Lactobacillus reuteri DSM 17938 for the Management of Functional Abdominal Pain in Childhood: A Randomized, Double-Blind, Placebo-Controlled Trial

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Objective To determine whether administration of *Lactobacillus reuteri* DSM 17938 is beneficial in functional abdominal pain (FAP) of childhood.

Study design A total of 101 children, aged 6-15 years, who fulfilled the Rome III criteria for FAP were enrolled in a randomized double-blind, placebo-controlled trial, and were randomly assigned to receive either *L reuteri* DSM 17938 or placebo for 4 weeks, with further follow-up of additional 4 weeks. Response to therapy was based on a self-reported daily questionnaire monitoring frequency and intensity of abdominal pain, using the faces scoring system by Hicks.

Results *L reuteri* (n = 47) was significantly superior to placebo (n = 46) in relieving frequency (1.9 ± 0.8 vs 3.6 ± 1.7 episodes/wk, $P < .02$) and intensity (4.3 ± 2.2 vs 7.2 ± 3.1 Hicks score/wk, $P < .01$) of abdominal pain following 4 weeks of supplementation. There was no difference in school absenteeism rate or other gastrointestinal symptoms, except for a lower incidence of perceived abdominal distention and bloating, favoring *L reuteri*.

Conclusions *L reuteri* DSM 17938, compared with placebo, significantly reduced the frequency and intensity of FAP in children. *(J Pediatr 2016;174:160-4)*.

Trial registration ClicalTrials.gov: NCT01180556.

Abdominal pain-related functional gastrointestinal disorders are very common in childhood and include 4 types: functional abdominal pain (FAP), irritable bowel syndrome (IBS), functional dyspepsia (FD), and abdominal migraine. This division has been based on the Rome III diagnostic criteria.[1] Although benign in nature, these disorders are commonly associated with significant anxiety, school absenteeism, frequent clinic visits, unnecessary testing, and a significant economic burden.[2] Children with IBS for instance represent up to 50% of all patients referred to pediatric gastroenterology clinics in the US.[3] Nevertheless, the therapeutic options for these common functional abdominal complaints are limited.[4]

Probiotics are defined as "live microorganisms which when administered in adequate amounts confer a health benefit on the host."[5] Various probiotic agents have been proposed as optional therapy for functional gastrointestinal conditions. Several studies in adults have demonstrated some clinical benefit of particular probiotic agents, mostly in IBS.[6,7]

Pediatric literature data are scarce and controversial, as they present a wide variability of study design and type of microorganisms.[8-12] Most of the trials studied patients with IBS using largely *Lactobacillus GG*.[13] *Lactobacillus reuteri* has been shown to have significant benefit as a pain relieving probiotic strain in infantile colic.[14,15] In one study, administration of *L reuteri* DSM 17938[12] to pediatric patients with FAP reduced the intensity, but not the frequency, of abdominal pain.

Our aim was to examine in a well-designed prospective randomized, double-blind, placebo-controlled trial whether *L reuteri* DSM 17938 is effective in the management of childhood abdominal pain-related functional gastrointestinal disorders, according to the Rome III criteria.

Methods

This randomized, double-blind, placebo-controlled trial was carried out between March 2011 and October 2013 (ClinicalTrials.gov: NCT01180556). The study protocol was approved by the Institutional Review Board of the Faculty of Health Sciences, Ben-Gurion University.

A written informed consent was obtained from the children's parents. Children with recurrent abdominal pain, aged 6-15 years, were recruited at random from outpatient pediatric clinics at Soroka Medical Center and at 3 community childcare centers in the Beer-Sheva area. Children were excluded if they had any

FAP	Functional abdominal pain
FD	Functional dyspepsia
IBS	Irritable bowel syndrome

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Study products were manufactured, packed, and supplied free of charge by BioGaia AB, Stockholm, Sweden, which had no role in the conception, design, and conduct of the study, or in the analysis or interpretation of the data. Z.W. has served as a speaker for BioGaia AB. The other authors declare no conflict of interest.

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chronic illness, growth failure, previous abdominal surgery, or any alarming signs of organic conditions (such as vomiting, chronic diarrhea, bloody stools).[16] Subjects who were treated with antibiotics, probiotics, or prebiotics in the previous 8 weeks were excluded. All included children underwent a careful physical examination, including growth variables within normal limits. Baseline laboratory workup, including complete blood count, erythrocyte sedimentation rate, renal and liver function tests, amylase, lipase, celiac serology, and urinalysis, was within normal limits. Additional tests, including stools for occult blood, culture, ova, parasites, *Helicobacter pylori*, abdominal ultrasound, and a lactose breath test, also yielded negative results. Eligible children and their parents were fully informed about the trial and signed an informed consent. After a careful review of patient history, the patients were diagnosed by 1 physician as having an abdominal pain-related functional gastrointestinal disorder and were divided into 4 groups: FAP, IBS, FD, and abdominal migraine based on the Rome III diagnostic criteria.[1]

After informed consent, eligible patients entered a run-in phase of 2 weeks during which each participant and family completed a self-reported daily questionnaire. Only patients with at least 1 episode of abdominal pain per week were included in the study.

Subjects were randomly assigned to receive either *L reuteri* DSM 17938 (1×10^8 colony-forming units/d) or placebo, once a day, as identical chewable tablets for 4 weeks, with further follow-up phase of additional 4 weeks with no supplementation. In the preliminary study protocol, prior to recruitment, supplementation period was planned to last 6 weeks. Later on, this was changed to 4 weeks supplementation, with additional 4 weeks of follow-up, for better compliance. The amount and viability of the probiotic bacteria were monitored every 3 months. The placebo consisted of an identical formulation without the probiotic bacteria.

Randomization was performed by the random-digit method on the basis of computer-generated numbers. To avoid disproportionate numbers of subjects in each group, randomization was performed in blocks of 6, 3 for placebo and 3 for product. Allocation concealment was ensured by an independent person. Participants and the entire research team were blinded to code assignment. The code was revealed from vendor only when recruitment, data collection, and statistical analyses were completed.

Each participant and family completed a self-reported daily questionnaire throughout the 8 weeks of the study. This included daily monitoring of frequency and intensity of abdominal pain based on the validated face scoring system by Hicks.[17] Each of the 6 face scoring system ranked 0, 2, 4, 6, 8, or 10, where 0 = no pain (relaxed face) and 10 = very severe pain (miserable face). This scoring system was validated in children with a similar age range.[18] Any associated gastrointestinal symptoms (diarrhea, nausea, vomiting, dyspepsia, flatulence, bloating) and adverse events were recoded daily as well. Each participant was contacted by the study staff once a week to monitor progress, compliance, and filling out of daily diaries.

Each subject underwent a physical examination, including determination of growth variables, at baseline and at 4 and 8 weeks. Patients were also interviewed with nonleading questions regarding their symptoms and adverse events. They had to return unused tablets and containers to ensure compliance.

The primary outcome measures included frequency and intensity of abdominal pain. Secondary measures included school absenteeism because of abdominal pain, additional gastrointestinal symptoms, and adverse effects.

Statistical Analyses

For the assessment of abdominal pain frequency (dichotomous outcome), we calculated the sample size based on the assumption that relief of pain would be expected in 40% of the placebo group and 70% of the probiotic group. We estimated that, with a power of 80% and a significance level of 0.05, a sample of 38 children in each group will be required, to show a 30% difference between the groups.

For the assessment of differences in pain intensity (continuous outcome), we set the sample size at 34 per group to achieve a power of 80%, to show at least a difference of 2 (SD 2) in the intensity score between groups. In total, we planned to enroll 90 subjects to account for 20% follow-up losses.

The data from all patients were analyzed on an intention-to-treat basis. Categorical variables were tested using the χ^2 test or Fisher exact test as appropriate. Continuous variables were tested for normality, and if normality was confirmed, groups were compared using the Student *t* test. For nonnormally distributed variables, the Mann-Whitney U test was used. Differences were considered to be significant at the level of $P < .05$. All reported *P* values are 2-sided. The analysis was performed with SPSS 13.0 software (SPSS Inc, Chicago, Illinois).

Results

A total of 177 subjects were assessed for eligibility between March 2011 and October 2013; 54 were excluded because of exclusion criteria (**Figure 1**; available at www.jpeds.com). Following the initial diagnosis, 13 patients were diagnosed as having IBS and 5 patients as having FD. In view of the small size of these 2 groups, we have decided to include only patients with FAP. This intention-to-treat population consisted of 101 patients with FAP, which were randomly assigned to the probiotic group (n = 52) or to the placebo group (n = 49). All 8 failures were the result of poor compliance and violation of the protocol. None of them were therapy-related or because of adverse effects.

There were no significant differences between groups at randomization in terms of age at entry, sex, body weight, duration of symptoms, use of drug treatment for abdominal