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Probiotics in the prevention and management of irritable bowel syndrome

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6.1 Introduction

Pediatric functional abdominal disorders comprise irritable bowel syndrome (IBS), functional dyspepsia, abdominal migraine, and functional abdominal pain not otherwise specified (Thapar et al., 2020). More than half of new pediatric gastrointestinal (GI) clinic patients fulfill Rome 3 criteria for at least one functional gastrointestinal disorder (FGID) (Rouster et al., 2016). Pain intensity, pain frequency, quality of life, school attendance, anxiety/depression, adequate relief, defecation pattern (disease specific, IBS), and adverse events were included in the final core outcome set for functional abdominal pain disorders in children (Zeevenhooven et al., 2020). Children with IBS suffer chronic abdominal pain related to defecation (Table 6.1) (Hyams et al., 2016; Thapar et al., 2020). Functional abdominal pain disorders are common and occur in 3%–16% of children depending on age, sex, and region (Thapar et al., 2020). Recurrent abdominal pain (RAP) was reported by 26.2% of children on at least one of different assessment timings: 1–2 years, 12 years, and 16 years, and 11.3% reported symptoms more than once (Sjölund et al., 2020).

IBS is considered to be a disorder of the gut–brain or brain–gut axis. The incidence of IBS varies in different regions of the world with a reported prevalence between 1.2% and 5.4% (Hyams et al., 2016). Children with RAP at 12 years had persistent symptoms at 16 years in 44.9% of cases and increased risks for RAP [relative risk (RR), 2.2; 95% confidence interval (CI): 1.7–2.8] and IBS (RR, 3.2; 95% CI: 2.0–5.1) at 16 years (Sjölund et al., 2020). However, RAP pain at 1–2 years was not significantly associated with any later outcome (Sjölund et al., 2020).

The subtypes of IBS reported in adults are also valid in children: IBS with constipation, IBS with diarrhea, mixed IBS with constipation and diarrhea, and unspecified IBS (Hyams et al., 2016; Thapar et al., 2020). The difference between functional constipation and IBS with constipation depends on the persistence of pain or not if the constipation has been adequately managed (Hyams et al., 2016; Thapar et al., 2020). If the abdominal pain resolves with efficacious constipation treatment, the patient suffers functional constipation (Hyams et al., 2016). If the pain does not improve despite resolution of the constipation, IBS with constipation is then the most probable diagnosis. It has been reported that a large number of patients labeled as IBS–diarrhea or IBS-mixed may actually present functional constipation and should be managed as such (Tosto et al., 2020).

TABLE 6.1 Definition of irritable bowel syndrome.

Disease	Definition
Irritable bowel syndrome	All criteria must be present since >2 months and
	the symptoms cannot be explained by another diagnosis after appropriate clinical evaluation
	abdominal pain >4 days/month associated with defecation and/or change in frequency and composition
	resolution of constipation does not result in sufficient decrease of pain

Source: Adapted from Thapar, N., Benninga, M. A., Crowell, M. D., Di Lorenzo, C., Mack, I., Nurko, S., Saps, M., Shulman, R. J., Szajewska, H., van Tilburg, M. A. L., & Enck, P. (2020). Paediatric functional abdominal pain disorders. *Nature Reviews Disease Primers*, 6(1), 89.

6.2 Probiotics in prevention and management of IBS

The available data are quite limited. Only few double-blind, randomized therapeutic trials were reported in pediatric patients with IBS. Moreover, most randomized pediatric studies grouped all children presenting with different subtypes of functional abdominal pain disorders. However, most of the treatment modalities have a direct or indirect impact of the GI microbiota composition.

There are also data supporting the utility of probiotics. The vast majority of the studies mix IBS, functional GI disorders, and RAP. Therefore we were not selective for this review. However, it is obvious that for future research, inclusion criteria for children with RAP, IBS, functional constipation, or other functional GI disorders should be more specific.

One of the first publications dated 2005 evaluated that the efficacy of probiotics in children with abdominal pain was negative (Bausserman & Michail, 2005). *Lactobacillus rhamnosus* GG (LGG) was not superior to the placebo in relieving abdominal pain (40.0% response rate in the placebo versus 44.0% in the LGG group; $P = .774$). There was no difference in GI symptoms, except for a lower incidence of perceived abdominal distention ($P = .02$ favoring LGG) (Bausserman & Michail, 2005). A trial published in 2007, including children with RAP showed that the LGG group had an increased treatment success (no pain) than the placebo group [25% vs 9.6%, relative benefit 2.6, 95% CI 1.05–6.6, number needed-to-treat (NNT) 7, 95% CI: 4–123] (Gawrońska et al., 2007). Specific for IBS ($n = 37$), those in the LGG group were more likely to have treatment success than those in the placebo group (33% vs 5%, relative benefit 6.3, 95% CI: 1.2–38, NNT 4, 95% CI: 2–36) and reduced frequency of pain ($P = .02$), but not pain severity ($P = .10$) (Gawrońska et al., 2007). For the functional dyspepsia group ($n = 20$) and functional abdominal pain group ($n = 47$), no differences were found (Gawrońska et al., 2007). LGG at a concentration of 1×10^{10} colony-forming units (CFU)/mL for a period of 4 weeks can lessen the severity of the patients' pain and improve the functional scale in patients with IBS (Gawrońska et al., 2007). According to another paper from 2010, in children with IBS, VSL3 was significantly superior to placebo ($P < .05$) regarding the subjective assessment of relief of symptoms; and for the relief of abdominal pain/discomfort ($P < .05$), abdominal bloating/gassiness ($P < .05$), and family assessment of life disruption ($P < .01$). No significant difference was found ($P = .06$) in the stool pattern (Guandalini et al., 2010). However, children in the placebo group improved as well (Guandalini et al., 2010). No adverse effect were recorded for any of the patients (Guandalini et al., 2010). Francavilla and coworkers reported that 8 weeks administration of LGG resulted in a significant reduction of frequency (<0.01) and severity (<0.01) of abdominal pain, with a persistent benefit at week 12 (Francavilla et al., 2010). Intestinal permeability had a baseline increase in 59% of the children, and was reduced in the LGG but not in the placebo group (Francavilla et al., 2010). A controlled, double-blind, randomized trial performed in Iran on children with IBS diagnosed by Rome III criteria confirmed that LGG significantly reduced pain already after 1 week of treatment (Kianifar et al., 2015).

According to a meta-analysis published in 2011, there was already evidence that LGG moderately increased treatment success in children with abdominal pain-related functional GI disorders, particularly in cases of IBS (Horvath et al., 2011). In 2014, a review concluded that probiotics are more effective than placebo in the treatment of patients with abdominal pain-related FGIDs, especially with respect to patients with IBS, but not in functional constipation (Guandalini, 2014). In 2015, six randomized, placebo-controlled clinical trials were included in a meta-analysis (Tiequn et al., 2015). No heterogeneity was found (66). The pooled relative risk for clinical improvement with *Lactobacillus* treatment was 7.69 (95% CI: 2.33–25.43, $P = .0008$) (Tiequn et al., 2015). For adults, the pooled relative risk for clinical improvement with *Lactobacillus* treatment reached 17.62 (95% CI: 5.12–60.65, $P < .00001$). For children, the pooled relative risk for clinical improvement with *Lactobacillus* treatment was much lower and reached only 3.71 (95% CI: 1.05–13.11, $P = .04$) (Tiequn et al., 2015). Two other meta-analyses including RCTs in children showed an improvement in abdominal pain for LGG, *Lactobacillus reuteri* DSM 17938 and the probiotic mixture VSL3 (Giannetti & Staiano, 2016; Korterink et al., 2014). The patients most benefiting from probiotics were those with predominant diarrhea or with a postinfectious IBS (Giannetti & Staiano, 2016). The systematic review by Giannetti and Staiano (2016) included 24 studies and found some evidence for beneficial effects of partially hydrolyzed guar gum, cognitive behavioral therapy, hypnotherapy and probiotics (LGG and VSL3).

In IBS, but not in functional dyspepsia, a mixture of *Bifidobacterium infantis* M-63, *Bifidobacterium breve* M-16V, and *Bifidobacterium longum* BB536 determined a complete resolution of abdominal pain in a significantly higher proportion of children, when compared with placebo ($P = .006$), and significantly decreased abdominal pain frequency ($P = .02$) (Giannetti et al., 2017). The proportion of IBS children with an improved quality of life was significantly higher after probiotics than after placebo (48% vs 17%, $P = .001$), but this finding was not confirmed in functional dyspepsia (Giannetti et al., 2017). Children receiving *L. reuteri* DSM 17938 had significantly more days without pain

(median 89.5 vs 51 days, $P = .029$) than a placebo group (Jadrešin et al., 2017). Abdominal pain was less severe in children taking probiotics during the second (<0.05) and fourth month (<0.01) (Jadrešin et al., 2017). Placebo and *L. reuteri* groups did not differ in the duration of abdominal pain, stool type, or absence from school (Jadrešin et al., 2017). Both groups experienced significant reduction in the severity of abdominal pain from first to the fourth month, with the reduction more prominent in the intervention group ($P < .001$ vs $P = .004$) (Jadrešin et al., 2017). Administration of *L. reuteri* DSM 17938 was associated with a possible reduction of the intensity of pain and significantly more days without pain (Jadrešin et al., 2017). A *Bacillus coagulans* Unique IS2 treated group of 4- to 12-year-old IBS children showed a greater reduction in pain scores evaluated by a weekly pain intensity scale (Sudha et al., 2018). There was a significant reduction ($P < .0001$) in pain intensity in the probiotic (7.6 ± 0.98) compared to the placebo group (4.2 ± 1.41) after 8 weeks (Sudha et al., 2018). There was also a significant improvement in stool consistency as well as reduction in abdominal discomfort, bloating, staining, urgency, incomplete evacuation, and passage of gas (Sudha et al., 2018). Bowel habit satisfaction and global assessment of relief was also observed in the *B. coagulans* Unique IS2 treated group as compared to the placebo group (Sudha et al., 2018).

Eleven randomized controlled trials for functional abdominal pain disorders and six for functional constipation were included in yet another meta-analysis, showing some evidence for LGG ($n = 3$) in reducing frequency and intensity of abdominal pain in children with IBS (Pärty et al., 2018). According to this analysis, there was no evidence to recommend *L. reuteri* DSM 17938 ($n = 5$), a mix of *B. infantis*, *B. breve*, and *B. longum* ($n = 1$), *Bifidobacterium lactis* ($n = 1$) or VSL3 ($n = 1$) for children with functional abdominal pain (Pärty et al., 2018). No evidence supported the use of *L. casei rhamnosus* LCR35 ($n = 1$), *B. lactis* DN173 010 ($n = 1$), *B. longum* ($n = 1$), *L. reuteri* DSM 17938 ($n = 1$), a mix of *B. infantis*, *B. breve*, and *B. longum* ($n = 1$), or Protexin mix ($n = 1$) for children with functional constipation. In general, studies had an unclear or high risk of bias (Pärty et al., 2018). Insufficient evidence exists for the use of probiotics in functional abdominal pain and functional constipation (Pärty et al., 2018). Only LGG seems to reduce frequency and intensity of abdominal pain but only in children with IBS (Pärty et al., 2018). A better understanding of differences in gut microbiota in health and disease might lead to better probiotic strategies to treat disease (Pärty et al., 2018). No single strain, combination of strains, or synbiotics can be recommended for the management of IBS, functional abdominal pain, or functional constipation in children. Limited, yet encouraging, evidence exists for LGG at the dose of 3×10^9 CFU and for a multistrain preparation for the treatment of IBS (Hojsak, 2019). In the treatment of functional abdominal pain, there is some evidence for the use of *L. reuteri* DSM 17938 at the dose of at least 108 CFU/day (Hojsak, 2019). Szajewska and Hojsak reported on 13 meta-analyses, 3 systematic reviews, and 15 randomized, controlled trials that assessed B., BB-12, and LGG, either alone or in combination, when administered to infants to improve growth or to children of any age to prevent or treat acute gastroenteritis, antibiotic-, or healthcare-associated diarrhea, respiratory infections, otitis media, and functional GI disorders including IBS (Szajewska & Hojsak, 2020). They found only moderate evidence regarding the benefits of LGG for treating respiratory infections and IBS in children and minimal evidence to support the use of BB-12 (Szajewska & Hojsak, 2020). Dietary treatment with an extensively hydrolyzed casein formula containing the probiotic *L. rhamnosus* GG was reported to prevent functional GI disorders (Nocerino et al., 2019).

The efficacy of a synbiotic treatment (5×10^9 CFUs of *B. lactis* B94 and 900 mg inulin) was compared to a probiotic (5×10^9 CFU *B. lactis* B94) or a prebiotic (900 mg inulin) twice daily for 4 weeks in 71 4- to 16-year-old children diagnosed with IBS (Başturk et al., 2016). Probiotic treatment alone improved belching-abdominal fullness ($P < .001$), bloating after meals ($P = .016$), and constipation ($P = .031$), and synbiotic treatment improved belching-abdominal fullness ($P \leq .001$), bloating after meals ($P = .004$), constipation ($P = .021$), and mucus in the feces ($P = .021$) (Başturk et al., 2016). The synbiotic group had a significantly higher percentage of patients with full recovery than the prebiotic group (39.1% vs 12.5%, $P = .036$) (Başturk et al., 2016). Administration of synbiotics and probiotics resulted in significant improvements in initial complaints when compared to prebiotics. Additionally, there was a significantly higher number of patients with full recovery from IBS symptoms in the synbiotic group than in the prebiotic group (Başturk et al., 2016). The risk–benefit plane for IBS straddles the risk–benefit threshold, so patients can expect a balance between a low chance of risk and also a low chance of benefit (Bennett, 2016).

6.3 Conclusion

Despite the evidence from the pathophysiological animal and laboratory data suggesting that an alternated microbiota plays a causative role in IBS, evidence from clinical trials that the manipulation of the GI microbiota resulting in benefits is limited. Differences in study designs and outcomes is insufficient to recommend administration of probiotics or other interventions that alter the GI microbiota composition in the management of IBS in pediatrics.

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