Original Article

The effectiveness of *Lactobacillus rhamnosus* GG in the treatment of infantile colic: a systematic review and meta-analysis

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Background: Infantile colic is common in pediatric patients, yet few probiotics effectively treat this condition. The efficacy of *Lactobacillus rhamnosus* GG (LGG) in managing colic remains unclear. In this meta-analysis, we aimed to evaluate the effectiveness of LGG in treating infantile colic.

Methods: We searched PubMed, Embase, the Cochrane Central Register of Controlled Trials, and Web of Science databases from their inception until January 2024. We used Version 2 of the Cochrane tool (ROB 2) to assess the risk of bias in randomized trials. Meta-analysis was conducted using RevMan 5.3 software. The inclusion criteria followed the PICOS framework: (I) participants: infants with colic; (II) intervention: LGG administration at any dose; (III) control: placebo or no treatment; (IV) outcomes: primary outcome was crying or fussing time (minutes/day) at the end of the intervention, secondary outcomes included fecal calprotectin content (μg/g) and adverse events; (V) Study type: randomized controlled trials.

Results: Four studies involving 168 infants with colic were included. The meta-analysis indicated that LGG significantly reduced daily crying time [mean difference (MD) =−32.59 minutes; 95% confidence interval (CI): −43.23 to −21.96; P<0.001] and fecal calprotectin content (MD =−103.28 μg/g; 95% CI: −149.30 to −7.26; P<0.001). Only one study reported adverse events.

Conclusions: LGG is effective in treating infantile colic. Further studies are needed to examine the effects of different doses, administration schedules, and durations of LGG treatment in infants with varying feeding methods.

Keywords: *Lactobacillus rhamnosus* GG (LGG); colic; calprotectin; meta-analysis

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Introduction

Infantile colic often presents as irritable or crying behavior that occurs for more than 3 hours per day, lasts for ≥3 days per week, and persists for more than 3 weeks (1). It is a common disease in children that occurs in approximately 11% of infants within their first 2 months of life (2) and often relieves between 4 to 5 months of life (3). Evidence suggests that children suffering from infantile colic are more likely to have recurrent abdominal pain, allergic disorders (eczema, rhinitis, asthma, and food allergies), sleep disturbances, and migraine headaches (4,5). The etiology of infantile colic is unknown but is likely multifactorial, including factors such as cow's milk protein allergy, lactose intolerance, excessive gas production, and neurodevelopment (3). Growing evidence suggests that intestinal flora dysbiosis and inflammation are also

associated with colic (3). Infants with colic have a lower proportion of *Bifidobacterium* and *Lactobacillus* in their gut microbiota and a higher proportion of *Escherichia coli* (6-8). Calprotectin is a cytosolic protein that increases under conditions such as inflammation, infection, and malignancy, and can be measured in various body fluids (9). Calprotectin concentration in feces is a measure of intestinal inflammation (10). Some meta-analyses have concluded that *Lactobacillus reuteri* is the only probiotic used in clinical practice for infantile colic (11-14). *Lactobacillus rhamnosus* GG (LGG) is a well-characterized acid- and bile-stable probiotic with a long history of safe use (15). Prenatal supplementation with LGG has been suggested to alter the composition of the neonatal gut microbiota, resulting in a bifidobacteria-dominated microbiota (16). In this meta-analysis, we aimed to evaluate the effectiveness of LGG in the treatment of infantile colic. We have registered on PROSPERO (CRD42024503375). This article is presented per the PRISMA reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-24-112/rc).

Methods

Literature search strategy

We searched PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Science from the establishment of the database to January 2024 with no language restrictions. We combined the free words and MeSH Terms.

The search strategies included the following words: ("*Lacticaseibacillus rhamnosus*" [MeSH Terms] OR *Lactobacillus casei rhamnosus* OR *Lactobacillus rhamnosus* OR *Lactobacillus* OR Culturelle) AND ("colic" [MeSH Terms] OR Abdominal Cramp* OR abdominal colic OR colicky pain OR gastrointestinal colic OR liver colic OR Infantile Colic OR crying OR fussing OR irritable OR irritating OR weeping) AND ("infant" [MeSH Terms] OR Newborn Infants OR Newborn* OR Neonate* OR newborn baby OR newborn child OR newborn infant OR newly born baby OR newly born child OR newly born infant).

Highlight box

Key findings

- *Lactobacillus rhamnosus* GG (LGG) could not only reduce daily crying time in colic infants, but also can reduce calprotectin content in stool.

What is known and what is new?

- In clinical practice, *Lactobacillus reuteri* is the only probiotic that has been found to be effective for treating infantile colic.
- Infantile colic can be effectively treated with LGG.

What is the implication, and what should change now?

- LGG is effective in the treatment of infantile colic.
- There is a need for further research on the role of LGG in infant colic.

Inclusion and exclusion criteria

The inclusion criteria were based on the PICOS framework. (I) Participants: infants with colic, any diagnostic criteria for colic are acceptable; (II) intervention: the intervention group received LGG (any doses); (III) control: the control group received placebo or no placebo; (IV) outcomes: the primary outcome is the crying or fussing time (minutes/day) at the end of treatment, the secondary outcome is the content of calprotectin in feces (μg/g) at the end of treatment and adverse events; (V) study type: randomized controlled trials.

Studies those use LGG for the prevention of colic or those do not use LGG alone in experimental groups are excluded. Systematic reviews, case reports, editorials, reviews, news, patents are also excluded.

Study selection and quality assessment

Two evaluators (H.L. and Q.F.) screened the retrieved studies independently according to the following three steps: (I) reading the title and abstract to exclude obviously irrelevant studies; (II) full-text screening based on the inclusion and exclusion criteria; (III) making a final decision on data extraction. Evaluators used standardized forms to independently extract the following information from the included studies: authors, year, age of participants, feeding mode, mode of delivery, diagnostic criteria for colic, dose of probiotics, and duration of treatment, outcomes indicators, as well as the methodology used in the study design, such as method of randomization, allocation, and blinding. Disagreement between them was resolved through discussion or by consulting a third party. In general, means and standard deviations (SDs) were calculated using medians, ranges, or interquartile ranges whenever appropriate using the method of Wan *et al.* (17). For missing data, we try to contact the corresponding author of the article by e-mail and we have to not include the date when we did not get the reply. Some data were extracted from the

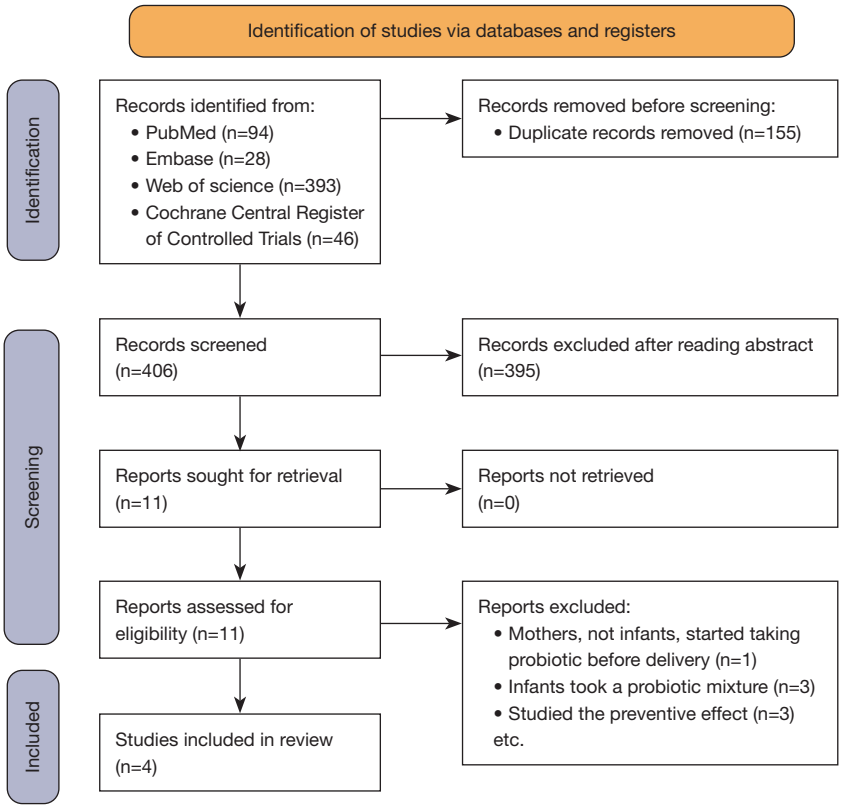

Figure 1 Flow chart of literature screening.

graphs by WebPlotDigitizer software (https://automeris.io/WebPlotDigitizer/). Two evaluators independently used the Version 2 of the Cochrane tool for assessing risk of bias in randomized trial (ROB 2) to independently assess the risk of bias of the included studies in five domains, including randomization process, effect of assignment to intervention, missing outcome data, measurement of the outcome, selection of the reported result, and the risk of bias for each domain could be categorized into three levels: low risk of bias, some concerns, and high risk of bias (18).

Statistical analysis

RevMan 5.3 software was used for meta-analysis. Mean difference (MD) was used to estimate the effect for continuous variables and 95% confidence intervals (CIs) were calculated. Heterogeneity among studies was estimated by the I^2 statistic, with I^2 of 25–50%, 50–75%, and >75% representing low, moderate, and high heterogeneity, respectively. If the heterogeneity was low (I^2<50%), a fixed-effects model was used. If the heterogeneity was high (I^2≥50%), a random-effects model was used. Sensitivity analyses were performed to explore the sources of heterogeneity. Sensitivity analyses were performed to exclude studies one by one, and then to exclude studies with significant heterogeneity.

Results

Article screening results

A total of 561 articles were searched through the preliminary search, of which 155 were duplicate records. By reading article titles and abstracts, 395 articles were excluded, of which 248 were irrelevant studies; 136 were reviews; 9 were animal experiments; 2 were case reports. And then the full text of 11 articles were examined according to the inclusion and exclusion criteria, finally 4 studies (19-22) were included in the meta-analysis and 7 articles were excluded for the following reasons: the mothers, not infants, started taking LGG before delivery (23), the baby took a probiotic mixture containing LGG (24-26), studied the preventive effect of LGG on colic (7,27,28). *Figure 1* shows the selection flow chart.

Table 1 The basic characteristic of included studies

Study	Grouping	Colic criteria	Patients (n)	Feeding mode (exclusively breastfed/ formula fed)	Age (days) (mean ± SD)	Girls/ boys (n)	Intervention	Follow-up (days)	Outcome indicators
Fatheree 2014 (19)	Experimental group	Wessel criteria	9	0/9	57±30	4/5	Formula with LGG, minimum 3×10^7 cfu's daily	90	Crying and fussing time at day 1, day 14, day 42, day 90. Fecal calprotectin levels at day 1, day14, day 42, day 90
	Control group		11	0/11	68±28	4/7	Formula		
Pärtty 2015 (20)	Experimental group	Wessel criteria	15	Breastfed or formula fed	38.0±10.8	8/7	LGG 4.5×10^9 cfu/d	28	Crying and fussing time at day 0 and day 28. Fecal calprotectin levels at day 0 and day 28
	Control group		15	Breastfed or formula fed	34.8±9.9	10/5	Placebo		
Savino 2020 (21)	Experimental group	Rome IV criteria	26	26/0	37.9±15	10/16	5 drops of LGG (5 10^9 drops colony for units per day)	28	Crying and fussing time at day 0 and day 28. Fecal calprotectin levels at day 0 and day 28
	Control group		21	21/0	41.8±17	9/12	Placebo		
Shulman 2022 (22)	Experimental group	Wessel criteria	36	0/36	19.3±0.8	14/22	PHF with LGG; 10^6 colony-forming units per gram of powder	21	Average crying/ fussing time at days 2–4, days 10–12, days 18–20. Adverse events
	Control group		35	0/35	19.7±0.8	14/21	PHF		

SD, standard deviation; LGG, *Lactobacillus rhamnosus* GG; PHF, partially hydrolyzed cow's milk protein infant formula.

Basic characteristics of articles

A total of 168 infants were included in these four studies, of which 86 comprised the experimental group and 82 were the control group. The diagnosis of colic was mostly based on the Wessel diagnostic criteria (19,20,22), and only the study by Savino *et al.* was based on the Rome IV diagnostic criteria (21). These 168 infants were breastfed or formula fed at the age of 2 weeks and more than 3 months after birth at enrollment. LGG was added to the diet of the experimental group, but the dose of LGG varied greatly between studies. The duration of the intervention also varied across studies, ranging from 21 days (22) to 90 days (19). Each study compared the change of crying and fussing time before and after enrollment, with 3 studies using diaries of the infants' parents to measure the change (19,21,22), and 1 study assessing it using two methods, diaries and retrospective interviews with the parents, respectively (20). All studies also compared changes in fecal calprotectin content before and after joining, and Shulman *et al.* (22) also reported differences in the gastroesophageal reflux, stool frequency, and milk protein allergy between the two groups. *Table 1* shows the basic characteristics of included studies.

Risk assessment of bias of included articles

ROB 2 was used to conduct the risk assessment of the included studies. Most of the items presented a low risk of bias (green color) in the assessment of the risk of bias. A high risk of bias (red color) was found in some items, such as missing outcome data, deviations from intended interventions. On the whole, 2 studies were judged to have some concerns (yellow color) (20,21), 2 studies were judged as at high risk of bias overall (19,22). *Figure 2* shows the result of the risk assessment of bias of studies.

Figure 2 Risk of bias graph summary.

Principal outcome: crying and fussing time (minutes/day)

Of the all four studies, three studies reported the crying and fussing time (minutes/day) between the experimental group and the control group as mean and standard deviation (19,20,22). However, one study did not report the standard deviation (21), and we failed to get a reply after two attempts to contact by email, so this study was not included in the meta-analysis. As is shown in the *Figure 3*, the result shows the low heterogeneity with an I^2=9% (P=0.33), LGG is effective in treat the infantile colic, resulting in a mean reduction of 33.82 min of crying per day (95% CI: −41.89 to −25.75, P<0.001).

Secondary outcome: fecal calprotectin (μg/g)

All four studies compared the value of fecal calprotectin between the two groups, but the study of Pärtty *et al.* (20) did not report the value in the article, and we failed to get a reply after two attempts to contact by email, so this study was not included in the meta-analysis. When we included the other three studies, we found that there was a statistical

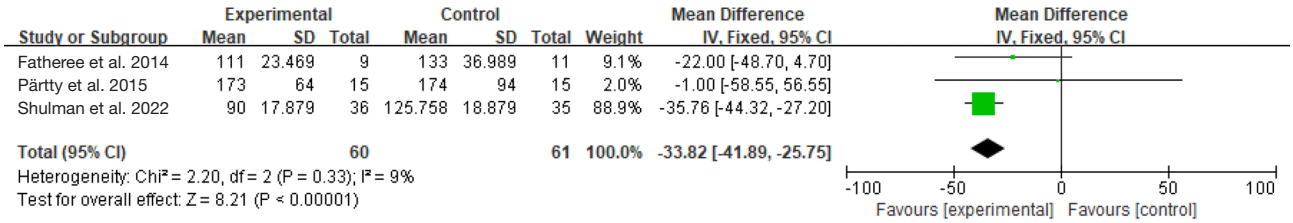

Figure 3 Comparison of the crying and fussing time (min/d) at the beginning and the end of intervention between two groups. SD, standard deviation; IV, Inverse Variance methods; CI, confidence interval.

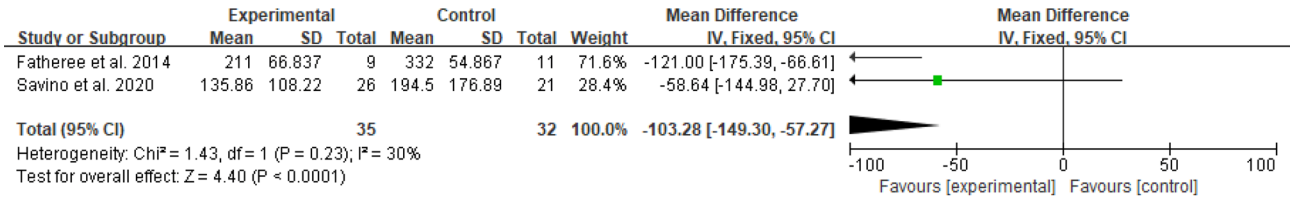

Figure 4 Comparison of the level of fecal calprotectin (μg/g) at the beginning and the end of intervention between two groups. SD, standard deviation; IV, Inverse Variance methods; CI, confidence interval.

heterogeneity between studies (I^2=89%, P<0.001) using a random effect model. Due to the significant heterogeneity, we conducted sensitivity analysis by excluding the studies one by one, and found that the study of Shulman *et al.* (22) had an obvious significance on the heterogeneity and combined results. If this study is not included, the analysis results are shown in *Figure 4*, and the heterogeneity between studies is reduced to I^2=30% (P=0.23). The fixed effect model shows that LGG can reduce calprotectin content in feces (μg/g) (MD: −103.28; 95% CI: −149.30 to −57.27, P<0.001).

Secondary outcome: adverse events

Only one study by Pärtty *et al.* (20) analyzed the adverse effects of two groups. The mean weight gain during the study was comparable between the two groups (P=0.54). The number of daily regurgitations increased more often in the placebo than in the probiotic group during the follow-up [odds ratio (OR): 6.19; 95% CI: 1.36 to 38.04; P=0.04]. Stool frequencies remained comparable (data not shown). The proportion of infants diagnosed with cow's milk protein allergy at the end of the study was comparable (OR: 3.50; 95% CI: 0.32 to 38.23; P=0.70).

Discussion

This is the first systematic review of randomized trials evaluating the efficacy of LGG in infantile colic. There was a significant reduction in crying times and calprotectin content in stool following LGG supplementation.

The pathogenesis of infant colic is unclear and multifactorial. Several factors can contribute to the development of infant colic, including altered intestinal microbiota, gastrointestinal factors (cow's milk allergy, excessive intestinal gas), imbalanced neurodevelopment, and eating moods. Among them, intestinal microbiota dysbiosis is getting more attention. It is possible that intestinal dysbiosis contributes to colic symptoms by increasing fermentation of lactose, carbohydrates, and proteins, leading to an increase in gas production and gut extension (29). Furthermore, colic in infants is associated with low-grade systemic inflammation, as reported by Pärtty *et al.* (30). Pathogen-associated lipopolysaccharides, present on the outer membranes of Gram-negative bacteria, such as *Escherichia* spp., *Bacteroides* spp., and *Klebsiella* spp., can promote production of pro-inflammatory cytokines and chemokines, provoke a pro-inflammatory response in gut epithelial cells, then affect central and enteric neuronal

function, including detection of pain and crying in infants through the microbiota–gut-brain axis (31,32).

The low proportions of *Bifidobacterium (*phylum Actinobacteria*)* and *Lactobacillus (*phylum Firmicutes*)* in infants' gut microbiota might be associated with infant crying and fussing (6,7). LGG was the first strain belonging to the genus *Lactobacillus* to be patented in 1989. It has good ability to survive, to proliferate at gastric acid pH and in medium containing bile, to adhere to enterocytes. LGG can adhere to mucosal surfaces, normalize the mucosal barrier, stimulate immune system and enhance intestinal functional maturation (33). Among preterm infants, LGG supplementation can promote gut health through a reduction of *Clostridium histolyticum* group bacteria in their stools via a variety of mechanisms such as competitive exclusion. *C histolyticum* can evoke proinflammatory cytokines such as tumor necrosis factor-α, and cause the degradation of antigen-specific immunoglobulin A in the gut, which can impair gut barrier function (34,35). In an animal model, LGG can alter some key brain neurotransmitters and biogenic amines that could be involved in pain modulation (36). In this study, we found that crying time was reduced by 33.82 min after LGG supplementation at the end of the intervention. The dose and duration of administration varied from study to study. In the individual participant data meta-analysis (IPDMA) by Sung *et al.* (11), they studied infant crying and fussing treatment success at 21days postintervention, crying and fussing duration (minutes per day) at 7, 14 and 21 days postintervention between the probiotic (*Lactobacillus reuteri* DSM17938) and placebo groups. They found that the crying and fussing were reduced significantly in the probiotic group at all follow-up time points. The reduction was significantly pronounced at 7 and 21 days. For breastfed infants with colic, the probiotic group was 2 to 3 times more likely than the placebo group to experience treatment success. However, the dose and duration of administration varied from study to study. We could not make subgroup analyses. This meta-analysis needs to be further investigated to determine the relationship between dose, duration, and probiotic efficacy. The sample size of Shulman *et al.* (22) makes its weight significantly greater (88.9%). In this study, no significant difference was noted between two groups. We tried to use a random-effects model to mitigate the impact of weight. We found that LGG supplement could also reduce the crying time of 32.59 min (95% CI: –43.23 to –21.96; P<0.01), while the weight decreased to 82.1%, which is still significant. To sum up, we need more trials to explore the efficacy of LGG on crying and fussing time.

In addition to microbiota alterations in the gut, infantile colic is associated with low-grade systemic inflammation (30). Calprotectin is a 36-kDa protein and a member of the S100 calcium-binding family. The S100 name derives from these proteins' solubility in 1005 ammonium sulfate at neutral pH (37). Calprotectin represents about 60% of the cytosolic protein in neutrophils, which are the primary source of calprotectin (38). At the site of inflammation in the gut wall, the interaction of activated monocytes with endothelial cells can increase leukocyte recruitment and activate calprotectin's release (39). Calprotectin is found in a number of body fluids, and its concentration is proportional to the degree of inflammation in the body. The levels in feces are about six times higher than in the blood, therefore, fecal calprotectin can reflect intestinal inflammation better (40). Animal experiments show that LGG components can inhibit the activation of some signaling pathways in cells stimulated by lipopolysaccharide, which can attenuate the production of inflammatory cytokines such as TNF-α and IL-6 (41). Prenatal supplementation with LGG can promote *bifidobacteria* dominance in the gut of neonates (16). Secreted bioactive factors from *Bifidobacterium* enhance epithelial cell barrier function (42). When analyzing the changes in the level of calprotectin in feces in this meta-analysis, we excluded the study of Shulman *et al.* (22) because of its significant influence on the result. We found stool calprotectin levels were low at baseline and remained low by study end. This difference may be related to differences in the populations. In their study, the infants were young. Studies showed that calprotectin levels in feces were higher in exclusively breast-fed infants than in formula-fed infants in the first 3 months of life (43-45). In this meta-analysis, all four studies compared fecal calprotectin between two groups. Pärtty *et al.* (20) did not report the value. The study by Shulman *et al.* (22) was excluded because of the obvious significance of the heterogeneity and combined results. Infants in this study were fed formula. Infants in the other two studies included in the quantitative meta-analysis were exclusively breastfed (21) or exclusively formula fed (19). Due to limited clinical data, we could not perform subgroup analyses according to feeding pattern.

Studies have shown that eliminating milk protein from the maternal diet relieves colic symptoms in one-third of breast-fed infants (46). While the symptoms of colic in infants are relieved after the milk protein formula is changed

to soybean protein formula (47). Thus, it is speculated that colic may be related to a milk protein allergy (29). Some studies suggest that supplementing LGG can alleviate infant milk protein allergy symptoms (48,49). However, only one study included in this meta-analysis compared the number of infants with milk protein allergy between the two groups at the end of the study (20), showing that the proportion of the two groups was comparable (OR: 3.50; 95% CI: 0.32 to 38.23; P=0.70), so more studies are needed to explore the relationship between LGG and milk protein allergy.

Previous meta-analyses have examined the effectiveness of other probiotics or the combination of probiotics and LGG in treating infantile colic. This is the first meta-analysis that studies only LGG in infantile colic treatment.

Conclusions

LGG is effective in treating infantile colic. However, more studies are needed to explore the effects of LGG with different doses, administration time, and duration on infants with different feeding moods.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-24-112/rc

Peer Review File: Available at https://tp.amegroups.com/article/view/10.21037/tp-24-112/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-24-112/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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