The effectiveness of *Lactobacillus reuteri* DSM 17938 as an adjunct to macrogol in the treatment of functional constipation in children. A randomized, double-blind, placebo-controlled, multicentre trial

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**KEYWORDS**
*Lactobacillus reuteri* DSM 17938; Children; Constipation

**Summary**

**Objective:** Constipation is one of the most common problems among children, with a prevalence ranging from 7 to 30%. It is treated with defecation training and laxative medications. However, many patients do not respond to the standard therapy. There is, therefore, an increasing interest in probiotics for the treatment of functional constipation.

**Study design:** The aim of this study was to assess the effectiveness of *Lactobacillus reuteri* DSM 17938 as an adjunct to macrogol in the treatment of functional, intractable constipation in children. A double-blind, placebo-controlled, randomized, multicentre trial involved a group of 129 children with functional constipation who were treated with a poor effect for at least two months prior to the study. Patients were randomly assigned to one of the two groups: 1. *L. reuteri* DSM 17938 and macrogol or 2. macrogol and matching placebo for 8 weeks.

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Results: 121 patients completed the study. Almost all patients (119/129) increased their bowel movements in both groups (59 vs 60, ns) and there was no statistically significant difference in the number of bowel movements per week in week 8 between the study and the placebo group (7.5 ± 3.3 vs 6.9 ± 2.5, respectively). Additionally, there were no significant differences between groups in the numbers of patients complaining of pain during defecation (13/47 vs 8/53), abdominal pain (19/41 vs 25/36), withholding stools (15/45 vs 13/48), passing hard stools (7/53 vs 3/58) or large stools (14/46 vs 12/49), and faecal incontinence (17/43 vs 11/50).

Conclusion: L. reuteri DSM 17938 supplementation as an additional therapy to macrogol did not have any beneficial effect on the treatment of functional constipation in children aged 3–7 years.

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Introduction

Constipation is one of the most common problems among children, with a prevalence ranging from 7 to 30% [1]. It is diagnosed in 0.3–8% of children in paediatric outpatient clinics and in 25% of children in gastrointestinal clinics [2]. In the majority of cases, constipation is functional, typically resulting from withholding faeces and avoiding painful defecation. The diagnosis of constipation is based on the Rome III Criteria for Functional Gastrointestinal Disorders, prepared in 2006, when two or more symptoms or signs of constipation occur during two or more months prior to diagnosis [3]. These criteria include two or fewer defecations per week, incontinence at least once per week, large-diameter stools, painful defecation, a history of retentive posturing or excessive volitional stool retention and the presence of a large faecal mass in the rectum. According to evidence-based guidelines from the European Society for Paediatrics, Gastroenterology, Hepatology and Nutrition (ESPGHAN), the North American Society of Paediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN), and the National Institute for Health and Clinical Excellence (NICE), the first stage of constipation therapy is disimpaction, followed by maintenance therapy. The therapeutic approach includes defecation training and treatment with osmotic laxatives such as lactulose and polyethylene glycol (macrogol, PEG) [4,5]. Macrogol is a generic name for polyethylene glycol which is a synthetic, water-soluble polymer that is minimally absorbed by the body, with its majority excreted via faeces, which diminishes its toxicity risk. Macrogol of various molecular weights has been proven to be an efficient treatment for functional constipation in infants and children [6]. According to the guidelines by ESPGHAN and NASPGHAN macrogol is recommended as a first-line treatment of functional constipation in infants and children, for the disimpaction of faecal mass and for maintenance therapy [5].

The efficacy of standard constipation treatment is 60% after one year, still a considerable number of patients require long-term treatment [7]. Despite therapy, constipation persists in 30% of children after puberty [7]. Some complaints, such as abdominal pain, often persist even with increased bowel movements under therapy. As chronic constipation often persists despite first-line laxatives, interest in additional and alternative therapies, including probiotics, has increased in recent years.

The intestinal flora of constipated children is different from that in healthy ones — the contribution of Clostridia, Enterobacteriacea and Bifidobacterium species increases when compared to bacteroides and Escherichia coli [8]. Probiotics can potentially improve the balance among different species and influence intestinal motility, by producing lactic acid and short-chain amino acids, and alter stool pH, stimulating gut peristalsis [9]. Several probiotic strains have been studied in a number of trials. Thus far, however, there has been insufficient evidence to support the use of probiotics in children affected by chronic constipation. On the other hand, Lactobacillus reuteri DSM 17938 has been proven to improve symptoms in functional gastrointestinal disorders including constipation in small groups of patients: infants [10], children [11] and adults [12]. L. reuteri DSM 17938, modifies the intestinal flora [12], and can inhibit the growth of Gram-negative and Gram-positive bacteria by producing reuterin, a broad-spectrum antibacterial substance [13,14]. Additionally, an animal study demonstrated strain- and colon-specific effects on motility by L. reuteri DSM 17938 [15], which were believed to be mediated by substances secreted by L. reuteri that affect neuron activity and increase gut muscular activity in the colon. An important step in communication between L. reuteri ATCC 55730 (the former strain of L. reuteri DSM 17938 with the same adhesion probiotic properties) and the gut epithelial cells is the binding of the bacteria to gut mucus, which is facilitated by a specific type of mucus-binding protein expressed on the surface of the bacterial cells [16]. The results of these studies might support the positive effects of L. reuteri DSM 17938 in humans with functional constipation.

The aim of this study was to assess the effectiveness of L. reuteri DSM 17938 as an adjunct to macrogol in the treatment of functional, intractable constipation in children.

Materials and methods

Patients

Between 2011 and 2014 we recruited patients in six paediatric gastroenterology departments in Poland: the
Department of Gastroenterology, Hepatology, Nutritional Disorders and Paediatrics at the Children’s Memorial Health Institute in Warsaw, the Department of Paediatric, Gastroenterology and Nutrition at the Medical University of Warsaw, the Department of Paediatrics, Gastroenterology and Eating Disorders at the Medical University of Gdansk, the Department of Paediatrics, Gastroenterology and Rheumatology at the Children’s Hospital in Szczecin, the Department of Paediatrics, the Gastroenterology Unit, at the Medical University of Silesia in Katowice, and the Department of Gastroenterology and Hepatology of Children at the Medical University of Silesia in Zabrze.

The study included 3–7-year-old patients with a history of constipation for at least two months, with less than 3 bowel movements per week who had been treated with poor results for at least two months prior to the study. The diagnosis of constipation was based on the Rome III Criteria for Functional Gastrointestinal Disorders. We excluded patients with hypothyroidism, Hirschsprung disease, cystic fibrosis, anatomic defects of the gastrointestinal tract, a history of abdominal surgery, or antibiotic or probiotic treatment during two weeks prior to the study.

The initial dose of macrogol was 10 grams per day. The parents of the patients were instructed to increase the amount of administered macrogol, according to stool frequency (when the patient has less than three bowel movements a week). A rescue medication enema was allowed only after 5 days without any bowel movement.

All the procedures were reviewed and approved by the Independent Review Board of the Children’s Memorial Health Institute in Warsaw (approval No. 133/KBE/2011). Written informed consent was obtained from caregivers.

**Endpoints**

The primary outcome measure was the comparison of the number of included patients with ≥3 bowel movements per week. The secondary outcome measures were a comparison of the frequency of defecation, stool consistency, the number of patients with painful defecation or faecal incontinence episodes at least once a week between the two groups.

**Statistical analysis**

The allocation sequence and randomization list were computer-generated by investigators at the Children’s Memorial Health Institute in Warsaw. Allocation concealment was achieved through the use of study products with similar appearances and tastes, which were packed identically and which were indistinguishable from each other. Throughout the duration of the study, all investigators, participants, outcome assessors, and data analysts were blinded to the assigned treatment.

The required calculated sample size was 124 patients (determined using a statistical programme, taking into account a 15% difference in the groups). Assuming a 15% difference between the groups in terms of achieving a therapeutic effect, with the success rate of 90% in the treatment group and 75% in the control group, with a power of 0.8, and assuming the test discontinuation by 10% of children, the final calculation of the required number of patients was 124 patients. The sample size was calculated with StatsDirect software version 2.7.9 (StatsDirect Ltd., England, UK).

The protocol requirement was to administer a minimum of 80% of the capsules within 8 weeks and to appear at each study visit.

A statistical analysis was carried out with StatsDirect version 3.0.121. An unpaired t-test was performed to compare the number of bowel movements between the two groups and the chi-square test was used to compare the number of patients with complaints in the groups. We regarded a p level below 0.05 as statistically significant.

We performed intention-to-treat and per-protocol analyses.

**Results**

We enrolled 129 children (57 girls, 72 boys) aged 4.66 ± 1.33 years (mean ± SD), with functional constipation (average disease duration: 23 months). Sixty-five patients were randomly assigned to treatment with macrogol and *L. reuteri* DSM 17938, and 64 were assigned to receive macrogol and a matching placebo. No significant difference was found between the patients in the probiotics and placebo group in terms of age, gender, weight, disease duration and their complaints at the beginning of the study (Table 1).

All of the patients were treated pharmacologically before the inclusion to the trial (for at least 2 months) with poor results, described as no signs of improvement after therapy (data from the parents’ interviews). Before the participation in the trial, one-third of the patients (43/129, 33%) were treated with lactulose as monotherapy, 7 patients (5%) took only macrogol. Additionally, 24 patients (19%) were treated
with both medicaments. Some participants received magnesium sulphate (3 patients), paraffin (24 patients), enemas (34 patients), as combination therapy with lactulose and/or macrogol or as monotherapy (paraffin — 2 patients, enemas — 4 patients) — Table 2.

One hundred and twenty-one patients completed the study. 8 patients dropped out, because of non-compliance (5 from Group 1, 1 from Group 2) or became lost to follow-up (1 from Group 1, 1 from Group 2). The study flow chart is presented in Fig. 1.

Almost all (119/129, 92%) patients increased their bowel movements in both groups (59 vs 60, P=0.14) over the 8 weeks of the trial.

There was no significant difference between the groups in the number of patients who improved their bowel movements to at least three a week (57 vs 59, P=0.97).

There was no statistically significant difference in the number of bowel movements a week in weeks 4 and 8, between the study and the placebo groups (7.69±4.3 vs 7.74±3.6 and 7.5±3.3 vs 6.9±2.5, respectively). Average defecation frequency per week increased from 1.75±1.11 to 7.5±3.3 in Group 1 (with L. reuteri DSM 17938), and from 1.77±1.11 to 6.9±2.5 in Group 2 (with placebo) after the completion of the 8-week course of treatment (Table 3).

Additionally, there were no significant differences in constipation-associated symptoms between the groups after 4 weeks of therapy (Table 4).

We also did not find any differences after 8 weeks of the therapy between Group 1 and Group 2 (Table 5).

Over 4 weeks of the trial 11 patients received enlarged doses of provided macrogol according to the stools frequency (6 patients from Group 1 — with L. reuteri DSM 17938, 5 patients from Group 2 — with placebo, ns). Over 4–8 weeks of the trial 8 patients received enlarged doses of provided macrogol according to the stools frequency (5 patients from Group 1, 3 patients from Group 2, ns). The maximum macrogol dose was 20 g per day.

The difference between the use of the rescue therapy (enema) was not statistically significant between the two groups — 4 patients from Group 1 vs 5 patients from Group 2 over 4 weeks of the trial and 3 patients from Group 1 vs 3 patients from Group 2 over 4–8 weeks of the trial.

A total of 2 adverse events (AE’s) were documented in 129 enrolled patients — there were episodes of abdominal pain in two patients from Group 1. The reported AE’s did not cause withdrawal from the trial.
In our study, we compared treatment with *L. reuteri* DSM 17938 as an adjunct to standard treatment with macrogol, in children with functional constipation aged 3–7 years. This probiotic therapy in combination with standard treatment was shown not to be superior to standard therapy.

According to the ESPGHAN and NASPGHAN recommendations of 2014, the routine use of probiotics in the treatment of constipation in children is not recommended, due to the lack of sufficient scientific evidence [5], and the present study does not challenge this recommendation. Our study does reinforce the recommendation to use macrogol as a first line agent [5,17]. However, according to the literature, the efficacy of standard constipation therapy is 60% and one third of children with chronic constipation continue to have problems after puberty [7,17].

Probiotics can constitute an interesting option in enhancing the standard therapy of constipation, and have been already studied. Still, it is well known that probiotic effects are strain-specific [18] and previous negative or positive studies cannot be used to recommend or discourage probiotic use for this clinical indication.

We decided to study *L. reuteri* DSM 17938 in functional constipation in children, as there were some positive effects reported in infants with functional constipation [10] and in adults [12].

Coccorullo et al. performed a double-blind, placebo-controlled, randomized study in 44 formula-fed infants aged 6–12 months with functional constipation, according to the Rome III criteria. One group received supplementation with the probiotic *L. reuteri* DSM 17938 and the other group received a placebo for 8 weeks. Infants treated with *L. reuteri* had a significantly higher defecation frequency than those treated with a placebo after 2, 4, and 8 weeks of treatment.

A similar trial design was implemented in adults with constipation [12]. In a double-blind, placebo-controlled randomized trial 40 adults with functional constipation diagnosed according to the Rome III criteria were randomly assigned to receive *L. reuteri* DSM 17938 or a matching placebo for 4 weeks. A significantly higher defecation frequency in the probiotic group was reported.

These trials employed a different methodology than we did in our study, as we compared the efficacy of *L. reuteri* as an adjunct to standard constipation therapy with macrogol. Additionally, there were also differences in age groups among the studies. Moreover, we selected children with chronic and severe forms of constipation, as all the patients had a history of unsuccessful laxative treatment for at least two months before inclusion in the trial. 82% of them had a history of painful defecation, 80% had episodes of withholding stools, 58% had episodes of incontinence, 67% of patients experienced passing large stools, and 82% of patients excreted hard stools. Previous trials did not report this category of data.

### Table 3 The number of bowel movements per week.

<table>
<thead>
<tr>
<th>BMs/week</th>
<th>Week 0 (mean ± SD)</th>
<th>Week 4 (mean ± SD)</th>
<th>Week 8 (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>1.75 ± 1.11</td>
<td>7.69 ± 4.3</td>
<td>7.5 ± 3.3</td>
</tr>
<tr>
<td>Group 2</td>
<td>1.77 ± 1.11</td>
<td>7.74 ± 3.6</td>
<td>6.9 ± 2.5</td>
</tr>
</tbody>
</table>

### Table 4 The constipation symptoms frequency in week 4 of the trial.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Group 1 (<em>L. reuteri</em> + macrogol) N = 59</th>
<th>Group 2 (Placebo + macrogol) N = 61</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Painful defecation</td>
<td>19 (32%)</td>
<td>19 (31%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>33 (56%)</td>
<td>35 (57%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Withholding stools</td>
<td>21 (35%)</td>
<td>16 (26%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Hard stools</td>
<td>9 (15%)</td>
<td>8 (13%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Large stools</td>
<td>20 (33%)</td>
<td>13 (21%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Faecal incontinence</td>
<td>23 (39%)</td>
<td>26 (42%)</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

### Table 5 Constipation symptoms frequency in week 8 of the trial.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Group 1 (<em>L. reuteri</em> + macrogol) N = 59</th>
<th>Group 2 (Placebo + macrogol) N = 61</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Painful defecation</td>
<td>13 (22%)</td>
<td>8 (13%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>19 (32%)</td>
<td>25 (41%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Withholding stools</td>
<td>15 (25%)</td>
<td>13 (21%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Hard stools</td>
<td>7 (12%)</td>
<td>3 (4%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Large stools</td>
<td>14 (23%)</td>
<td>25 (41%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Faecal incontinence</td>
<td>17 (29%)</td>
<td>11 (18%)</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>
Olgac et al. compared the efficacy of *L. reuteri* DSM 17938 with lactulose in children with functional constipation. This was a different concept than the one in our study [11]. The study was conducted in a group of 53 children who were randomized into two groups, with Group 1 receiving *L. reuteri* and Group 2 receiving lactulose. After 4 weeks of the trial, defecation frequency increased in both groups and no significant differences between the groups were found. Olgac et al. confirmed a similar efficacy of *L. reuteri* to that of lactulose. Furthermore, they noticed that lactulose effects appeared earlier than those of *L. reuteri*. Finally, both treatments restored Quality of Life scores to the level of the comparison group of healthy children.

In our trial, the use of *L. reuteri* as an adjunct to standard therapy with macrogol could have significantly influenced the final results and served as an explanation of the differences compared to other studies. A similar study design was used in the Banaszkiewicz et al. trial when they applied lactulose with a probiotic *Lactobacillus rhamnosus* GG (LGG), which was compared to lactulose alone. They showed no significant difference between the groups (defined as more than 3 spontaneous stools weekly with no faecal soiling) at week 12 and 24 of therapy [19]. The effect of lactulose therapy alone was relatively high and additional probiotic supplementation did not increase it further. Thus, the group of patients had different characteristics. In our trial one of the inclusion criteria was previous constipation treatment proving ineffective for at least two months, while in Banaszkiewicz et al. no such criterion is found.

Designing a study, when probiotics are being added to standard therapy, seems reasonable, as already standard therapy is not effective in relative terms. Nevertheless, the adjunct use of probiotics may be limited by the effects of macrogol. There are data indicating that macrogol interacts with the gut wall and can also affect the gut microbiota composition and metabolic activities [20]. Bohnik et al. compared the effects of macrogol (PEG) and lactulose on colonic microbiota and their metabolism in a group of 65 adult patients with functional constipation. Bacterial mass was significantly decreased in the macrogol group, as well as the counts of *Bifidobacteria*, but no changes in the counts of total anaerobes, *Lactobacilli, Bacteroides, Clostridia* or *Enterobacteria* were noted. Moreover, macrogol significantly decreased the total concentration of short-chain fatty acids (SCFA), which are substrates for gut microbiota, and they exert physiological effects on bodily functions. It confirms other observations from the trial conducted on rats, where microbiota tended to present a reduced total number of faecal bacteria with macrogol therapy. There were changes in the microbiota composition in macrogol treated rats compared to untreated ones: a relative increase in mucus-associated bacteria (mainly *Akkermansia*), and a decrease in *Bifidobacteria* and *Firmicutes*. There was a significant decrease in the total production of SCFA and an inhibited production of propionate, butyrate and lactate [21].

In our study the interaction of *L. reuteri* DSM 17938 with enterocytes, immune cells and neurons of the gut wall could have been diminished, which could inhibit the probiotic action.

The group of patients participating in our trial included children who suffered from chronic constipation, the mean duration time before inclusion to the trial were 23 months. All of them had a history of laxative therapy before inclusion to the trial, without effect after two months of therapy. The result of the trial was found to be the improvement in almost all patients from both groups, which was defined as normalized bowel movement frequency. Other constipation symptoms persisted only in 12–32% of patients from group 1 and 4–41% of patients from group 2. The difference between groups was statistically insignificant. The macrogol therapy during our trial was effective, despite the fact that a vast majority of patients were treated in that way before participation in our trial. During the study they had an opportunity to have frequent doctors’ consultations, receive information about high-fibre diets, and macrogol’s dose modification. Additionally, the use of diaries by parents during the trial facilitated the regular medication’s administration. It could be the reason for the better outcome after laxative treatment.

In our study there were no significant probiotics-related adverse events, except for abdominal pain in two patients receiving *L. reuteri*. This supports the current data on probiotic safety [22,23].

**Conclusion**

*L. reuteri* supplementation as an additional therapy to macrogol did not provide any beneficial effect to the treatment of functional constipation in children aged 3–7 years.

In order to further explore the questions raised by this study, another trial aiming at determining the role of *L. reuteri* in constipation therapy in children is required.

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**Disclosure of interest**

The authors declare that they have no competing interest.

**References**


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