THE USE OF *LACTOBACILLUS GG* IN IRRITABLE BOWEL SYNDROME IN CHILDREN: A DOUBLE-BLIND RANDOMIZED CONTROL TRIAL

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Objective To determine whether oral administration of the probiotic *Lactobacillus GG* under randomized, double-blinded, placebo-controlled conditions would improve symptoms of irritable bowel syndrome (IBS) in children.

Study design Fifty children fulfilling the Rome II criteria for IBS were given *Lactobacillus GG* or placebo for 6 weeks. Response to therapy was recorded and collected on a weekly basis using the Gastrointestinal Symptom Rating Scale (GSRS).

Results *Lactobacillus GG* was not superior to placebo in relieving abdominal pain (40.0% response rate in the placebo group vs 44.0% in the *Lactobacillus GG* group; $P = .774$). There was no difference in the other gastrointestinal symptoms, except for a lower incidence of perceived abdominal distention ($P = .02$ favoring *Lactobacillus GG*).

Conclusions *Lactobacillus GG* was not superior to placebo in the treatment of abdominal pain in children with IBS but may help relieve such symptoms as perceived abdominal distention. *(J Pediatr 2005;147:197-201)*

Irritable bowel syndrome (IBS) is a common functional gastrointestinal (GI) disorder in children and adolescents. Although benign, IBS is frequently associated with anxiety, school absenteeism, and frequent physician visits.[1] Children with IBS represent 25% to 50% of all patients presenting to gastroenterology clinics.[2] The diagnosis of IBS is based on clinical grounds, with specific clinical diagnostic criteria. The most recent and sensitive are the Rome II criteria, which apply to the pediatric population.[3] IBS is associated with altered bowel habits with specific symptoms of diarrhea, constipation, abdominal distention, bloating, and urgency to defecate.[4] The therapeutic options for this common and potentially incapacitating disorder remain limited.

The influence of the gut flora in patients with IBS has been reported in a few studies. Patients with IBS show a great homogeneity in the fecal flora with a decrease in coliforms, lactobacilli, and bifidobacteria compared with healthy individuals.[5] Recent studies also imply that several factors implicated in IBS pathogenesis have the capacity to induce changes in the intestinal ecosystem.[6]

Probiotics play an important role in preventing overgrowth of potentially pathogenic bacteria and maintaining the integrity of the gut mucosal barrier.[7] The beneficial effects of probiotics have been previously studied in adult patients with IBS. Even though most of the studies demonstrate efficacy,[8-10] other studies do not support these observations.[11] None of the published studies addresses the efficacy of probiotics in children with IBS. The goal of the present study was to determine whether oral administration of the probiotic *Lactobacillus GG* under randomized, double-blind, placebo-controlled conditions would improve symptoms of IBS in children.

See related articles, p 186 and p 192.

METHODS

Sixty-four children (12 male and 52 female) were enrolled in this controlled, double-blind, randomized study from the Children's Medical Center Pediatric Gastroenterology outpatient clinic between July 2003 and June 2004 (Figure). Mean patient age was 12 years, with a range of 6 to 20 years. All children had a previous evaluation by a pediatric gastroenterologist, who made the diagnosis of IBS and excluded organic disease as a cause of abdominal pain. Testing for organic disease was performed on a subset of patients based on the clinical presentation. Organic diseases were ruled out by laboratory studies,

GI	Gastrointestinal	IBS	Irritable bowel syndrome
GSRS	Gastrointestinal Symptom Rating Scale		

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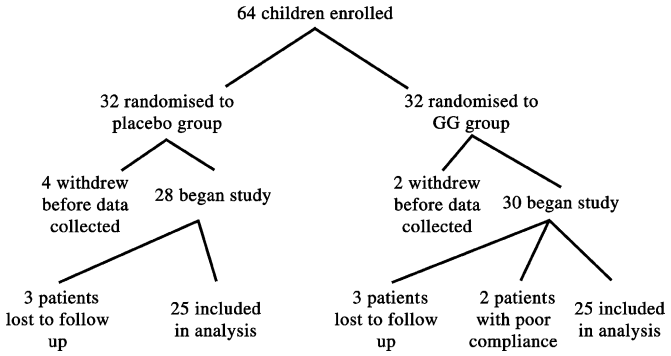

Figure. Schematic of Enrolled Participants.

radiographic imaging, endoscopy, disaccharidase assays, breath hydrogen testing, and/or hepatobiliary scans. All children fulfilled Rome II criteria for IBS. Patients had active symptoms of abdominal pain over a period of at least 2 weeks before initiating the study. Children were excluded if they were under age 5 years or over age 21 years, receiving medication for the treatment of IBS (including alternative medical therapy, such as herbal remedies or probiotics), receiving antibiotic therapy, or receiving drugs known to cause abdominal pain.

The same pediatric gastroenterologist obtained a standardized history and performed a physical examination concentrating on IBS and associated symptoms. Each potential participant and caregiver was interviewed, and all recent medications were recorded. The interview included history of GI symptoms, food intolerances, and associated complaints. The same physician recorded pretrial and posttrial measures, initially and at the termination of the study. The measures included (1) a detailed physical examination, (2) the 15-item Gastrointestinal Symptom Rating Scale (GSRS),[12] (3) a severity of symptom scale, (4) a change of symptom scale, and (5) questions to assess other variables that may have affected study results (eg, intercurrent infections, life events). The child and family ranked each of the symptoms on a 4-point Likert scale (0 = no or transient symptoms, 1 = occasional symptoms, 2 = frequent symptoms, 3 = severe or continuous symptoms). Previous studies have reported an interrater reliability ranging from .86 to 1.00 for this scale when used in an adult population.[9] The scale has been used in pediatric populations with a .84 interrater reliability in children.[13,14] The information was collected before the start of therapy and weekly thereafter.

Patients were randomly assigned to receive either *Lactobacillus GG* or placebo treatment. The probiotic and placebo were provided by Con Agra (Omaha, Neb) in capsule form and included either *Lactobacillus GG* in concentration of 10^{10} bacteria or placebo. Placebo was composed of inulin as a sole ingredient; inulin was also present in the *Lactobacillus GG* capsules. The placebo and probiotic capsules were similar in size, color, and taste. Both placebo and probiotic were prescribed 1 capsule twice daily for a period of 6 weeks. A computer-generated randomization list was created by the pharmacy department. The researchers allocated the next available number on entry into the trial, and each patient collected the capsules directly from the pharmacy. Participants and all members of the research team, including a statistican, were blinded to code assignment. The code was revealed from vendor after recruitment, data collection, and statistical analyses were complete.

Patients were withdrawn from the study at any time based on patient's desire or their experience of any unexpected intolerance or side effect from the therapy. Data pertaining to any patient given oral or intravenous antibiotics was excluded from the study. The study was done in accordance with the institutional review board.

Statistics

Age, weight, and duration of symptoms were compared between the patients included in the study (n = 50) and those who were excluded (n = 14) with 2-sample *t*-tests, and gender was compared with Fisher's exact test. For the patients included in the study, the primary outcome was the change in abdominal pain severity score from baseline to the end of the treatment period. Secondary outcomes included the number of responders versus nonresponders in each group and changes in the remaining symptoms of the GSRS by syndrome. Patients were classified as responders if they experienced a decrease in abdominal pain severity of 1 or more levels (1 point or more) on the 4-point Likert scale from baseline to the end of treatment. Baseline abdominal pain and other GSRS scores were averaged from the daily scores recorded by the patients/parents during the week preceding treatment. Posttreatment scores were averaged for each week of data collected after baseline measurements.

Sample size was calculated based on a difference between groups in the change in abdominal pain severity score of 1.0 point or more, which was considered a clinically relevant difference. Using $\alpha = .05$, $\beta = .20$, and an estimated standard deviation within groups of 1.0, 17 patients were needed in each group.

Comparisons between placebo and control groups for baseline age, weight, duration of symptoms, and length of follow-up were made with 2-sample *t*-tests, and gender was compared with Fisher's exact test. Changes in abdominal pain and all other GSRS scores before and after treatment were compared between groups using Wilcoxon's rank-sum test. Proportions in each group (responders vs nonresponders) were compared using the χ^2 test or Fisher's exact test for small samples. All statistical analyses were performed with SPSS version 11.5 for Windows (SPSS, Chicago, Ill). For all comparisons, *P* values < .05 were considered statistically significant.

RESULTS

Six patients withdrew from the study after randomization before beginning treatment (Figure). Reasons given for discontinuation included lack of time for daily record keeping, preference for other therapy, and desire not to participate. Twenty-eight patients were randomized into the placebo

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