at least once during a 2-week period.

Longstreth GF et al. Gastroenterology 2006;130: 1480-91.
Subtypes of Irritable Bowel Syndrome in Children: Prevalence at Diagnosis and at Follow-Up

1. C-IBS was the prevalent subtype (45%), with a significantly higher frequency in girls (62%), and D-IBS was more frequent in boys (69%);

2. The prevalent subtype did not change during the 12-month follow-up period;

3. There was a variation in bowel pattern in 24% of children during the follow-up period;

4. Among the intestinal and extraintestinal symptoms considered, none was related to IBS subtypes.

Giannetti E. J Pediatr 2014. May;164(5):1099-1103.e1
Subtypes of Irritable Bowel Syndrome in Children: Prevalence at Diagnosis and at Follow-Up

- Constipation-IBS is the prevalent subtype in children, with a higher frequency in girls.
- In boys, diarrhea-IBS is the most common subtype.

It is important to acquire knowledge about IBS subtypes to design clinical trials that may eventually shed new light on subtype-specific approaches to this condition.

Giannetti E. J Pediatr 2014. May;164(5):1099-1103.e1
Subtypes of Irritable Bowel Syndrome in Children and Adolescents

• Prospective study to investigate the distribution of IBS subtypes among children and adolescents and compared subtypes according to demographic and pain characteristics.

• IBS with constipation was the most common subtype of the disorder (58.1% of subjects), whereas mixed IBS was the least common (2.3% of subjects); 34.1% of subjects were unsubtyped IBS and 5.4% had IBS with diarrhea.

• The groups of different IBS subtypes did not differ significantly by sex, age, ethnicity, or pain characteristics.

CONCLUSIONS: In contrast to adults, in children, IBS with constipation and unsubtyped IBS are the most common subtypes, whereas IBS with diarrhea and mixed IBS are less common. Demographic and pain characteristics cannot distinguish subtypes.

PATHOGENESIS OF IBS

- Altered sensation
- Altered motility
- Psychosocial distress
Biopsychosocial Model of FAPD

Sensitizing medical events:
- Distension
- Inflammation (infection, allergies)
- Motility disorder

Changes in central pain processing and visceral hypersensitivity

Genetic predisposition
- Early life events

Sensitizing psychosocial events:
- Depression
- Anxiety
- Family stress
- Coping style
- Secondary gains
- Abuse history
- Stress

Abdominal pain and other gastrointestinal problems
Post-Infectious Functional Gastrointestinal Disorders in Children

- A cohort study of children 3 to 19 years old with a positive result on a bacterial stool culture. 44 patients in each arm

- 88 patients (46 boys; mean age, 8.1 years; age range, 3-19 years) were recruited.

- Bacteria included Salmonella (54%), Campylobacter (32%), and Shigella (14%).

- 36% of exposed patients and 11% of control subjects complained of abdominal pain (P< .01). 87% had irritable bowel syndrome and 24% had dyspepsia. 56% reported onset of pain following the AGE.

- **Conclusion There is a significant increase in cases of FGIDs after bacterial infections in children.**

*Saps M et al. J Pediatr 2008;152:812-6*
FGIDs were significantly more common in exposed patients compared with controls within 1 month from acute, 3 months, and 6 months later.

Among exposed children, abdominal pain–related FGIDs were significantly more frequent compared with controls after 6 months from infection.

**Conclusion** This prospective cohort multicenter study supports postinfectious FGIDs as a true entity in children. There seems to be a significant increase in abdominal pain–related FGIDs after acute diarrhea in children within 1 month and 3 and 6 months later.

*Pensabene L et al. J Pediatr 2015;166:903-7*
Gut Microbiota Dysbiosis as Risk and Premorbid Factors of IBD and IBS Along the Childhood–Adulthood Transition

Key pathways involved in microbiota–gut–brain signaling

**Gut symbiosis**
- Physiological levels of inflammatory cells/mediators

**Gut dysbiosis**
- Increased levels of inflammatory cells/mediators
  - Functional GI disorders
    - IBD (Ulcerative colitis and Crohn's diseases), post-infectious IBD
  - Cytokines
    - TGF, TNF-α, IFNγ, IL-1β, IL12, IL23, IL2, IL6, chemokines
  - Heuractive molecules
    - GABA, Triptophan, 5-HT precursors, SCFAs, peptide YY, inflammatory cytokines

**Brain-gut axes**

**Gut epithelium**
- Microbiota

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The gut microbiota communicates with the CNS — possibly through neural, endocrine and immune pathways — and thereby influences brain function and behaviour.

Studies in germ-free animals and in animals exposed to pathogenic bacterial infections, probiotic bacteria or antibiotic drugs suggest a role for the gut microbiota in the regulation of anxiety, mood, cognition and pain.

The emerging concept of a microbiota–gut–brain axis suggests that modulation of the gut microbiota may be a tractable strategy for developing novel therapeutics for complex CNS disorders.

Bi-directional Interactions Between Brain and Gut

The microbiota is in constant bidirectional communication with this interface via multiple signaling pathways, and this communication is modulated in response to perturbations of the microbiota, or the brain.

The integrated output of the brain-gut microbial interface is transmitted to the brain via multiple afferent signaling pathways, including endocrine and neurocrine (vagal, spinal afferents) pathways.

A distributed network of brain regions showing decreases in the FMPP group during the emotional faces attention task is shown in the shaded regions.

Three regions of interest selected from the network for study in the resting state are highlighted in pink (insula), green (periaqueductal gray), and blue (somatosensory regions). The change in network strength with intervention is depicted graphically.
Irritable bowel syndrome (IBS)

Treatment Options

- Cognitive Behavioral Therapy
- Cyproheptadine
- Hypnotherapy
- Probiotics
- Diet therapies
- Antispasmodics
- Antidepressants
- Reassurance and education

FAPD disorders
Acceptance of the biopsychosocial model of FGIDs has provided the basis for the use of psychosocial interventions, including parental education, family therapy, cognitive–behavioral techniques, relaxation, distraction, hypnotherapy, guided imagery and biofeedback.

Many of these strategies aim not only to have direct effects on somatic symptoms, but also promote the child’s ability to self-manage symptoms.

On the other hand, psychosocial interventions is not feasible in many centers.

Pharmacological interventions for recurrent abdominal pain (RAP) and irritable bowel syndrome (IBS) in childhood.

• This review provides weak evidence of benefit on medication in children with RAP.

• The lack of clear evidence of effectiveness for any of the recommended drugs suggests that there is little reason for their use outside of clinical trials.

• Clinicians may choose to prescribe drugs in children with severe symptoms that have not responded to simple management.

• If using drugs as a "therapeutic trial", clinicians should be aware that, RAP is a fluctuating condition and any "response" may reflect the natural history of the condition or a placebo effect rather than drug efficacy.

Nonpharmacologic Treatment of Functional Abdominal Pain Disorders: A Systematic Review

✓ Significant improvement of abdominal pain was reported after hypnotherapy compared with standard care/wait-list approaches and after cognitive behavioral therapy compared with a variety of control treatments/wait-list approaches.

✓ Compared with placebo, Lactobacillus rhamnosus GG (LGG) and VSL#3 were associated with significantly more treatment responders.

✓ Guar gum significantly improved irritable bowel syndrome symptom frequency; however, no effect was found for other fiber supplements or a lactose-free diet.

✓ Although high-quality studies are lacking, some evidence shows efficacy of hypnotherapy, cognitive behavioral therapy, and probiotics (LGG and VSL#3) in pediatric AP-FGIDs. Data on fiber supplements are inconclusive.

<table>
<thead>
<tr>
<th>Study characteristics</th>
<th>First author</th>
<th>No. of participants (age range)</th>
<th>Diagnostic criteria</th>
<th>Probiotics</th>
<th>Follow-up</th>
<th>Primary outcome</th>
<th>Secondary outcomes</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain-related FGD</td>
<td>Bausemann and Michail (13), USA</td>
<td>50 (6–17)</td>
<td>ROME II for IBS</td>
<td>LGG 2 x 10^10 cfu, for 6 weeks</td>
<td>None</td>
<td>Change in abdominal pain severity</td>
<td>Number of responders versus non responders in each group, changes in GSRS</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Gawonska et al. (26), Poland</td>
<td>104 (6–16)</td>
<td>ROME II for IBS, FAP, FD</td>
<td>LGG 2 x 10^9 cfu, for 4 weeks</td>
<td>None</td>
<td>Treatment success defined as no pain at the end of intervention</td>
<td>Improvement in abdominal pain (frequency/severity) defined as a change in FPS by at least two faces score, use of medication, school absenteeism</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Francavilla et al. (14), Italy</td>
<td>136 (5–14)</td>
<td>ROME II for IBS, FAP</td>
<td>LGG 2 x 10^9 cfu, for 8 weeks</td>
<td>8 weeks</td>
<td>Change in abdominal pain (frequency/severity)</td>
<td>Treatment success, perception of children’s pain according to their parents, modification of intestinal permeability</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Romano et al. (19), Italy</td>
<td>56 (6–16)</td>
<td>ROME III for FAP</td>
<td>Lactobacillus reuteri DSM 17 938 2 x 10^6 cfu, for 4 weeks</td>
<td>4 weeks</td>
<td>Change in abdominal pain intensity</td>
<td>Abdominal pain (frequency)</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Guandalini et al. (25), Italy, India</td>
<td>59 (4–18)</td>
<td>ROME II for IBS</td>
<td>VSL#3, for 6 weeks</td>
<td>None</td>
<td>Change in global assessment of relief (SGARC)</td>
<td>Abdominal pain, stool pattern, bloating/gassiness, quality of life</td>
<td>None</td>
</tr>
<tr>
<td>Defecation-related FGD</td>
<td>Banaskiewicz and Szajewska (16)</td>
<td>84 (2–16)</td>
<td>Constipation Defined as: stools &lt;3x/week, &gt;12 weeks</td>
<td>LGG + Lactulose 2 x 10^6 cfu, for 12 weeks</td>
<td>12 weeks</td>
<td>Treatment success defined as ≥3 spontaneous BM per week with no episodes of fecal soiling</td>
<td>Number of spontaneous bowel movements, episodes of fecal soiling, stool consistency, straining frequency</td>
<td>Vomiting and abdominal pain, comparable to placebo</td>
</tr>
<tr>
<td></td>
<td>Bu et al. (24), Taiwan</td>
<td>45 (&lt;10)</td>
<td>Constipation Defined as: stools &lt;3x/week, &gt;2 months, and anal fissures or soiling or hard/large stools</td>
<td>Lactobacillus casei DN 114 001 2 x 10^6 cfu, for 4 weeks</td>
<td>None</td>
<td>Treatment success defined as ≥3 spontaneous BM per week with no episodes of fecal soiling</td>
<td>Frequency of defecation, consistency of stools, episodes of soiling, abdominal pain, use of lactulose enema</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Tabbers et al. (15), Holland, Poland</td>
<td>148 (3–16)</td>
<td>ROME III for constipation</td>
<td>Bifidobacterium lactis DN 173 010 2 x 10^6 cfu, for 3 weeks</td>
<td>None</td>
<td>Change in stool frequency</td>
<td>Treatment success, rate of responders, frequency of defecation, stools consistency, frequency of fecal incontinence episodes, digestive symptoms (abdominal pain, flatulence), use of Bisacodyl</td>
<td>Gastroenteritis and vomiting, comparable to placebo</td>
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<tr>
<td></td>
<td>Guerra et al. (20), Brazil</td>
<td>59 (5–15)</td>
<td>ROME III for constipation</td>
<td>Bifidobacterium longum 1 x 10^6 cfu, for 5 weeks</td>
<td>None</td>
<td>Change in defecation frequency</td>
<td>Stool consistency, abdominal pain, defecation pains</td>
<td>None</td>
</tr>
</tbody>
</table>

Cfu = Colony-forming units; IBS = Irritable bowel syndrome; FAP = Functional abdominal pain; FD = Functional dyspepsia; LGG = Lactobacillus rhamnosus GG; GSRS = Gastrointestinal symptom rating scale; FPS = Faces pain scale; BM = Bowel movements; cl/d = cl/day per day.
Conclusion:

- Probiotics are more effective than placebo in the treatment of patients with abdominal pain-related FGID, especially with respect to patients with irritable bowel syndrome.

- The meta-analysis concluded that the use of Lactobacillus GG, Lactobacillus reuteri DSM17938 and VSL#3 significantly increased treatment success in children with abdominal pain-related FGID, particularly those with associated bowel changes.
Although large adult trials have shown that patients with IBS improve significantly with probiotic strains of Lactobacillus and B infantis, these results have not been duplicated in pediatric populations.

Other probiotic combinations, such as VSL #3, were found to be safe and effective in ameliorating IBS symptoms, abdominal pain, bloating, and family life disruption but not in stool pattern in a double-blinded RCT of 57 school-aged children.

Children with IBS had less pain intensity and frequency after taking L rhamnosus GG according to a meta-analysis by Horvath et al.

Barnes D and Ming Yeh A. Nutr Clin Pract.2015;30:747-759
VSL#3 improves symptoms in children with irritable bowel syndrome: A multicenter, randomized, placebo-controlled, double-blind, crossover study.

VSL#3 is safe and more effective than placebo in ameliorating symptoms and improving the quality of life in children affected by IBS.

Compared with placebo, LGG supplementation was associated with a significantly higher rate of treatment in the overall population with abdominal pain-related functional gastrointestinal disorders and in the irritable bowel syndrome subgroup.

No difference was found in the rate of treatment responders between children with functional abdominal pain or functional dyspepsia who received placebo or LGG.

The intensity of pain was significantly reduced in the overall study population and in the IBS subgroup. The frequency of pain was significantly reduced in the IBS subgroup only.

The use of Lactobacillus rhamnosus GG moderately increases treatment success in children with abdominal pain-related functional gastrointestinal disorders, particularly among children with IBS.

The *L. reuteri*-supplemented children had significantly lower pain intensity at both 4 weeks and 8 weeks compared with placebo-supplemented children.

There was no significant difference between the groups at any of the time points in the frequency of episodes of pain, but in both groups of children, there was a significant reduction in frequency with time.

**Conclusions:** Supplementation with *L. reuteri* reduced perceived abdominal pain intensity, which may encourage clinicians to use this probiotic in children with FAP.

The comparison between the 2 treatment groups showed that AP completely disappeared in a significantly higher proportion of IBS children receiving probiotics (42% vs. 14.5%, P=0.006), but this finding was not confirmed in FD subjects (20% vs. 36%, P=0.3)
The proportion of IBS children who reported an improvement in QoL was significantly higher after probiotics than after placebo (48% vs. 17%, P=0.002)

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**Take home messages**

- The overall management of children with IBS should be tailored to the patient’s specific symptoms and identifiable triggers.

- In IBS, some strains of probiotics offer a modest but meaningful benefit in the treatment of FGID in children, and especially in the treatment of abdominal pain. Considering their outstanding safety profile and the scarcity of alternative safe treatment options, they appear to have an interesting role.

- However, in adults and children with IBS, there is a proportion of patients who respond to placebo; the proportion of responders to placebo and active treatment in phase III trials depends on the stringency and the nature of the endpoint. Placebo administered without deception may also be effective in the treatment of IBS.

- Well-structured, clinical trials conducted in children and adults are now needed to explore these promising treatments.