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The Potential for use of Probiotics in Pediatric Irritable Bowel Syndrome and Inflammatory Bowel Disease

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Abstract Controlled trials of probiotics in irritable bowel syndrome are promising, but most are limited by suboptimal design and small sample size. A recent report from the Rome foundation group included 32 randomized clinical trials of probiotics. Seventy-five percent of these studies (including the 4 pediatric ones) did show an improvement in symptoms, but the therapeutic gain over placebo was generally modest. The patients most benefitting from probiotics appear to be those with predominant diarrhea and those who have developed irritable bowel syndrome after an episode of gastroenteritis. A review focusing only on children with functional gastrointestinal disorders concluded that probiotics are more effective than placebo in the treatment of patients with abdominal pain-related functional disorders, but no effect on constipation was evident for any strain. In spite of a solid conceptual and experimental basis for successful use of probiotics in inflammatory bowel diseases (Crohn's disease and ulcerative colitis), research in humans has been overall quite limited and overall disappointing. To summarize current evidence, no probiotic has proven successful in Crohn's disease, while in ulcerative colitis data are more promising. In fact, a recent meta-analysis, that included 23 randomized controlled trials, concluded that there is evidence of efficacy for the probiotic mixture VSL#3 in helping inducing and maintaining remission. In summary, for both irritable bowel syndrome and inflammatory bowel diseases, there is a definite need for well-designed, randomized clinical trials.

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Introduction

The interest in the intestinal microbiome during the past decade has exploded. With it, there has been a growing interest in the possible utilization of agents affecting it (prebiotics—intended to be a metabolic fuel for beneficial microorganisms—and probiotics—strains selected for their ability to survive the passage in the gastrointestinal tract and eventually provide health benefits to the host). Among the areas that appear more interesting is their potential application in 2 different but equally important conditions: irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD), conditions that have a strong conceptual basis for a potentially useful implementation of their use. In spite of a large body of experimental evidence in various in vitro and animal models, randomized controlled clinical trials—especially in children—are not numerous. This mini review will examine the current status of the use of prebiotics and probiotics in children affected by either disorder.

Probiotics in IBS

Irritable bowel syndrome is a functional gastrointestinal disorder (FGID), and a very frequent one, as up to 25–50 % of the children and teenagers that present to gastroenterology clinics are affected [1, 2]. Thus, IBS involves significant health care costs and has an important negative impact on quality of life and social functioning in many patients [3].

As well defined by the so-called Rome III criteria [4], IBS is characterized by the association of abdominal pain with a change in stool consistency or frequency in the absence of an organic cause.

The underlying pathophysiological mechanisms of this disorder are incompletely known, and it is quite likely that IBS is an umbrella term encompassing various etiological and pathogenetic factors eventually leading to the same syndromic phenotype [5]. Abnormal gastrointestinal motility, altered brain/gut function, low-grade inflammation, psychosocial disturbance, visceral hypersensitivity, and intestinal microbiota all appear to contribute substantially [6, 7] and probably in various degrees in different patients.

The potential role for probiotics in such syndrome is based on a number of observations. Alterations in the intestinal microbiota that have been described in patients with IBS versus non-IBS populations have been reported [8–10]; the development of IBS after a gastrointestinal infection is well documented ("post-infectious IBS") [11]; colonic fecal microbiota transplantation [12] has been utilized; and it is quite conceivable that microbiota may interfere with additional factors involved in the pathophysiology of IBS, such as visceral hypersensitivity and the brain-gut axis [13, 14, 15••].

In adults, several trials have been published, with sometimes conflicting results, although overall the outcomes have been quite promising [6, 16, 17].

In children, fewer randomized clinical trials (RCTs) are available. Earlier investigations were not particularly encouraging: a Cochrane systematic review in 2009 [18] aiming at determining the efficacy of dietary interventions in recurrent abdominal pain and analyzing published RCT up to 2007, included two trials comparing supplementation with *Lactobacillus* GG against placebo [2, 19]. The authors concluded that there was lack of high-quality evidence that the probiotic supplementation could be considered effective in the management of children with recurrent abdominal pain.

Since then, new RCTs have been published, prompting interest in reevaluating the role of probiotics in the management of IBS in children.

In fact, a very recent systematic review and meta-analysis [20•] on the effect of different probiotics as a treatment for FGID in children and adolescents included 9 trials, 5 linked to the abdominal pain-related FGID [2, 19, 21–23], and 4 with defecation-related FGID [24–27].

The trials on abdominal pain used were *Lactobacillus* GG, *Lactobacillus reuteri* DSM 17 938, and the probiotic mixture VSL#3. The meta-analysis concluded that the use of such probiotics significantly increased treatment success in children with abdominal pain-related FGID, especially children with IBS. In our double-blinded, placebo-controlled, cross-over RCT [21], we found that the patients taking VSL#3 compared with placebo experienced a significant ($P < 0.05$) improvement in the score for abdominal pain/discomfort from baseline to 6 week. More importantly, the global subjective relief of symptoms likewise improved more significantly for children on VSL#3 than on placebo.

As for *Lactobacillus reuteri* DSM 17 938, it significantly decreased the intensity of abdominal pain [22, 28]; in Romano's study, its effect did persist after the removal of the probiotic, indicating a lasting effect of the supplementation [22].

Of interest, the two RCTs that assessed the effect of treatment with probiotics (*Lactobacillus* GG and VSL#3) did not show any benefit of the intervention on the parameter of functional diarrhea [2, 21].

Four studies included in the meta-analysis assessed constipation-related FGID. The probiotics used were *Lactobacillus* GG associated with Lactulose, *Lactobacillus casei rhamnosus Lcr35*, *Bifidobacterium longum*, and *Bifidobacterium lactis* DN-173 010 [24–27]. The results were disappointing, with no evidence that probiotics are more effective than placebo in overall outcome of treatment or in increasing defecation frequency in constipated children and with inconsistent data on the improvement in stool consistency [25, 26].

Thus, in summary, it appears that at present, some strains of probiotics offer a modest but significant benefit in the treatment of FGID in children. Considering their general safety and the lack of viable and safe treatment options for these frequent and annoying conditions, they may have a potentially interesting role. Clearly, a long way is in front of us as we need to define strain selections, the choice of single organisms versus mixtures, dosage, safety and especially long-term efficacy, and tolerability.

Probiotics in IBD

The introduction of biological agents has markedly improved our ability to treat patients with the chronic, incurable inflammatory disorders grouped under the name of IBD, namely Crohn's disease, ulcerative colitis, and indeterminate colitis. However, improved clinical efficacy has come at the cost of increased risks, including malignancies [29, 30]. Thus, it is not surprising that the use of "alternative" remedies is very frequent in patients with IBD, and especially in children [31]. In this regard, the possible use of probiotics appears as a natural consideration, especially at the light of the fact that the intestinal microbiota does play an important role in IBD [32•].

In fact, on one side probiotics display features, such as anti-inflammatory action and enhancement of the gut barrier, that seem logically suited to be helpful in IBD; and on the other, there is convincing evidence that the inflammation in IBD results from an altered mucosal immune response to luminal bacterial antigens, thus suggesting that

the use of live microorganisms may have a positive impact on shifting the microbial balance of the microbiota. Support for this hypothesis comes also from a study showing that children with Crohn's disease treated with exclusive and partial polymeric enteral nutrition and experiencing remission with this regimen also showed profound changes in their microbiota, as measured by temperature gradient gel electrophoresis [33].

In the last few years, the IBD microbiota—both in CD and in UC—has been found to be less diverse and to have a different composition compared with healthy controls, and differences have also been found between the microbiota composition in UC versus CD patients [34–36]), to the point that such "dysbiosis" has been called one of the major factors involved in the course of inflammation in IBD [37•].

A large body of data shows efficacy of several probiotic strains in ameliorating the inflammation induced in various animal models of colitis, considered to some extent as models of IBD, and especially ulcerative colitis. Some examples include:

In mice models of colitis: *Enterococcus faecalis, L. acidophilus, C. butyricum* and *B. adolescentis* [38], VSL#3 [39, 40], *E. coli* M-17 [41], *Lactobacillus salivarius* [42]; a mixture of *Lactobacillus* strains— *Lactobacillus* GG, *L. plantarum*, *L. casei* and *L. lactis*, *Bifidobacterium bifidum*, *B. infantis*, *B. lactis* and *B. Adolescentis* [43]; *Lactobacillus fermentum* [44], *Saccharomyces boulardii* [45], *Lactobacillus casei* [46, 47] *Bifidobacterium lactis* and *Lactobacillus acidophilus* [47].

In *rat model of colitis*, other strains have been found effective: *Lactobacillus* GG and a mixture of *Streptococcus thermophilus, Lactobacillus acidophilus,* and *Bifidobacterium longum* [48], VSL#3 [49]; *Lactobacillus plantarum* HY115 and *L. brevis* [50]); *Lactobacillus reuteri* and *Lactobacillus fermentum* [51]. VSL#3 results in a decrease of tumor necrosis factor-a, IL-6 and an increase of IL-10, which may due to exert the anti-inflammatory activity by inhibiting PI3K/Akt and NF-kB pathway [52]

In spite of the strength of the conceptual basis for the beneficial use of probiotics, and of the extensive experimental data in animal models, the existing literature—and in particularly concerning papers reporting RCT—on the use of probiotics in IBD in adults and even more so in children is indeed extremely limited. The analysis will be limited to papers reporting RCT with a comparator, either a placebo or an accepted standard therapy.

Crohn's Disease

A 2012 meta-analysis [36] detected only 3 small uncontrolled studies and one placebo-controlled trial in adults patients with active CD. The trial reported a lower relapse rate after 12 months receiving E. coli Nissle 1917 added to prednisolone therapy [53].

The same review included 4 studies in patients with inactive CD: two using *Lactobacillus* GG [54, 55] and two using *Lactobacillus johnsonii* [56, 57]. None of them could demonstrate that probiotics were more effective than placebo in preventing relapses.

A small study published in 2000 found a significantly lower relapse rate in CD when *Saccharomyces boulardii* was combined with mesalazine [58]; however, a subsequent larger randomized, double-blind placebo-controlled trial utilizing the same probiotic yeast showed no significant difference in the frequency of relapses in the *Saccharomyces boulardii* group (47.5 %) compared to the placebo one (53.2 %); the time to relapse was also not statistically different [59••].

A 2014 meta-analysis [60] included 23 randomized controlled trials (only 3, however, conducted in children) published up to 2011, with a total of 1763 participants: 12 in UC, 4 in "pouchitis," and 7 in CD.

None of the trials [53, 55, 61] that were the remission/response rates in acute CD were reported, showed any significant benefit in favor of probiotics supplementation ($P = 0.35$, $RR = 0.89$).

As for efficacy of probiotics in maintaining remission, an obvious major goal in the potential use of probiotics, 7 RCTs (including only one in children, reported in more detail below) examined the frequency of and timing to clinical relapses, finding that there was actually again no difference between the probiotics-supplemented patients and the control ones ($P = 0.71$, $RR = 1.09$).

In children, a randomized, placebo-controlled trial of the probiotic *Lactobacillus* GG [62] with the aim of comparing the remission in patients that receive *Lactobacillus* GG added to standard therapy was unable to demonstrate that this probiotic would prolong remission time in patients with CD already in remission on standard therapy. In fact, the time to relapse and proportion of patients relapsing was essentially identical in both *Lactobacillus* GG and placebo groups.

Ulcerative Colitis

A more favorable picture is obtained when looking at the use of probiotics in UC. As mentioned, of the 23 RCTs included in the 2014 meta-analysis [60], twelve were realized in UC patients.

Nine studies analyzed the remission/response in acute UC, utilizing Bifidobacteria, E. Coli, and VSL#3: while the overall analysis of these RCTs showed significant benefit from the use of probiotics, the sub-analysis based on probiotic utilized documented such significant effect only for VSL#3 [63••, 64–67].

As for their efficacy in maintaining remission once pharmacologically obtained, the analysis included 5 trials in UC and there was no advantage of probiotics compared with placebo (RR 0.89, 95 %CI 0.66–1.21). However, the only pediatric trial, conducted with VSL#3 [63••], showed efficacy of the probiotic (RR 0.29, 95 % CI 0.10–0.83). The trial included 29 children, with a recent diagnostic of UC who received initially prednisone and mesalamine plus either placebo or VSL#3 for induction; once remission had been obtained, they were continued on mesalamine plus either placebo or VSL#3 for maintenance. The patients were evaluated at 1, 2, 6 months, and 1 year after diagnosis or at the time of relapse. An endoscopy was additionally performed at the time of diagnosis and then repeated at 6, 12 months or at the time of relapse. As mentioned, not only the remission rate, but also the relapse rates were better in the patients treated with VSL#3 vs placebo; furthermore, endoscopic and histological scores were significantly better in the VSL#3 group than in the placebo group ($P < 0.05$).

A recent pediatric trial included 31 children with mild to moderate ulcerative proctitis/proctosigmoiditis with mild to moderate disease activity [68•]; they received enema solution with *L. reuteri* ATCC 55730 or placebo during 8 weeks added to the oral treatment with mesalazine. A clinical, endoscopic, histological, and immune evaluation (IL-10, IL-1b, TNFa, IL-8) was performed. Clinical and endoscopic improvements were shown to be better in the probiotic group, and the histological score was significantly decreased in the *L. reuteri* group ($P < 0.01$). As for the cytokines evaluation, a significant increase in the mucosal expression levels of IL-10 and a significant decrease in the levels of IL-1b, TNFa, and IL-8 mucosal expression levels ($P < 0.01$) were documented only in the *L. reuteri* group.

Conclusion

Both IBS and IBD, as conditions originating at least in part by an abnormal interaction between microbiota and the host immune system, are potential candidate to be addressed by interventions aiming at normalizing such imbalance. In this regard, probiotics have been studied extensively in various animal models of IBS as well as of IBD, with encouraging results. Their clinical applications in children with these conditions, however, are still limited, and in many cases hampered by limited size or short duration studies. At the present time, the following conclusions appear valid:

1. IBS. Some probiotic strains, namely the probiotic mixture VSL#3, *Lactobacillus* GG, and possibly *Lactobacillus reuteri* DSM 17 938, have shown some efficacy in improving overall symptoms and especially abdominal pain in children with IBS. Considering the limited role for safe and effective pharmacological agents, they may represent useful options.
2. IBD. To date, there is no evidence of efficacy for any strain in pediatric (or adult) Crohn's disease. It is, however, quite possible that, given the array of genotypes and phenotypes of Crohn's disease, the investigators have yet to identify the specific probiotics that may be beneficial in specific forms of this chronic, multiform inflammatory process. As for ulcerative colitis, there is promising evidence of efficacy for the probiotic mixture VSL#3.

Clearly, progress in the field will require on one side the better identification of probiotic strains, and their testing in adequately powered, long-term pluricentric RCT.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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