VSL#3 Improves Symptoms in Children With Irritable Bowel Syndrome: A Multicenter, Randomized, Placebo-Controlled, Double-Blind, Crossover Study

*Stefano Guandalini, †Giuseppe Magazzù, †Andrea Chiaro, ‡Valeria La Balestra, ‡Giovanni Di Nardo, §Sarath Gopalan, §A. Sibal, ||Claudio Romano, ¶Roberto Berni Canani, #Paolo Lionetti, and *Mala Setty

ABSTRACT

Background and Objectives: Irritable bowel syndrome (IBS) is a common problem in pediatrics, for which no safe and effective treatment is available. Probiotics have shown some promising results in adult studies, but no positive study has been published on pediatric age. We aimed at investigating the efficacy of VSL#3 in a population of children and teenagers affected by IBS, in a randomized, double-blind, placebo-controlled, crossover study conducted in 7 pediatric gastroenterology divisions.

Patients and Methods: Children 4 to 18 years of age, meeting eligibility criteria, were enrolled. The patients were assessed by a questionnaire for a 2-week baseline period. They were then randomized to receive either VSL#3 or a placebo for 6 weeks, with controls every 2 weeks. At the end, after a ''wash-out'' period of 2 weeks, each patient was switched to the other group and followed for a further 6 weeks.

Results: A total of 59 children completed the study. Although placebo was effective in some of the parameters and in as many as half of the patients, VSL#3 was significantly superior to it ($P < 0.05$) in the primary endpoint, the subjective assessment of relief of symptoms; as well as in 3 of 4 secondary endpoints: abdominal pain/discomfort ($P < 0.05$), abdominal bloating/gassiness ($P < 0.05$), and family assessment of life disruption ($P < 0.01$). No significant difference was found ($P = 0.06$) in the stool pattern. No untoward adverse effect was recorded in any of the patients.

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

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From the *University of Chicago Section of Pediatric Gastroenterology, Hepatology and Nutrition, Chicago, IL, the †Pediatric Gastroenterology Unit, University of Messina, Messina, the ‡University of Rome ''La Sapienza,'' Rome, Italy, the §CRNSS, New Delhi, India, the ||Pediatric Endoscopy Unit, University of Messina, Messina, the ¶Department of Pediatrics, University ''Federico II,'' Naples, and the #Department of Pediatrics, University of Florence, Florence, Italy.

Address correspondence and reprint requests to Stefano Guandalini, MD, Professor of Pediatrics, University of Chicago Section of Pediatric Gastroenterology, Hepatology and Nutrition, 5839 S. Maryland Ave, MC 4065, Chicago, IL 60637 (e-mail: sguandalini@peds.bsd.uchicago.edu).

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The syndrome of functional recurrent abdominal pain associated with abdominal distension and changes in bowel habits (constipation, diarrhea, or a combination of both) is referred to as ''irritable bowel syndrome'' (IBS). Symptoms associated with IBS are common complaints of children and teenagers (1) and a condition for which no safe and effective pharmacological (2) or dietetic (3) treatment is available.

IBS in children and adolescents accounts for a significant number (2%–4%) of office visits to primary care physicians (1,4,5). Although the etiology of IBS remains elusive, there is growing recognition of the role played by intestinal infections and disturbances of the colonic microflora in the genesis of this condition (6,7). Hence, the use of probiotics has been proposed with recent evidence of effectiveness in adults (8); in pediatric age, *Lactobacillus GG* has been tried, with conflicting results (9,10). So far no investigation has been done in pediatric age with the probiotic mixture ''VSL#3,'' a patented probiotic preparation that in adult investigations showed some efficacy in IBS (11,12). VSL#3 contains live, freeze-dried lactic acid bacteria, at a total concentration of 450 billion lactic acid bacteria per sachet, comprising 8 different strains: *Bifidobacterium breve, B longum, B infantis, Lactobacillus acidophilus, L plantarum, L casei, L bulgaris, and Streptococcus thermophilus*. We aimed, therefore, at assessing the efficacy of the oral administration of the probiotic mixture ''VSL#3'' in children affected by IBS.

PATIENTS AND METHODS

This investigation was a randomized, double-blind, placebo-controlled, crossover trial conducted in 5 pediatric tertiary care centers located in Italy (4) and in India (1). The center in Chicago, IL, served as the coordinating center, the center where the data were gathered and analyzed. The protocol of the study was approved by the proper institutional ethical committee in each of the participating centers. Patients eligible for enrollment were male and female children in the age range 4 to 18 years with IBS diagnosed according to the Rome II criteria (13), namely at least 12 weeks, not necessarily consecutive, in the preceding 12 months of abdominal discomfort or pain that had at least 2 of 3 features: relieved with defecation; and/or onset associated with a change in frequency of stool; and/or onset associated with a change in form (appearance) of stool, and in the absence of structural or metabolic abnormalities to

explain the symptoms. The diagnosis was further supported by the presence of any of the following symptoms: abnormal stool frequency defined as greater than 3 bowel movements per day or less than 3 bowel movements per week; abnormal stool form (lumpy/hard or loose/watery); abnormal stool passage (straining, urgency, or feeling of incomplete evacuation); passage of mucus with stool; and bloating or feeling of abdominal distension.

Exclusion criteria were any chronic organic gastrointestinal disorders, as assessed by full clinical history and examination, and supported by normal results of initial limited laboratory investigation including complete blood cell count with differential, erythrocyte sedimentation rate, C-reactive protein, amylase and lipase, tissue transglutaminase antibodies with total serum IgA, and fecal occult blood. All of the above tests were performed in every patient; additionally, fecal calprotectin was checked in some cases at the physician's discretion. Any abnormality in any of the tests resulted in the patient's exclusion from the study.

Also excluded were patients presenting any disease that may affect bowel motility such as diabetes mellitus, sarcoidosis, connective tissue disease, or poorly controlled hypo-/hyperthyroidism. Additional exclusion criteria were previous abdominal surgery, as well as significant concomitant psychiatric, neurological, metabolic, renal, hepatic, infectious, hematological, cardiovascular, or pulmonary illnesses. Finally, patients who had been using any commercial preparation of probiotics during the previous 3 months were likewise excluded. The study period lasted between April 2006 and October 2007. The study was articulated in 16 weeks as follows (Table 1).

After informed consent, eligible patients entered a run-in phase of 2 weeks (baseline period) during which they recorded data on a daily basis on a questionnaire/diary provided at study entry by the physician. At the completion of the 2 weeks, patients returned to the center where they were assigned in a double-blinded fashion to the placebo or intervention group according to a computer-generated randomization allocation table prepared by VSL Pharmaceuticals, Inc (Gaithersburg, MD), which also provided both the probiotic product and the placebo. The company did not provide any additional resources for this investigator-initiated study.

Patients were randomized to receive either 1 sachet of VSL#3 (once per day for children 4–11 years of age; twice per day for those 12–18 years old) or an identical looking and tasting placebo for 6 weeks. No other medications other than analgesics were allowed for the duration of the study.

As part of the initial evaluation, a careful dietetic history, including assessment of fiber intake, was conducted. No changes in any of the dietetic habits of the patients were allowed throughout the duration of the study. Patients and/or their caregivers were instructed to fill out the data collection packet throughout the study period, with ratings for the following elements: (1) overall assessment of relief of symptoms. This questionnaire was taken from a validated instrument of assessment of relief of symptoms in patients with IBS (''SGAR'' for Subject's Global Assessment of Relief) (14), modified for children (''SGARC''); (2) frequency and intensity of episodes of abdominal pain/discomfort; (3) presence and severity of abdominal bloating or gassiness; (4) number and characteristics of the stools; (5) caregivers were also asked to comment on the disruption by IBS of their child's family life (eg, disruption of social activities, need for doctor's visits, use of medications). Each of the above ratings was expressed on a 5-point scale from 0 (normal) to 4 (worst). Details of the questions asked for each of the parameters investigated are reported in the Appendix.

Subsequently, the patients returned every 14 days for data collection, verification of compliance, and distribution of the preparation until completion of the 6-week period. At the completion of the 6 weeks, a ''wash-out'' period of 2 weeks was given, when no preparation was administered. Then each patient was switched to the other group and followed likewise for a further 6 weeks. The study period ended with the final clinical visit and completion of the final questionnaire. Forms for each patient were sent from all participating centers to the coordinating center, and after collection of all forms, the data were analyzed and the code was broken. Responders were defined as patients who reported an improvement of at least 1 point ($\geq$1.0) in the score at week 6 compared with start of study.

None of the investigators involved in the recruitment and follow-up of the patients, nor those coordinating the study and analyzing the data, and none of the patients or their caregivers were aware of the group to which the patients were assigned.

Outcome Parameters

The primary endpoint was improvement in the subject's global assessment of relief (SGARC). The secondary endpoints were improvements in abdominal pain/discomfort, stool pattern, bloating/gassiness, and family assessment of the impact of their child's IBS on the family's life.

TABLE 1. Scheme of the study

Visit no.	1	2	3	4	5	6	7	8	9–End of study
Time of visit	Day 1	Day 15	Day 29	Day 43	Day 57	Day 71	Day 85	Day 99	Day 113
Inclusion/exclusion criteria	X	X							
Information and informed consent	X								
Physical examination including vital signs	X				X	X			X
Randomization		X							
IBS questionnaire	X	X	X	X	X	X	X	X	X
Dispense study medication		X	X	X		X	X	X	
Laboratory tests	X				X				X
Dispense/check patient diary	X	X	X	X	X	X	X	X	X
Drug compliance assessment			X	X	X		X	X	X
Adverse events			X	X	X		X	X	X
Medicine d/c					X				X

IBS = irritable bowel syndrome.

TABLE 2. Baseline characteristics of the 59 patients

Age (mean, range), y	12.5 (5–18)
Sex (no. girls, percentage)	28, 47%
Predominant type of IBS (no. of patients)	
Constipation	16
Diarrhea	20
Mixed/alternating pattern	23
Abdominal pain severity score at baseline	2.7 ± 0.9
Abdominal bloating/gassiness	2.9 ± 1.0
Stool changes (constipation or diarrhea)	2.8 ± 0.8
Family assessment of disruption	2.2 ± 0.4

Values are mean ± SD (range). Scores are in a 5-point scale, 0–4. IBS = irritable bowel syndrome.

Statistical Analysis

The data were analyzed with the repeated-measures 1-way ANOVA, with posttest analysis of group means using the Bonferroni multiple comparison test. The statistical significance was conservatively assessed at a $P < 0.05$. Additionally, for each of the 5 endpoints, differences were constructed such that each patient contributed a measurement equating to {(end of placebo arm – start of placebo arm) – (end of treatment arm – start of treatment arm)}. For these difference measures, a Wilcoxon signed-rank test was conducted to test the null hypothesis that the difference of differences was equal to zero.

RESULTS

Sixty-seven patients with a new diagnosis of IBS based on the Rome II criteria were initially enrolled. A total of 59 children completed the study. Table 2 reports the baseline characteristics of these patients. All 8 patients who did not complete the study dropped from phase I: 4 from the placebo arm and 4 from the study arm. Reasons for dropouts were inability/unwillingness to complete questionnaires (6 patients) and dislike of the preparation given (1 each from the study and the placebo group). The analysis of the 59 patients who completed the study was performed in a per-protocol fashion.

Mean age of the patients was 12.5 years (range 5–18). No adverse event was recorded in any of the participating patients throughout the duration of the study.

Primary Endpoint: SGARC

Figure 1 reports the progression of the subject's assessment of relief of symptoms. To allow for a clearer interpretation of the data, results have been grouped so that data from each patient are reported as either being into the experimental or into the placebo group, regardless of the arm in which the patients were enrolled first. It can be seen that the patients reported a progressive overall improvement in their IBS symptoms as the study progressed, both when taking the VSL#3 and when taking placebo. The changes from baseline were already statistically significant ($P < 0.05$) at week 2 on the probiotic, and remained such at weeks 4 ($P < 0.01$) and 6 ($P < 0.001$), whereas they were only significant at weeks 4 ($P < 0.05$) and 6 ($P < 0.05$) while taking placebo. The comparison between the magnitude of the change in score between study start and end of treatment seen after VSL#3 and that seen after placebo—referred to as (end of placebo arm – start of placebo arm) – (end of treatment arm – start of treatment arm)—was statistically significant ($P < 0.05$) in favor of the probiotic. Of interest, 44 of the 59 patients responded to VSL#3; 2 of the 15 nonresponders did respond to placebo. Of the 44 who responded to VSL#3, 17 did not respond to placebo.

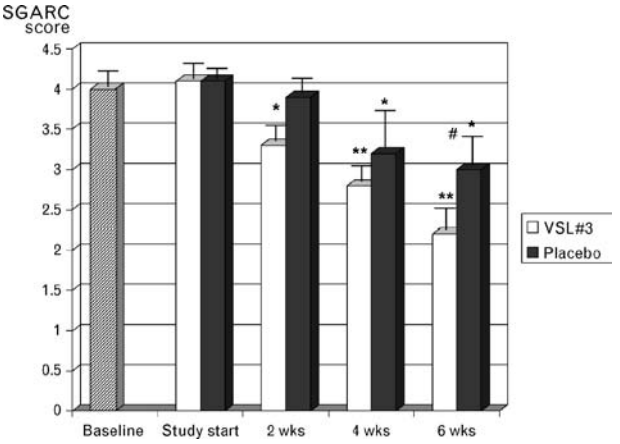

FIGURE 1. Effect of VSL#3 and of placebo on the subject's global relief of symptoms (''SGARC''). Results are reported on a 0–4 scale (see text). Bars indicate 1 SD. $*P < 0.05$ compared with study start. $**P < 0.01$ compared with study start. $***P < 0.001$ compared with study start. # $P < 0.05$ between patients while taking probiotic vs patients while taking placebo.

Abdominal Pain/Discomfort

Figure 2 illustrates the progression of the scores for episodes of abdominal pain/discomfort by the patients undergoing treatment with either VSL#3 or placebo. The results have been grouped in the 2 arms as described above for the SGARC. For this symptom, it can be seen that the simple intervention consisting of monitoring (the run-in phase of 2 weeks) resulted per se in an improvement, as the score declined by 0.5 for the probiotic arm and by 0.65 for the

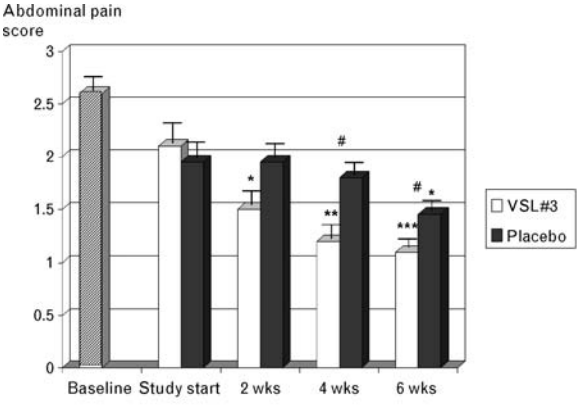

FIGURE 2. Effect of VSL#3 and of placebo on abdominal pain/discomfort. Results are reported on a 0–4 scale (see text). Bars indicate 1 SD. $*P < 0.05$ compared with study start. $**P < 0.01$ compared with study start. $***P < 0.001$ compared with study start. $P < 0.05$ between patients while taking probiotic vs patients while taking placebo.

placebo arm. After the study began, the decline in the score for abdominal pain/discomfort was better when taking the probiotic than when taking placebo. From baseline to week 6, the patients taking VSL#3 reported a decline in score of 1.0 ± 0.2 ($P < 0.001$) compared with a decline of 0.5 ± 0.2 while taking placebo ($P < 0.05$). The difference between these 2 changes was significant at $P < 0.05$. In terms of responders, 40 of the 59 patients responded to VSL#3 and 19 did not; none of these responded to the placebo. Of the 40 who responded to VSL#3, 20 did not respond to placebo.

Abdominal Bloating/Gassiness

Results for changes in the score of abdominal bloating/gassiness are reported in Figure 3. Again, they have been grouped in the 2 arms as described in the previous section. Also in this case, the 2-week run-in phase of the study produced an improvement in the reporting of the symptom, which declined from 2.9 at enrollment to 2.4 in the probiotic arm and to 2.1 for the placebo arm. Subsequently, the 6 weeks of study period resulted in a further reduction of the score by 1.35 ± 0.4 ($P < 0.001$) to a final 1.05 ± 0.3 in the group receiving VSL#3, while the score only declined by 0.5 ± 0.2 ($P < 0.01$) to a final 1.6 ± 0.2 after 6 weeks receiving placebo. Again, the difference between these 2 changes was significant at $P < 0.05$. For this symptom, 42 of the 59 patients responded to VSL#3 and 17 did not; only 1 of them responded instead to the placebo. Of the 42 that responded to VSL#3, 16 responded also to placebo.

Number and Characteristics of the Stools

Figure 4 illustrates the changes in scores for the parameter of stooling pattern. As indicated in the Appendix, patients with either diarrhea or constipation (or with a mixed pattern) were combined in this score. Twenty of our patients had a predominant diarrhea IBS, 16 had predominant constipation, and 23 had an alternating pattern. After an improvement of approximately 0.5 points for both groups at the end of the 2 weeks run-in phase, the subsequent decline of the score was as follows. At the completion of the 6 weeks receiving VSL#3 the score was reduced by 1.05 ± 0.6 ($P < 0.001$), from

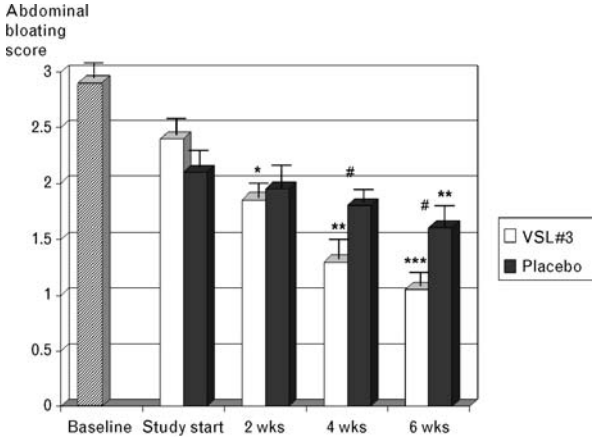

FIGURE 3. Effect of VSL#3 and of placebo on abdominal bloating/gassiness. Results are reported on a 0–4 scale (see text). Bars indicate 1 SD. $*P < 0.05$ compared with study start. $**P < 0.01$ compared with study start. $***P < 0.001$ compared with study start. $P < 0.05$ between patients while taking probiotic vs patients while taking placebo.

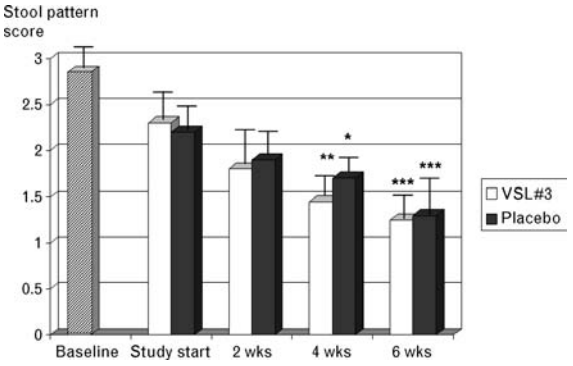

FIGURE 4. Effect of VSL#3 and of placebo on stool pattern (diarrhea and/or constipation). Results are reported in a 0–4 scale (see text). Bars indicate 1 SD. $*P < 0.05$ compared with study start. $**P < 0.01$ compared with study start. $***P < 0.001$ compared with study start. $P = 0.06$ (NS) between patients while on probiotic vs patients while on placebo.

2.3 ± 0.5 to 1.25 ± 0.3. While receiving placebo, the patients went from 2.2 ± 0.5 to 1.3 ± 0.4, a decline of 0.9 ± 0.3 ($P < 0.001$). In this case, the difference between these 2 changes did not reach statistical significance ($P = 0.06$). A subset analysis of the 3 subtypes of IBS could not be conducted given the small number for each category. However, the overall highest prevalence of responders was found in the group of patients presenting diarrhea-predominant IBS (14/20 patients responded to VSL#3; 3 of these also responded to placebo; of the 6 nonresponders, 1 responded to placebo).

Caregivers' Assessment of Family Life Disruption

One of the most important consequences of IBS in children is the way this condition affects their family lives. We thus included in the questionnaire a specific item aimed at reporting perceived changes in the overall functioning of the family during the study period. (See Appendix for details of the questions asked). Figure 5 shows results for this parameter. An initial improvement with a score reduction of 0.8 points was reported at the end of the 2-week run-in phase. Subsequently, a further significant decline of 0.9 ± 0.2 points ($P < 0.001$) was seen at the end of the 6 weeks on VSL#3, although a nonsignificant reduction of 0.51 ± 0.3 points was reported at the end of the 6 weeks on placebo. For this parameter, the difference between these 2 changes in favor of the probiotic was significant at $P < 0.01$.

DISCUSSION

IBS is a prevalent functional gastrointestinal disorder, likely to be multifactorial, that causes considerable distress for patients, especially children and teenagers, and results in a large number of medical referrals. In spite of important progress made in the last several years in understanding its causes and mechanisms, treatment options are lagging behind. In fact, a recent large meta-analysis (2) of available evidence on the efficacy of pharmacological treatment of IBS in children concluded that there was ''weak evidence of benefit on medication in children with recurrent abdominal pain. 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.'' The same authors reached

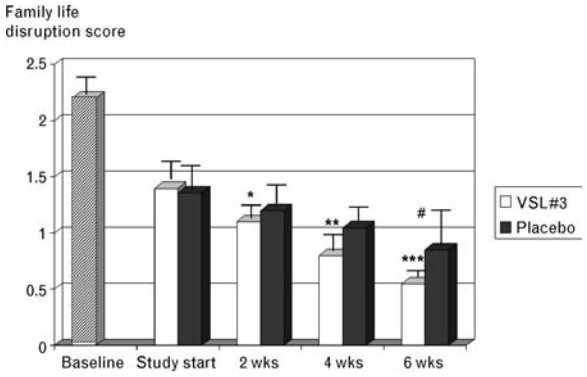

FIGURE 5. Effect of VSL#3 and of placebo on the caregivers' assessment of family life disruption. Results are reported on a 0–4 scale (see text). Bars indicate 1 SD. $*P < 0.05$ compared with study start. $**P < 0.01$ compared with study start. $***P < 0.001$ compared with study start. $^{\#}P < 0.01$ between patients while taking probiotic vs patients while taking placebo.

essentially identical conclusions when reviewing evidence of efficacy for dietetic interventions (3). Recently, Bahar et al (15) studied the efficacy of amitriptyline in adolescents with IBS, but even though the authors' conclusions were favorable, amitriptyline remains a drug that doctors and most parents are reluctant to use to treat IBS, because of concerns about potential cardiotoxicity of these drugs (16) and the potential of antidepressants in children and teenagers for increasing suicidal ideation (17).

One of the most promising developments in our understanding of IBS and, thus of its potential treatment, was the recognition that many episodes of IBS can be traced to intestinal infections (18–20), and that disturbances of the intestinal microbiota (including higher numbers of facultative organisms and low numbers of lactobacilli and bifidobacteria) can be detected in a substantial portion of patients with IBS (21,22). This opened the way to the concept that interventions aimed at modifying the interplay between luminal, especially bacterial, agents and enterocytes could be beneficial to patients with IBS by regulating the intestinal barrier and normalizing the inflammatory status (6,23). Thus, a number of investigations have appeared in recent years using probiotics in this condition. Although results have been variable and hard to compare in consideration of different strains used, different populations tested, and different outcome measured, in general the conclusions that can be drawn from the majority of the published studies, as also reviewed in recent reviews and meta-analyses (7,24–26), appear to be in favor of these agents. For example, in their recent meta-analysis, McFarland and Dublin (25) present a Forest plot of randomized controlled trials of 14 treatment arms from 12 published studies measuring relative risk of IBS symptoms after probiotic treatment compared with placebo, concluding that probiotics were significantly protective with a pooled relative risk of 0.77 (confidence interval 0.62–0.94). Likewise, these authors found probiotics to be associated with significantly less abdominal pain compared with placebo (pooled relative risk 0.78, confidence interval 0.69–0.88). Recently, the American College of Gastroenterology Task Force on IBS (27), in an evidence-based position article, stated that probiotic therapies show a trend for being efficacious in IBS, and that probiotic combinations improve symptoms in patients with IBS.

These data, however, were almost exclusively obtained in studies on adults, because the pediatric literature on probiotics and IBS is surprisingly scanty, only addressing the potential efficacy of *Lactobacillus GG* with rather discouraging results (9,10). Thus, for our analysis we chose the preparation VSL#3, a proprietary brand consisting of a mixture of 8 different strains of probiotics that had already been tested in various gastrointestinal disorders of adults, including IBS (11,12). In their studies, these investigators found that VSL#3 was significantly effective in ameliorating abdominal bloating (11) and improving the symptom of flatulence while prolonging colonic transit time (12) in adults with IBS; however, no statistically significant effect could be shown for the other parameters investigated.

We opted for a crossover trial, because we believed this offered the most stringent criteria for efficacy because it minimizes the variability between patients, which is a known major problem in simple double-blind studies, especially when addressing the issue of functional disorders. In fact, an evident placebo effect is to be expected when investigating patients with a functional gastrointestinal disorder, and especially IBS, as widely known in the literature (28). In this regard, the placebo effect observed in our study is not different from previously reported observations. One possible drawback of such an approach is the potential for a ''carryover'' effect between treatments; to obviate it, we conducted a 2-week wash-out period that is considered adequate when dealing with probiotics and has been used previously (29,30).

The mechanisms underlying the beneficial effects of this probiotic in children with IBS are not known. Of interest, in a previous study on 10 adult patients with IBS, Brigidi et al (31) found that the administration of VSL#3 resulted in significant changes in the composition of their microbiota, with increase in lactobacilli, bifidobacteria, and *S thermophilus*, whereas enterococci, coliforms, *Bacteroides*, and *Clostridium perfringens* were not affected. In addition, fecal β-galactosidase increased and urease activities decreased as a result of changes in the intestinal microbiota induced by VSL#3 administration. Thus, it is conceivable that such modifications may at least in part be responsible for the observed efficacy.

Thus, in summary, our study is the first to address the possible use of the probiotic mixture VSL#3 in children affected by IBS. We found this preparation to be effective in improving the overall perception of symptoms, the severity and the frequency of the abdominal pain, abdominal bloating, and caregivers' assessment of ''life's disruption'' due to IBS; a nonsignificant trend was found for number and characteristics of the stools. In conclusion, we believe that VSL#3 is a welcome addition to the remarkably poor armamentarium of therapeutic strategies available for children and teenagers with IBS.

APPENDIX

Questions asked of the child or caregiver at each encounter

- **SGARC—Subject's Global Assessment of Relief for Children with IBS**
  Consider how your child felt this past week in regard to his or her IBS; especially the overall well-being, symptoms of stomach discomfort, pain, and altered bowel habits. Compared with the way he or she usually felt before entering the study, how do you rate the relief of symptoms during the last week?

0. Complete relief
1. Considerable relief
2. Somewhat relieved
3. Unchanged
4. Worse

- **Frequency and intensity of the abdominal pain/discomfort:**
  0. Absent
  1. 1 episode in the preceding 2-week period with scarce or no interference on social activities, and no school absence
  2. 1 to 2 episodes per week with occasional interference in social activities and at least 1 absence from school in the preceding 2-week period
  3. 2 or more episodes per week, but not every day, in the preceding 2-week period with frequent interference in social activities and causing 1 to 2 days of missed school in the preceding 2-week period
  4. Daily episodes of pain with major limitation of social activities and at least 2 days of missed school in the preceding 2-week period
- **Abdominal bloating or gassiness:**
  0. Absent
  1. Occasionally present, with minimal or no interference with social activities
  2. Occurring approximately once per week in the preceding 2-week period and causing some distress
  3. Occurring between 1 and 4 times per week in the preceding 2-week period and causing interference with social activities
  4. Occurring >4 times per week in the preceding 2-week period and causing major disruption of social activities
- **Number and characteristics of the stools:**
  0. Normal stooling pattern
  1. Feeling of incomplete evacuation, stools hard or mushy/loose for no longer than 1 day/week in the preceding 2-week period
  2. As for 1, but with episodes more frequent (2–3/week in the preceding 2-week period)
  3. Less than 3 bowel movements per week or >3 episodes per week but not daily of mushy, loose, or watery stools in the preceding 2-week period
  4. As for #3, but with fecal urgency and tenesmus, or daily passage of mushy, loose, or watery stools
- **Family assessment of the impact of their child's IBS on the family's life:**
  0. None
  1. Mild-to-moderate stress, concerns about patient's health
  2. As for #1, plus occasional disruption of working, social activities
  3. As for #2, plus frequent consultations to health care providers, use of pain killers
  4. Major stress in and concern from family members with frequent disruption of working, social activities, and frequent use of painkillers and/or ''diets''

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