A Randomized Controlled Trial of Lactobacillus GG in Children With Functional Abdominal Pain

ARTICLE in PEDIATRICS · NOVEMBER 2010
Impact Factor: 5.47 · DOI: 10.1542/peds.2010-0467 · Source: PubMed

CITATIONS 50
READS 56

12 AUTHORS, INCLUDING:

Ruggiero Francavilla
Università degli Studi di Bari Aldo Moro
256 PUBLICATIONS 3,595 CITATIONS

Vito Leonardo Miniello
Università degli Studi di Bari Aldo Moro
60 PUBLICATIONS 847 CITATIONS

Lorenzo Polimeno
Università degli Studi di Bari Aldo Moro
125 PUBLICATIONS 2,377 CITATIONS

Luciano Cavallo
Policlinico di Bari
203 PUBLICATIONS 2,054 CITATIONS

Available from: Vito Leonardo Miniello
Retrieved on: 12 March 2016
A Randomized Controlled Trial of Lactobacillus GG in Children With Functional Abdominal Pain
Ruggiero Francavilla, Vito Miniello, Anna Maria Magistà, Angela De Canio, Nunzia Bucci, Francesca Gagliardi, Elena Lionetti, Stefania Castellaneta, Lorenzo Polimeno, Lucia Peccarisi, Flavia Indrio and Luciano Cavallo
Pediatrics 2010;126;e1445-e1452; originally published online Nov 15, 2010; DOI: 10.1542/peds.2010-0467

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://www.pediatrics.org/cgi/content/full/126/6/e1445
A Randomized Controlled Trial of Lactobacillus GG in Children With Functional Abdominal Pain

WHAT'S KNOWN ON THIS SUBJECT: Chronic abdominal pain is one of the most common reasons for referral to a specialist. Effective measures for the treatment of recurrent abdominal pain are lacking. Data on the use of probiotics in adults with irritable bowel syndrome (IBS) have demonstrated their efficacy.

WHAT THIS STUDY ADDS: Lactobacillus rhamnosus strain GG (LGG) is effective for reducing the frequency and severity of pain in children with IBS. The beneficial effect of LGG persists beyond the cessation of the administration and represents a valid therapeutic option. Small intestinal permeability is significantly increased in children with IBS.

OBJECTIVE: Our aim was to determine whether Lactobacillus rhamnosus GG (LGG) relieves symptoms in children with recurrent abdominal pain.

PATIENTS AND METHODS: A total of 141 children with irritable bowel syndrome (IBS) or functional pain were enrolled in 9 primary care sites and a referral center. Children entered a randomized, double-blind, placebo-controlled trial and received LGG or placebo for 8 weeks and entered follow-up for 8 weeks. The primary outcome was overall pain at the end of the intervention period. At entry and at the end of the trial, children underwent a double-sugar intestinal permeability test.

RESULTS: Compared with baseline, LGG, but not placebo, caused a significant reduction of both frequency (P < .01) and severity (P < .01) of abdominal pain. These differences were significant at the end of follow-up (P < .02 and P < .001, respectively). At week 12, treatment success was achieved in 48 children in the LGG group compared with 37 children in the placebo group (P < .03); this difference was present at the end of follow-up (P < .03). At entry, 59% of the children had abnormal results from the intestinal permeability test; LGG, but not placebo, determined a significant decrease in the number of patients with abnormal results from the intestinal permeability testing (P < .03). These effects mainly were in children with IBS.

CONCLUSIONS: LGG significantly reduces the frequency and severity of abdominal pain in children with IBS; this effect is sustained and may be secondary to improvement of the gut barrier. Pediatrics 2010;126: e1445–e1452

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.
Recurrent abdominal pain (RAP) primarily is a functional disorder that affects 10% to 15% of school-aged children and is one of the most common reasons for referral to a pediatric gastroenterologist.\(^1,2\)

Authors of the pediatric Rome criteria,\(^3\) in an attempt to improve the management of children with RAP, have proposed 4 diagnostic symptom-based categories: irritable bowel syndrome (IBS); functional dyspepsia; childhood functional abdominal pain (FAP); and abdominal migraine. Conventional interventions include reassurance and general advice about managing pain. Although this level of intervention has been associated with clinical improvement,\(^4\) medication and psychological therapies also may be necessary. Only a few small randomized clinical trials have been conducted on children with abdominal pain, and their results have shown inconclusive evidence of the ef-ficacy of these treatments.\(^5\) The authors of 2 recent Cochrane systematic reviews\(^6,7\) have concluded that there is weak evidence for the benefit of medication and/or dietary manipulation in children with RAP and called for larger randomized clinical trials. A recent multicenter, randomized, placebo-controlled trial\(^8\) revealed that amitriptyline was as effective as placebo in the treatment of children with functional gastrointestinal disorder, thus reinforcing the need for exploring different therapeutic options.

Probiotics are “live microorganisms which, when consumed in adequate amounts, confer a health benefit on the host.”\(^9\) Clinical applications of probiotics include treatment or prevention of different gastrointestinal disorders.\(^10,11\) Possible mechanisms of action include (1) binding to small- and large-bowel epithelium and production of substances that may inhibit pathogenic organisms,\(^12\) (2) modulating the gastrointestinal lumen toward an anti-inflammatory state,\(^15\) and (3) converting undigested carbohydrates into short-chain fatty acids, improving gut function.

One of the best-studied probiotic bacteria in clinical trials for treating and/or preventing several intestinal disorders is Lactobacillus rhamnosus strain GG (LGG).\(^14\) This probiotic has been tested in children with intestinal functional disorders; results have been inconclusive.\(^15,16\) Effective measures for the treatment of RAP are lacking, and given the disorder’s high prevalence, the need for an appropriate treatment is critical. Data on the possible use of probiotics in adults with IBS have indicated their efficacy; however, given the limitations of the existing data in children, we performed a randomized, double-blind, placebo-controlled trial to establish whether LGG relieves symptoms in children with IBS or FAP.

**Patients and Methods**

A randomized, double-blind, placebo-controlled, parallel-group trial was conducted in southern Italy between 2004 and 2008. The study was planned according to the recommendations established by the consensus report on clinical trials in IBS.\(^17\) The institutional review board of the University of Bari approved the study. Written informed consent was obtained from the children’s parents.

**Eligibility of Patients**

Patients were recruited from 9 primary care pediatrics chosen from communities throughout the territory by random selection. Children (5–14 years of age) of either gender with a diagnosis of IBS or FAP, according to the Rome II diagnostic criteria,\(^13\) valid at the time of the design of the study, were considered eligible. The diagnosis of IBS or FAP was based on a clinical interview performed by the same physician (Dr Magistà).

Children were excluded if they (1) had any chronic diseases, (2) received treatment with antibiotics/probiotics in the previous 2 months, (3) had a pain history suggestive of functional dyspepsia/aerophagia/abdominal migraine, (4) exhibited growth failure, (5) had gastroparesis, (6) had gastrointestinal obstructions/stricture, (7) displayed alarming signs of organic conditions,\(^18\) (8) had previous abdominal surgery, or (9) had abnormal baseline test results (including complete blood counts; erythrocyte sedimentation rate; liver-pancreas-kidney function tests; tissue transglutaminase with immunoglobulin A measurement; stool examination for occult blood, ova, and parasites; fecal calprotectin; urinalysis: \(^13\)C-urea breath test; and abdominal ultrasound).

**Study Design**

The 8-week treatment period (weeks 5–12) was preceded by a 4-week run-in phase (weeks 1–4) and followed by an 8-week follow-up phase (weeks 13–20). To undergo randomization, patients must have had at least 1 episode of abdominal pain per week and negative results in their baseline studies. Children were assigned consecutive numbers, starting with the lowest number available, and were randomly assigned, with the use of a computer-generated randomization list created by using permuted block design, to receive either oral LGG (3 × 10^9 colony-forming units) or oral placebo twice per day. Enrolled children were entered sequentially to receive the assigned treatment. The boxes that contained placebo and LGG had the same shape, the placebo’s taste, dimension, indication, and appearance were the same as those of the viable LGG, and the placebo was provided by the probiotic producer (Dicofarm SpA, Rome, Italy), which ensured that the study was blinded for investigators and patients. Group assignment was concealed from participants and investigators.
Assessments, Compliance, and Adherence

On a daily basis from week 1 to week 20, patients recorded the frequency/severity of pain and school absence (Supplemental Appendix).

To assess the severity of pain, a combination of the self-reported visual analog scale (VAS) and the Faces Pain Scale (FPS) was used. The 0- to 10-mm VAS scale (0, no pain; 10, worst possible pain) included a horizontal color gradient (green to red) plus a rating. When asked to evaluate pain, the child would point to a level and trace a line. This particular VAS is a validated standard for evaluating pain in children older than 5 years.19 Assessment was eased by coupling the VAS with the FPS, which consists of 6 faces that range from a relaxed face to a face that shows intense pain.20

The impact on parents’ overall assessment of pain relief with treatment was obtained by interviewing them before and after treatment. Symptom amelioration was assessed by the question, “How do you feel the medication relieves the pain of your child?” Possible answers included significant, mild, or no relief.

To ensure compliance, 1 investigator contacted the families every 4 weeks to monitor the process of the study. Adherence was assessed by counting the number of capsules returned; children who missed taking more than 20% of the medication were considered noncompliant.

Intestinal Permeability Test

The lactulose-to-mannitol ratio (La/Ma) test was performed 1 day before and after the 8-week treatment period according to the methods of Generoso et al.21 Fifty-five children with no history of RAP (n = 25 female subjects; ages 5–12 years) were recruited among children of the department staff to assess the normal range of La/Ma and were referred to as the control group.

Outcome Measures

The primary outcome was the change in abdominal pain (frequency/severity) according to the VAS score from baseline to the end of the treatment period. We chose pain as the primary outcome measure consistent with the proposed points to consider for IBS trials.17 Secondary outcomes were (1) a decrease of at least 50% in the number of episodes and intensity of pain (treatment success), (2) a decrease in the perception of children’s pain according to their parents, and (3) modification of intestinal permeability.

Adverse Events and Disallowed Medication

Adverse events were monitored throughout the study. Children were not allowed to consume any probiotics or prebiotics other than those provided, and they were instructed to continue their usual eating and physical exercise habits. Concomitant use of medications that affect gastrointestinal motility and/or pain perception was allowed, providing their parents registered the intake.

Statistical Analysis

With the assumption that relief of pain would be expected in 70% of those who were receiving the probiotic and in 40% of those who were receiving the placebo, we calculated that a sample of 65 children per group would be required. This number would allow for 90% power to show at least a 2.5-U (SD: 3.0) advantage of LGG over placebo with respect to pain on the basis of a 2-sided type 1 error rate of 5%.

Secondary outcomes were analyzed as binary variables. Treatment success was evaluated as either achieved or failed and as a decrease in the perception of children’s pain according to their parents, rated as either significant or no relief. The χ² or Fisher’s exact test was used, as appropriate, to compare percentages and nominal variables.

For continuous variables, differences between children in the 2 treatment arms were compared by using analysis of variance, and the Wilcoxon test was used for comparison of the mean values. The average frequency/intensity of pain during the run-in period was used as a baseline, and change in pain frequency/intensity was measured. Odds ratios and 95% confidence intervals and the number needed to treat were calculated. All statistical tests were 2-tailed and performed at the 5% level of significance. All analyses were performed on the intention-to-treat basis, in which all of the participants in a trial are analyzed according to the intervention to which they were assigned, regardless of whether they received it. Data are presented as mean and standard deviation. Data were analyzed with SPSS 13.0 software (SPSS, Chicago, IL).

RESULTS

Of 353 potential participants, 141 met the inclusion criteria and were randomly assigned to a study group (71 subjects in the LGG group and 70 subjects in the placebo group); 83 subjects had IBS, and 58 had FAP. Figure 1 shows the number of participants involved in the trial from the assessment of intestinal permeability. For eligibility through follow-up. At the final assessment, complete data were available for 136 of 141 participants (96%). The baseline characteristics of the participants in the 2 groups were similar (Table 1).

Primary Outcome

The number of episodes of pain per week at baseline was 3.7 (2.5) in the probiotic and 3.5 (2.4) in the placebo group. The episodes of pain at 12
weeks decreased to 1.1 (0.8) and 2.2 (1.2), respectively (P < .01). At the end of the follow-up period, episodes of pain decreased to 0.9 (0.5) in the probiotic group and 1.5 (1.0) in the placebo group (P < .02) (Fig 2A).

The severity of pain at baseline was 4.3 (1.8) in both groups. The severity of pain at 12 weeks had decreased to 2.3 (1.3) and 3.4 (2.1), respectively (P < .01). At the end of follow-up, the episodes of pain had decreased to 0.9 (0.5) in the probiotic and 1.5 (1.0) in the placebo group (P < .001) (Fig 2B). Table 2 shows the results for children with IBS and FAP.

### Secondary Outcome

#### Treatment Success

At week 12, treatment success was achieved in 48 children in the LGG group compared with 37 in the placebo group (72 vs 53%, P < .03). Treatment success at week 12 was sustained at week 20. The effect was present only in children with IBS (Table 3).

#### Perception of Children’s Pain According to Their Parents

Parents rated global improvement of pain after LGG use as significant in 54% of the cases at week 12 (n = 36) and in 70% at week 20 (n = 49). In the placebo group, a significant relief of pain was seen in 33% (n = 23) and 55% (n = 38) of the children, respectively (P < .02 and P < .04, respectively).

#### Intestinal Permeability Test

The intestinal permeability test (IPT) in children from the control group showed a mean La/Ma of 0.028 (0.008) (95% confidence interval: 0.025–0.034); therefore, the cutoff value for the normal range was set at a La/Ma of less than 0.034. In the study population, the IPT was available for 141 children (71 in the probiotic group and 70 in the placebo group). The mean La/Ma was 0.025 (0.008) in the probiotic group and 0.030 (0.011) in the placebo group (P < .01).

Table 1 shows the demographic characteristics and baseline symptoms of the study population. The baseline characteristics were similar between the two groups, with the exception of the frequency of pain, which was higher in the placebo group (P < .05). The severity of pain was also higher in the placebo group (P < .01). The duration of symptoms was similar between the two groups (P > .05).

**Table 1** Demographic Characteristics and Baseline Symptoms

<table>
<thead>
<tr>
<th></th>
<th>LGG (N = 67)</th>
<th>Placebo (N = 69)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, y</td>
<td>6.5 ± 2.1</td>
<td>6.3 ± 2.0</td>
<td>.5</td>
</tr>
<tr>
<td>Male/female, n/n</td>
<td>43/24</td>
<td>35/23</td>
<td>.8</td>
</tr>
<tr>
<td>Frequency of pain, means ± SD, n/wk</td>
<td>4.4 ± 3.1</td>
<td>3.5 ± 3.4</td>
<td>.6</td>
</tr>
<tr>
<td>Intensity of pain (VAS), mean ± SD</td>
<td>4.3 ± 2.3</td>
<td>4.3 ± 2.2</td>
<td>.9</td>
</tr>
<tr>
<td>School absenteeism because of pain, d/mo</td>
<td>3</td>
<td>3</td>
<td>.9</td>
</tr>
<tr>
<td>Duration of symptoms, mean ± SD, y</td>
<td>2.1 ± 1.7</td>
<td>2.6 ± 2.5</td>
<td>.7</td>
</tr>
<tr>
<td>FAP, n</td>
<td>25</td>
<td>31</td>
<td>.9</td>
</tr>
<tr>
<td>IBS, n</td>
<td>42</td>
<td>38</td>
<td>.8</td>
</tr>
</tbody>
</table>

FIGURE 1

Enrollment, assignment, intervention, and follow-up.

TABLE 2 shows the results for children with IBS and FAP.
at weeks 4 and 12 in 54 cases: 49 children refused the test, and 28 did not show up for a follow-up IPT. Compared with the control subjects, 32 of 54 children (59%) at entry had an abnormal IPT result (mean La/Ma: 0.035 [0.01], irrespective of the disorder [FAP/IBS]), and it was significantly higher than in control subjects ($P < .01$). At week 12, we found that LGG, but not placebo, determined a significant decrease in (1) the number of patients with an altered IPT result (−40% vs −21%; $P < .03$) and (2) the La/Ma (mean La/Ma: 0.030 [0.005] vs 0.039 [0.011]; $P < .02$). The effect of the probiotic was mainly seen in children with IBS compared with those with FAP (Fig 3). Mean values of the percentage recovery of mannitol, lactulose, and La/Ma are reported in Table 4. We found no correlation between the La/Ma test and severity of symptoms.

**Compliance and Safety**

Compliance was similar in the LGG and placebo groups (89% and 86%, respectively). LGG was well tolerated, and no adverse effects were reported.

**DISCUSSION**

Results of this large, prospective, randomized study show that LGG was effective, over 8 weeks, for reducing the frequency and severity of pain in children with IBS. The efficacy of the

![Figure 2](https://www.pediatrics.org/content/pediatrics/126/6/e1449/Figure2.jpg)

**TABLE 2** Outcome Measure at Baseline and During Treatment and Follow-up for Children With IBS and FAP

<table>
<thead>
<tr>
<th></th>
<th>LGG</th>
<th>Placebo</th>
<th>$P$</th>
<th>LGG</th>
<th>Placebo</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBS, N</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weeks 1–4</td>
<td>3.4</td>
<td>3.0</td>
<td>.22</td>
<td>4.4</td>
<td>3.6</td>
<td>.55</td>
</tr>
<tr>
<td>Weeks 5–12</td>
<td>1.8</td>
<td>2.1</td>
<td>.001</td>
<td>2.5</td>
<td>3.8</td>
<td>.01</td>
</tr>
<tr>
<td>Treatment success, %</td>
<td>79</td>
<td>82</td>
<td>.01</td>
<td>1.8</td>
<td>1.6</td>
<td>.001</td>
</tr>
<tr>
<td>Weeks 13–20</td>
<td>0.9</td>
<td>1.6</td>
<td>.001</td>
<td>1.2</td>
<td>1.4</td>
<td>.006</td>
</tr>
<tr>
<td>Treatment success, %</td>
<td>82</td>
<td>50</td>
<td></td>
<td>1.2</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>FAP, N</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weeks 1–4</td>
<td>4.2</td>
<td>4.0</td>
<td>.1</td>
<td>4.1</td>
<td>4.6</td>
<td>.6</td>
</tr>
<tr>
<td>Weeks 5–12</td>
<td>1.9</td>
<td>1.7</td>
<td>.7</td>
<td>2.6</td>
<td>2.1</td>
<td>.1</td>
</tr>
<tr>
<td>Treatment success, %</td>
<td>48</td>
<td>44</td>
<td>.6</td>
<td>50</td>
<td>60</td>
<td>.4</td>
</tr>
<tr>
<td>Weeks 13–20</td>
<td>1.1</td>
<td>1.4</td>
<td>.6</td>
<td>2.2</td>
<td>2.2</td>
<td>.05</td>
</tr>
<tr>
<td>Treatment success, %</td>
<td>84</td>
<td>76</td>
<td>.3</td>
<td>62</td>
<td>68</td>
<td>.7</td>
</tr>
</tbody>
</table>
treatment with LGG translated into a significantly higher proportion of treatment successes and a decreased perception of children’s pain according to their parents. For children with IBS, we could demonstrate an improvement of the intestinal permeability after probiotic administration. To the best of our knowledge, this is the largest independent clinical trial to investigate the effect of probiotics in children and adolescents with chronic abdominal pain referred from primary care pediatricians.

Most data on the possible use of probiotics in functional disorders and on the rationale for their use are derived from studies of adults with IBS. For children, the issue is more complicated, because they complain of non-specific chronic abdominal pain that encompasses a heterogeneous group of patients. We also enrolled children with FAP, because this condition may be a precursor of IBS in adults. The hypothesis that changes in the intestinal microbiota could participate in symptom generation in functional disorders was previously proposed and is supported by recent data obtained by using real-time polymerase chain reaction techniques.

Given their safety profile, probiotics seem to be an attractive therapeutic option for chronic abdominal pain. However, few data are available from children with this condition, and differences in study design and the use of non-validated and differing end points complicate the interpretation of the results. LGG was evaluated in 2 different randomized, placebo-controlled trials. In 1 trial, LGG was administered for 6 weeks to 50 children with IBS. The authors did not find an increased benefit of the probiotic over the placebo, probably because of a high response rate in the latter group. LGG was subsequently evaluated in 104 children with RAP, and treatment success (no pain) occurred in 25% of patients in the LGG group and in 10% of patients in the place-
cebo group (P < .03). Both studies had some limitations. In the study by Bausserman and Michail, the inulin used as a placebo may act as a prebiotic and might have exerted a positive effect on the indigenous health-promoting microbiota. In addition, the effect on the indigenous health of the placebo may act as a prebiotic, as used by Bausserman and Michail, might have allowed for the inclusion of more severely affected patients; therefore, patients were less likely to respond. Moreover, in this study, the probiotic was used for only 4 weeks, and children with dyspepsia were not excluded. We tried to reduce the possible confounding factors by using an inert powder for a placebo; excluding children with functional dyspepsia in whom the rational for the use of a probiotic is hard to establish, which increased the number of children enrolled; and planning the study in a primary care setting to avoid the various issues with recruitment in a tertiary referral population. Indeed, because most children with IBS are seen and treated in primary care, it may be speculated that the results of a trial conceived in such a setting are more easily applicable to daily practice.

Probiotics have several potential mechanisms of action that may intervene in the multifactorial pathogenesis of childhood chronic abdominal pain. Consistent with previous studies in adults, our results yield experimental evidence that small-intestinal permeability is significantly increased in children with IBS and that the administration of LGG is able to ameliorate it.

The intestinal tract features a mucosal epithelial cell barrier that is critical in providing the first line of defense against external insults. Tight junctions represent the luminal-most portion of a broader “apical junction complex,” and their disruption plays a crucial role in the pathogenesis of a number of gastrointestinal diseases such as inflammatory bowel disease and IBS. That LGG has a direct effect on tight junction integrity is not surprising because LGG (1) prevents Escherichia coli–induced derangement of tight junctions, (2) secretes proteins that stabilize intestinal tight junctions, (3) reverses increased intestinal permeability caused by cow’s milk in suckling rats, and (4) reduces, in a rat model, the severity of alcohol-induced gut hyperpermeability. The design of our study does not allow us to assess whether altered intestinal permeability is the cause or the effect of the functional disorder but shows that LGG has a positive effect on gut permeability. We believe that our study has some strengths, including the random assignment of a high number of well-characterized children, the investigation of a possible mechanism of action of the probiotic, and the long-term administration of the probiotic and follow-up of patients with evaluation of the family effect of the intervention. Indeed, when the outcome was evaluated by the measure of the family effect, we found that the therapeutic gain for LGG was ~20% over placebo, which suggests a positive influence of the probiotic therapy on parents’ perceptions of their children’s pain. Finally, the long-term follow-up has clearly shown that the beneficial effect of the probiotic extends beyond its administration; therefore, it represents a valid therapeutic option for children with RAP.

We are aware of the limitations of our study. The beneficial effect may not be unique to LGG, because other probiotic strains have been shown to play a protective role on the gut mucosal barrier disruption. We have not performed an analysis of the gut microbiota, which makes it difficult to support the hypothesis that LGG has the ability to establish a “healthy” gut microbiota community. The reduced number of children who attended the IPT may have decreased the power of the study for this particular analysis. Finally, given the chronic and relapsing nature of functional disorders and the failure of supplementation with probiotics to persist in the human gut for more than a few weeks beyond the cessation of administration, we cannot exclude the possibility that the positive effect is temporary.

CONCLUSIONS

LGG significantly reduces the frequency and severity of abdominal pain in children with IBS. Therefore, as more probiotic compounds become available on the market or are in the process of being approved, demonstration of the efficacy of a given probiotic for a specific therapeutic target will help clinicians choose which probiotic to use when dealing with a specific disease. We are entering the era of targeted probiotic use.

REFERENCES

5. Weydert JA, Ball TM, Davis MF. Systematic review of treatments for recurrent abdominal pain.
11. Lemberg DA, Ooi CY, Day AS. Probiotics in
18. Rasquin-Weber A, Hyman PE, Cucchiara S, et
15. Bausserman M, Michail S. The use of
16. Gawron’ska A, Dziechciarz P, Horvath A, Sza-
6. Huertas-Ceballos A, Logan S, Bennett C,
7. Huertas-Ceballos AA, Logan S, Bennett C,
17. Corazziari E, Bytzer P, Delvauz M, et al. Con-
16. Gawron’ska A, Dziechciarz P, Horvath A, Sza-
10. Brown AC, Valiere A. Probiotics and medical nu-
11. Lemberg DA, Ooi CY, Day AS. Probiotics in
12. Silva M, Jacobus NV, Deneko G, Gorbach SL,
bacillus acidophilus
20. von Baeyer CL. Children’s self-reports of
14. Doron S, Snydman DR, Gorbach L. Lactobacil-
FRANCAVILLA et al
17. Corazziari E, Bytzer P, Delvauz M, et al. Con-
19. Macarthur C. Pharmacological interventions for
14. Huertas-Ceballos A, Logan S, Bennett C,
27. Wyatt GM, Bayliss CE, Lakey AF, Bradley HK,
23. Barbara G, Stanghellini V, Cremon C, et al. Pro-
24. Johnson-Henry KC, Donato KA, Shen-Tu G,
25. Wyatt GM, Bayliss CE, Lakey AF, Bradley HK,
26. Di Lorenzo C, Youssef NN, Sigurdsson L, Scharff L, Griffiths J, Wald A. Visceral hyper-
algesia in children with functional abdomi-
nal pain.
27. Wyatt GM, Bayliss CE, Lakey AF, Bradley HK,
29. Wyatt GM, Bayliss CE, Lakey AF, Bradley HK,
31. Chen CC, Louie S, Shi HN, Walker WA. Prein-
coulouculation with the probiotic
32. Rousseaux C, Thuru X, Gelot A, et al. Lacto-
bacillus acidophilus
lobiose and lactulose coupled with mannosil and
determined using ion-exchange chromatogra-
phy with pulsed amperometric detection, are
34. Dunlop SP, Hebben J, Campbell E, et al. Abnor-
mal intestinal permeability in subgroups of
testinal permeability in patients with irrita-
bile bowel syndrome after a waterborne out-
36. Camilleri M. Gorman H. Intestinal perme-
ability and irritable bowel syndrome. Neu-
rogastroenterol Motil. 2007;19(7):545–552
37. Shulman RJ, Eakin MN, Czyzewski DL, Jarrett M, Du CN. Increased gastrointestinal perme-
ability and gut inflammation in children with
functional abdominal pain and irritable bowel
38. Johnson-Henry KC, Donato KA, Shen-Tu G,
39. Gordonpour M, Sherman PM. Lactobacillus rhamnosus strain GG prevents enterohem-
orrhagic Escherichia coli O157:H7-induced changes in epithelial barrier function. In-
40. Seth A, Yan F, Polk DB, Rao RK. Probiotics
ameliorate the hydrogen peroxide-induced epithelial barrier disruption by a PKC- and
MAP kinase-dependent mechanism. Am J Physiol Gastrointest Liver Physiol. 2008;
294(4):G1060–G1069
41. Iosuari E, Majamma H, Arvola T, Rantalai I, Vir-
tanen E, Arvolloni H. Lactobacillus casei strain GG reverses increased intestinal permeability in-
42. Forsyth CB, Farhadi A, Jakate SM, Tang Y,
Shaikh M, Keshavarzian A. Lactobacillus GG treatment ameliorates alcohol-induced in-
testinal oxidative stress, gut leakiness, and liver injury in a rat model of alcoholic ste-
43. Madsen K, Cornish A, Soper P, et al. Probi-
otic bacteria enhance murine and human intestinal epithelial barrier function. Gas-
troenterology. 2001;121(3):580–591
44. Preidis GA, Versalovic J. Targeting the hu-
man microbiome with antibiotics, probiotics,
and probiotics: gastroenterology enters the

pediatrics.org/cgi/content/full/111/1/e1

Cochrane Database Syst Rev. 2008;
(1):CD003017

Cochrane Database Syst Rev. 2008;(21):CD003019


A Randomized Controlled Trial of Lactobacillus GG in Children With Functional Abdominal Pain
Ruggiero Francavilla, Vito Miniello, Anna Maria Magistà, Angela De Canio, Nunzia Bucci, Francesca Gagliardi, Elena Lionetti, Stefania Castellaneta, Lorenzo Polimeno, Lucia Peccarisi, Flavia Indrio and Luciano Cavallo

*Pediatrics* 2010;126:e1445-e1452; originally published online Nov 15, 2010; DOI: 10.1542/peds.2010-0467