# *Lactobacillus casei rhamnosus* Lcr35 in the Management of Functional Constipation in Children: A Randomized Trial

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**Objective** To assess the effectiveness of *Lactobacillus casei rhamnosus* Lcr35 (Lcr35) in the management of functional constipation in children.

**Study design** A randomized, double-blind, placebo-controlled trial was conducted in 94 children aged <5 years with functional constipation according to the Rome III criteria. Children were assigned to receive Lcr35 ($8 \times 10^8$ colony-forming units, n = 48) or placebo (n = 46), twice daily, for 4 weeks. The primary outcome measure was treatment success, defined as 3 or more spontaneous stools per week, without episodes of fecal soiling, in the last week of the intervention. Analyses were by intention to treat.

**Results** Eighty-one (86%) children completed the study. There was no significant difference in treatment success between the placebo and the Lcr35 group (28/40 vs 24/41, respectively; relative risk, 0.6, 95% CI 0.24-1.5, $P = .4$). There was a significant increase in the frequency of defecation from baseline to week 4 in both the placebo group (median [IQR] 2.0 [1.0, 2.0] to 6.0 [4.0, 9.0], $P < .001$) and in the Lcr35 group (2.0 [1.0, 2.0] to 4.0 [3.0, 5.0], $P < .001$), but the defecation frequency in the placebo group was significantly greater than that in the Lcr35 group at weeks 1, 2, 3, and 4.

**Conclusion** Lcr35 as a sole treatment was not more effective than placebo in the management of functional constipation in children <5 years. This study adds to current recommendations that do not support the use of probiotics in the treatment of childhood constipation. *(J Pediatr 2017;184:101-5).*

**Trial registration** ClinicalTrials.gov: NCT01985867

Functional constipation is a common problem in children, with a prevalence of approximately 3%.[1] According to current guidelines developed by the European and North American Societies for Paediatric Gastroenterology, Hepatology and Nutrition, for children presenting with fecal impaction, polyethylene glycol (PEG) with or without electrolytes given orally 1-1.5 g/kg/d for 3-6 days is recommended as first-line treatment. PEG also is recommended as first-line maintenance treatment. If PEG is not available, lactulose is recommended.[2]

For many patients, however, current treatment options do not provide sustained relief of symptoms, prompting interest in adjunctive treatments. Experimental studies have shown that constipation often is associated with gut microbiota dysbiosis, consisting of the modified abundance of certain taxa of the colonic microbiome.[3] For example, some data have suggested the decreased abundance of *Bifidobacteria*, *Lactobacillus*, *Bacteroides*, and *Prevotella*[4-6]; however, it remains to be determined whether these alterations are a cause or a consequence of altered gut motility. With the recognition of the role of gut microbiota in health and disease, there is interest in its modification via the provision of probiotics and/or prebiotics.

Although not recommended currently,[2] probiotics (defined as live micro-organisms that, when administered in adequate amounts, confer a health benefit on the host)[7] commonly are used to treat functional constipation in children. Although the exact mechanisms of action of probiotics remain unclear, among other mechanisms, it has been hypothesized that probiotic metabolites may alter gut function, including sensation[8,9] and motility.[10,11] Some probiotics may influence colonic motility by softening the stool, changing secretion and/or absorption of water and electrolytes, modifying smooth muscle cell contractions, increasing the production of lactate and short-chain fatty acids, and lowering intraluminal pH. These mechanisms have been proposed to enhance colonic peristalsis and shorten whole gut transit time.[12,13]

A small number of clinical trials have addressed the clinical efficacy of probiotics in the management of constipation. One randomized controlled trial (RCT) evaluated the effects of administering *Lactobacillus casei rhamnosus* Lcr35 (hereafter referred to as Lcr35) at a dose of $8 \times 10^8$ colony-forming units (CFUs) per day for 4 weeks; Lcr35 was effective in treating children <10 years of age with constipation.[14] The mechanism of action of Lcr35 was

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| CFU | Colony-forming unit |
| Lcr35 | *Lactobacillus casei rhamnosus* Lcr35 |
| MD | Median difference |
| PEG | Polyethylene glycol |
| RCT | Randomized controlled trial |
| RR | Relative risk |

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unclear, although the investigators speculated that the greater defecation frequency in the Lcr35 group might be due to the stimulation of intestinal motility by *Lactobacillus*. The results of the trial were promising, although the overall effects were modest clinically and the sample size was small. There was some potential effectiveness, however, that warrants further, larger, more rigorous studies. Thus, the aim of our study was to further assess the effectiveness of Lcr35 in the management of functional constipation in children.

## Methods

This was a randomized, double-blind, placebo-controlled trial. The study was conducted in the Department of Pediatrics, the Medical University of Warsaw. The study was approved by the ethical committee of the Medical University of Warsaw (KB/203/2013). The protocol for this study was registered at ClinicalTrials.gov (NCT01985867) before the enrollment of the first patient. The guidelines from the CONSORT statement were followed for reporting this study.[15]

Eligible participants were children <5 years of age with functional constipation according to the Rome III criteria, which must include 2 or more of the following criteria: (1) ≤2 defecations per week, (2) at least 1 episode per week of incontinence after the acquisition of toileting skills, (3) history of retentive posturing or excessive volitional stool retention, (4) history of painful or hard bowel movements, (5) presence of a large fecal mass in the rectum, and (6) history of large-diameter stools that may obstruct the toilet. Those criteria must have been fulfilled for at least 1 month in infants up to 4 years and 2 months in children >4 years.[16,17] Exclusion criteria included irritable bowel syndrome, intellectual disability, metabolic disease (hypothyroidism), Hirschsprung disease, spinal anomalies, anorectal pathology, previous gastrointestinal surgery, functional nonretentive fecal incontinence, or treatment with medication that influences gastrointestinal motility. Written informed consent was obtained from the parents of each included patient.

### Study Procedure

The study period included 3 appointments with the investigators. At the inclusion visit, parents of patients who met the inclusion criteria were asked to assess the bowel patterns of their children and record them in a stool diary for 1 week. At the randomization visit, the enrollment criteria were re-evaluated. If rectal impaction was noted on physical examination, PEG 3350 at a dose of 1.5 mg/kg/d for 6 days was recommended. If there was no defecation for 3 days, a phosphate enema (or saline enema in children <1 year of age) administered once a day, until a child successfully passed a stool, was recommended.

After the rectal disimpaction, patients were assigned randomly to receive Lcr35 $8 \times 10^8$ CFU or a comparable placebo (containing 99% milk powder and 1% magnesium stearate), twice daily orally, for 4 weeks. When there was no defecation for 3 consecutive days, PEG 3350 was allowed at a single dose of 1.5 mg/kg/d until the child passed a stool. All patients were asked to discontinue any laxatives if they used them previously. All subjects' parents received a stool diary to record the frequency of bowel movements; stool consistency according to Bristol Stool Form Scale (which refers to 7 pictures of different forms of stool; 1 for hard lumps to 7 for watery stools)[18]; frequency of episodes of fecal soiling, pain during defecation, or abdominal pain or flatulence; use of additional laxative treatment; and adverse effects during the 4 weeks of the intervention. The last visit was after the conclusion of product consumption. During this visit, the investigators checked all diaries of the participants for compliance. The latter also was checked by regular telephone contacts made by one of the investigators.

The study products (Lcr35 and placebo) were manufactured by Biose Industrie (Arpajon sur Cere, France) and supplied by Sequoia (Warsaw, Poland), free of charge, as powder in identical capsules with an identical taste, smell, and appearance; they were kept refrigerated until use. Each capsule was either swallowed whole or opened with the contents administered in milk or another fluid. The manufacturer and supplier had no role in the conception, design, or conduct of the study or in the analysis or interpretation of the data.

### Outcome Measures

The primary outcome measure was treatment success, defined as ≥3 spontaneous stools per week, without episodes of fecal soiling (in toilet-trained children), in the last week of the intervention (week 4). The secondary outcome measures were stool consistency (according to the Bristol Stool Form Scale), frequency of defecation, frequency of fecal soiling, frequency of pain during defecation, frequency of abdominal pain or flatulence, need for intake of additional laxative treatment, and adverse events.

### Sample Size

To show a difference of 30% in the treatment effect in the study groups with $\alpha = 0.05$ and 80% power (unpaired Student *t* test), and assuming a 20% withdrawal rate, a total of 94 participants was needed. Sample size calculations were performed with StatsDirect (version 2.3.8, StatsDirect statistical software; StatsDirect Ltd, Chesire, United Kingdom).

### Randomization and Blinding

The randomization list was generated by an investigator with no clinical involvement in the trial, via a computer program (StatsDirect) with an allocation ratio of 1:1 and with a block of 6. The allocation sequence was concealed from the researchers responsible for enrolling and assessing participants in sequentially numbered, white, opaque, sealed, and stapled envelopes; these envelopes were opened only after the enrolled patients completed all of the baseline assessment and it was time to allocate the intervention. Throughout the duration of the study, all investigators, participants, outcome assessors, and data analysts were blinded to the assigned treatment.

### Statistical Analyses

Descriptive statistics are presented as the median and first and third quartiles. Between-group comparisons were done with