Probiotics for the Management of Pediatric Gastrointestinal Disorders: Position Paper of the ESPGHAN Special Interest Group on Gut Microbiota and Modifications

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ABSTRACT

Background: Probiotics, defined as live microorganisms that, when administered in adequate amounts, confer a health benefit on the host, are widely used despite uncertainty regarding their efficacy and discordant recommendations about their use. The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Special Interest Group on Gut Microbiota and Modifications provides updated recommendations for the use of probiotics for the management of selected pediatric gastrointestinal disorders.

Methods: All systematic reviews and/or meta-analyses, as well as subsequently published randomized controlled trials (RCTs) (until December 2021), that compared the use of probiotics in all delivery vehicles and formulations, at any dose, with no probiotic (ie, placebo or no treatment), were eligible for inclusion. The recommendations were formulated only if at least 2 RCTs on a similar well-defined probiotic strain were available. The modified Delphi process was used to establish consensus on the recommendations.

Results: Recommendations for the use of specific probiotic strains were made for the management of acute gastroenteritis, prevention of antibiotic-associated diarrhea, nosocomial diarrhea and necrotizing enterocolitis, management of *Helicobacter pylori* infection, and management of functional abdominal pain disorders and infant colic.

Conclusions: Despite evidence to support the use of specific probiotics in some clinical situations, further studies confirming the effect(s) and defining the type, dose, and timing of probiotics are still often required. The use of probiotics with no documented health benefits should be discouraged.

Key Words: children, infants, microbiota, microbiome

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What Is Known

- Probiotics are increasingly being used in the pediatric population.
- Uncertainty remains about how to appropriately use probiotics.
- The effects of probiotics are considered to be strain specific.

What Is New

- Indications for the use of probiotics for selected gastrointestinal disorders in children covered in earlier documents are updated.
- Indications not covered in earlier documents are included.
- The recommendations formulated are meant to be broadly applicable and should be viewed as the preferred management. However, they are not the only approach and depend on individual clinical scenarios.

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SUMMARY OF RECOMMENDATIONS

Acute Gastroenteritis

- Healthcare professionals (HCPs) may recommend *Lacticaseibacillus rhamnosus (L rhamnosus)* GG [at a dose of ≥10^{10} CFU/day, for 5–7 days] for the management of acute gastroenteritis in children, since there is evidence of reduced duration of diarrhea, length of hospitalization, and stool output (certainty of evidence: low; grade of recommendation: weak).
- HCPs may recommend *Saccharomyces (S) boulardii** (at a dose of 250–750 mg/day, for 5–7 days) for the management of acute gastroenteritis in children, since there is evidence of reduced duration of diarrhea (certainty of evidence: low; grade of recommendation: weak).
- HCPs may recommend *Limosilactobacillus reuteri (L reuteri)* DSM 17938 (at daily doses 1×10^8 to 4×10^8 CFU, for 5 days) for the management of acute gastroenteritis in children, since there is evidence of reduced duration of diarrhea (certainty of evidence: very low; grade of recommendation: weak).
- HCPs may recommend the combination of *L rhamnosus* 19070-2 and *L reuteri* DSM 12246 (at a dose of 2×10^{10} CFU for each strain, for 5 days) for the management of acute gastroenteritis in children, since there is evidence of reduced duration of diarrhea (certainty of evidence: very low; grade of recommendation: weak).
- HCPs should *not* recommend the combination of *Lactobacillus helveticus* R0052 and *L rhamnosus* R0011 for the management of acute gastroenteritis due to the lack of efficacy (certainty of evidence: moderate; grade of recommendation: strong).
- HCPs may *not* recommend *Bacillus clausii* strains O/C, SIN, N/R, and T for the management of acute gastroenteritis in children due to the lack of efficacy (certainty of evidence: very low; grade of recommendation: weak).

Prevention of Antibiotic-Associated Diarrhea

- If the use of probiotics for preventing antibiotic-associated diarrhea (AAD) is considered because of the existence of risk factors such as class of antibiotic(s), duration of antibiotic treatment, age, need for hospitalization, comorbidities, or previous episodes of AAD, HCPs may recommend high doses (≥5 billion CFU/day) of *S boulardii** or *L rhamnosus* GG started simultaneously with antibiotic treatment to prevent AAD in outpatients and hospitalized children (certainty of evidence: moderate; grade of recommendation: strong).

Prevention of Nosocomial Diarrhea

- HCPs may recommend *L rhamnosus* GG (at least 10^9 CFU/day) for the duration of the hospital stay for the prevention of nosocomial diarrhea in children (certainty of evidence: moderate; grade of recommendation: weak).
- HCPs should *not* recommend *L reuteri* DSM 17938 for the prevention of nosocomial diarrhea in children due to the lack of efficacy (certainty of evidence: high; grade of recommendation: strong).

Prevention of Necrotizing Enterocolitis

- For reducing the risk of necrotizing enterocolitis in preterm infants, provided all safety issues are met, HCPs may recommend *L rhamnosus* GG (at a dose ranging from 1×10^9 CFU to 6×10^9 CFU) (certainty of evidence: low; grade of recommendation: weak) or the combination of *Bifidobacterium (B) infantis* BB-02, *B lactis* BB-12, and *Streptococcus thermophilus* TH-4 at 3.0 to 3.5×10^8 CFU (of each strain) (certainty of evidence: low; grade of recommendation: weak).
- Due to insufficient evidence, no recommendation can be made *for* or *against L reuteri* DSM 17938 or the combination of *B bifidum* NCDO 1453 & *Lactobacillus acidophilus* NCDO 1748 (certainty of evidence: for both, very low to moderate).
- Due to the lack of efficacy, HCPs may *not* recommend *B breve* BBG-001 (certainty of evidence: low to moderate; grade of recommendation: weak) or *S boulardii* (certainty of evidence: very low to moderate; grade of recommendation: weak).

Helicobacter pylori Infection

- In children with *H pylori* infection, HCPs may recommend, along with *H pylori* therapy, *S boulardii** for increasing the eradication rates and decreasing gastrointestinal adverse effects (certainty of evidence: very low; grade of recommendation: weak).

Inflammatory Bowel Disease

- No recommendation can be made *for* or *against* the use of probiotics studied so far in the management of children with ulcerative colitis due to insufficient evidence.
- No recommendation can be made *for* or *against* the use of probiotics studied so far in the treatment of children with Crohn disease due to insufficient evidence.

Disclaimer: ESPGHAN is not responsible for the practices of physicians and provides guidelines and position papers as indicators of best practice only. Diagnosis and treatment are at the discretion of physicians.

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Infant Colic

- HCPs may recommend *L reuteri* DSM 17938 (10^8 CFU/day for at least 21 days) for the management of infant colic in breastfed infants (certainty of evidence: moderate; grade of recommendation: weak).
- No recommendation can be made *for* or *against* the use of *L reuteri* DSM 17938 in formula-fed infants due to insufficient evidence.
- HCPs may recommend *B lactis* BB-12 (10^8 CFU/day, for 21–28 days) for the management of infant colic in breastfed infants (certainty of evidence: moderate; grade of recommendation: weak).
- No recommendation can be made *for* or *against* the use of any of the probiotics studied so far for preventing infant colic due to insufficient evidence.

Functional Abdominal Pain Disorders

- HCPs may recommend *L reuteri* DSM 17938 (at a dose of 10^8 CFU to 2×10^8 CFU/day) for pain intensity reduction in children with functional abdominal pain disorders (certainty of evidence: moderate; grade of recommendation: weak).
- HCPs may recommend *L rhamnosus GG* (at a dose of 10^9 CFU to 3×10^9 CFU twice daily) for the reduction of pain frequency and intensity in children with irritable bowel syndrome (certainty of evidence: moderate; grade of recommendation: weak).

Functional Constipation

- HCPs may *not* recommend the use of probiotics as a single or adjuvant therapy for treatment of functional constipation in children due to the lack of efficacy (certainty of evidence: moderate; grade of recommendation: weak).

Celiac Disease

- No recommendation can be made *for* or *against* the use of probiotics in children with celiac disease due to insufficient evidence.

Small Intestinal Bacterial Overgrowth

- No recommendation can be made *for* or *against* the use of probiotics in the treatment or prevention of small intestinal bacterial overgrowth due to insufficient evidence.

Pancreatitis

- As no randomized controlled trial on the use of probiotics for pancreatitis in children was identified, no recommendation can be made *for* or *against* the use of probiotics for the management of pancreatitis.

*Note: In many of the trials, the strain designation of *S boulardii* was not available. However, if available, or assessed retrospectively, most used was that recently designated as *S boulardii* CNCM I-745.

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INTRODUCTION

In previous years, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Working Group (WG) on Probiotics and Prebiotics (since 2019 working within the ESPGHAN Special Interest Group on Gut Microbiota & Modifications) published several clinical guidelines on the use of probiotics for preventing or treating selected gastrointestinal disorders in children (1–4). Only some conditions were covered, and new evidence has become available. Thus, the purpose of this document is to provide updated practical recommendations for the use of probiotics for the management of selected pediatric gastrointestinal disorders in a single document. Indications covered in earlier documents were updated. Indications not covered in earlier documents were included. The recommendations formulated are meant to be broadly applicable and should be viewed as the preferred management (only in the context of probiotics). However, they are not the only approach and depend on individual clinical scenarios.

METHODS

The methods used for the development of this document are described in Table S1, Supplemental Digital Content, *http://links.lww.com/MPG/C954*. In brief, all systematic reviews and/or meta-analyses, as well as subsequently published randomized controlled trials (RCTs) (until December 2021) that compared the use of probiotics in all delivery vehicles and formulations, at any dose, with no probiotic (ie, placebo or no treatment), were eligible for inclusion. One exception was that studies evaluating probiotic-supplemented formulas were not included. For diseases recently evaluated by ESPGHAN and for recommendations formulated in previously published ESPGHAN/Working Group/Committee on Nutrition guidelines or position papers, subsequently published systematic reviews and/or meta-analyses and peer reviewed RCTs were considered for inclusion.

The WG followed the internationally accepted definition of probiotics stated as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" (5). Non-viable microorganisms, that is, those not meeting the definition of a probiotic (5), were not considered.

The WG followed the approach developed earlier (6) and did not provide a recommendation on the use of probiotics in general. Instead, the WG is reporting evidence and recommendations related to specific individual probiotic strains or their combinations. The recommendations were formulated only if at least 2 RCTs that used a given probiotic were available.

The WG acknowledged that the genus of *Lactobacillus* has been recently reclassified into 25 genera, which include 23 novel genera (7). For example, the new name for *Lactobacillus rhamnosus* is *Lacticaseibacillus rhamnosus.* However, the abbreviations of microorganisms remained the same (ie, *L rhamnosus).* Species names and strain designations did not change (7). Throughout the manuscript, the strain names were used as in the original publications. However, when formulating the recommendation, the new strain names were used.

The WG acknowledges that safety of probiotics is an important issue. However, the WG abstained from evaluating the safety of probiotics, as this issue was recently thoroughly systematically reviewed elsewhere (for review, see reference (8)).

The prefinal draft of this document was submitted for public consultation on April 30, 2022, via the ESPGHAN website. ESPGHAN members and all interested parties were invited to submit written comments within 16 days. Members of the WG assessed and discussed all comments. If found to be relevant, the comments were taken into consideration and, potentially, guided revisions to the manuscript.

Treatment of Acute Gastroenteritis

Until 2019, many, if not all, professional societies and groups of experts advocated use of probiotics with documented efficacy for the management of acute gastroenteritis (6,9–11). Currently, the recommendations differ, possibly reflecting negative (null) studies questioning the efficacy of some strains with previous positive recommendations (12,13).

In 2020, the ESPGHAN Working Group on Probiotics and Prebiotics identified (search date: September 2019) 16 systematic reviews and meta-analyses published since 2010, which included more than 150 RCTs (1). The WG made weak (also known as conditional) recommendations *for* (in descending order in terms of the number of trials evaluating any given strain): *Saccharomyces (S) boulardii* (low to very low certainty of evidence); *L rhamnosus GG* (very low certainty of evidence); *Lactobacillus reuteri* (currently known as *Limosilactobacillus reuteri,* hereafter *L reuteri)* DSM 17938 (low to very low certainty of evidence); and *L rhamnosus* 19070-2 & *L reuteri* DSM 12246 (very low certainty of evidence). The WG made a strong recommendation *against Lactobacillus helveticus* R0052 & *L rhamnosus* R0011 (moderate certainty of evidence) and a weak (conditional) recommendation *against Bacillus clausii* strains O/C, SIN, N/R, and T (very low certainty of evidence).

In contrast, also in 2020, the American Gastroenterology Association (AGA), based on the evaluation of 89 trials, made a conditional recommendation *against* the use of probiotics in children from North America with acute infectious gastroenteritis (moderate quality of evidence) (14). The rationale for the negative AGA recommendation was that most of the studies were performed outside of North America. Moreover, 2 large, high-quality null trials, performed in Canada and the United States, questioned the efficacy of probiotics, or more specifically the probiotic strains evaluated in these studies, for the management of children with acute gastroenteritis (12,15). The AGA attributed the divergence in evidence of efficacy to differences in host genetics, diet, sanitation, and endemic enteropathogens between North America and the other global regions and therefore did not consider the results of RCTs conducted outside of North America applicable to the scope of the AGA. Schnadower et al (16) recently reported the results of a secondary pre-planned analysis demonstrating that the lack of probiotics' impact on diarrheal outcomes was independent of child's age, weight, and probiotic dose. However, it is possible that also other factors such as rotavirus vaccination might have affected the reported differences in efficacy.

Since 2019, 4 meta-analyses focusing on the use of probiotics for the treatment of acute infectious diarrhea have been published (17–20).

In 2020, an updated Cochrane review (17) included 82 RCTs (n = 12,127 participants), mainly in children (n = 11,526). Overall, probiotics, as a general group, reduced the risk of diarrhea lasting ≥48 hours [36 RCTs, n = 6053, relative risk (RR) 0.64, 95% confidence interval (CI): 0.52–0.79] and reduced the mean duration of diarrhea [56 RCTs, n = 9138, mean difference (MD) −21.3 hours, 95% CI: −26.9 to −15.7]. However, based on the analysis of trials with low risk of bias, the reviewers concluded that probiotics have no effect on the risk of diarrhea lasting ≥48 hours (2 RCTs, n = 1770, RR 1.00, 95% CI: 0.91–1.09) or duration of diarrhea (6 RCTs, n = 3058, MD 8.64 hours, 95% CI: −29.4 to 12.1 hours longer). Based on a criterion of 5 or more RCTs reporting the primary outcomes, 3 strains were evaluated. Several subgroup analyses were performed, including those based on individual probiotic strains. The risk of diarrhea lasting ≥48 hours was reduced by *L rhamnosus* GG only (6 RCTs, n = 1557, RR 0.79, 95% CI: 0.65–0.97, substantial heterogeneity $X^2 = 15.06$, $I^2 = 67\%$). The duration of diarrhea was reduced by *L rhamnosus* GG (14 RCTs, n = 3344, MD −22.5, 95% CI: −32.7 to −12.3), *S boulardii* (11 RCTs, n = 1617, MD −24.6 hours, 95% CI: −35.3 to −13.9), and *L reuteri* (6 RCTs, n = 433, MD −22.8 hours, 95% CI: −31.95 to −13.7). Except for the latter strain, there was substantial statistical heterogeneity. Note that specific strain numbers or designations were not always used in the analysis, so that different strains of the same species may have been analyzed together; an approach which we do not advise.

A 2021 Bayesian network meta-analysis aimed at identifying the most effective probiotic strains for the treatment of acute gastroenteritis (20). Its conclusion partially differed from the ESPGHAN WG recommendations, as the authors included several probiotic strains based on a single RCT, which is different from the methodology applied in the present position paper.

Two other meta-analyses focused on probiotics and synbiotics used in children living in developed countries (18) or on probiotics used in dehydrated children (19). As the results were not reported based on a single probiotic strain (or their combination), data from these analyses were not interpretable for the purposes of this document.

In addition, 4 other studies were published in the last 2 years reporting the results of pre-planned analyses of the North American pediatric RCTs whose original results were already included in an earlier meta-analysis and ESPGHAN document. These studies may add information about the timing of probiotic administration (21), the etiology-dependent efficacy (22), and barriers to implementation of probiotics (23). However, as most of these studies merged data on different populations (with different settings, enrollment criteria, and outcomes) and different probiotic formulations (ie, *L rhamnosus* GG and *L rhamnosus* R0011 & *L. helveticus* R0052), they were not included in single-strain evaluation, but were considered during the methodological process of recommendation building.

Several new RCTs were identified in the current search. In addition to the strains identified in our earlier document (1), the strains evaluated include *L plantarum* LRCC5310 (n = 18) (24); *Bifidobacterium* (*B) lactis* Bi-07, *L rhamnosus* HN001, and *L acidophilus* NCFM (n = 194) (25).

Below only strains for which recommendations were formulated are summarized.

L rhamnosus GG (ATCC 53103)

A single-strain meta-analysis focusing exclusively on *L rhamnosus* GG and including 19 RCTs was identified (26). As this review did not include any new RCT compared to previous meta-analyses, the results were substantially in line with previous evidence and demonstrated that children receiving *L rhamnosus* GG had a 1-day reduction in the duration of diarrhea (15 RCTs, n = 3721, MD −24 hours, 95% CI: −37 to −12). In addition, the risk of diarrhea lasting more than 3 days (OR 0.5, 95% CI: 0.4–0.8) or 4 days (OR 0.6, 95% CI: 0.4–0.8) was reduced. For hospitalized children, the administration of *L rhamnosus* GG was related to a significant reduction in the length of hospitalization for rotavirus infection (2 RCTs, n = 115, MD −21 hours, 95% CI: −27 to −15) or any cause of diarrhea (6 RCT, n

= 1823, MD −39 hours, 95% CI −72 to −6). The strongest effect of *L rhamnosus* GG on the duration of diarrhea (12 RCTs, n = 2949, MD −23 hours, 95% CI: −36 to −9) and stool output (6 RCTs, n = 2262, MD −1.1, 95% CI −2 to −0.3) was demonstrated for doses higher than 10^{10} CFU/day. Overall, the included studies had a low quality and showed high heterogeneity. However, according to the authors, the differences in methodological quality could not explain the statistically significant heterogeneity. A subgroup analysis according to the geographical setting of the clinical trials demonstrated a higher efficacy of *L rhamnosus* GG in RCTs performed in European [5 RCTs, n = 744, MD −32 hours (−49 to −15)] and Asian countries [6 RCTs, n = 1740, MD −24 hours (−47 to −1.8)] compared to other continents providing a possible explanation for the differences between the ESPGHAN WG and AGA recommendations.

- HCPs may recommend *Lacticaseibacillus rhamnosus (L rhamnosus)* GG ATCC 53103 [at a dose of ≥10^{10} CFU/day, for 5–7 days] for the management of acute gastroenteritis in children, since there is evidence of reduced duration of diarrhea, length of hospitalization, and stool output.
- Certainty of evidence: Low.
- Grade of recommendation: Weak.

Of note, as a result of voting, the certainty of evidence for *L rhamnosus* differs from that reported in our earlier document (1), changing from very low certainty of evidence to low certainty of evidence. Factors supporting the previous rating of a very low certainty of evidence included a high level of heterogeneity (98%), which was not justified by the different settings and dates of publication, and moderate-to-high risk of bias for most studies supporting the positive recommendation. Moreover, 5 studies enrolling more than half of the entire treated population (954/1866 patients receiving *L rhamnosus* GG) did not demonstrate efficacy on the duration of diarrhea outcome. Finally, there was serious inconsistency (even in high-income settings), with the largest and most recent RCT not supporting previous evidence. On the other hand, a subgroup meta-analysis based on geographical location showed a higher efficacy of *L rhamnosus* GG in clinical trials performed in European countries (5 RCTs) and the demonstration of a dose-response gradient. The latter factors, which prevailed, were in favor of the change to a low certainty of evidence.

S boulardii

A 2020 ESPGHAN document (1) and a 2020 meta-analysis (27) based on 29 RCTs provided low- to very low-quality evidence that *S boulardii* reduced the duration of diarrhea (23 RCTs, n = 3450, MD −1.06 day, 95% CI: −1.32 to −0.79; high heterogeneity); reduced duration of hospitalization (8 RCTs, n = 999, MD −0.85 day, 95% CI: −1.35 to −0.34; high heterogeneity), and risk of diarrhea on day 2 to day 7.

Since these publications, 2 new RCTs examining effects of *S boulardii* versus placebo or only oral rehydration solution (ORS) have been published. In the study by Mourey et al (28), 100 children aged 3 to 36 months with acute diarrhea were randomly allocated to the *S boulardii* CNCM I-3799 group (at a daily dose of 5 billion CFU twice daily) or to the placebo group for 5 days. The time to recovery from diarrhea was significantly shorter in the probiotic group compared with the placebo group (66 ± 12 hours vs 95 ± 18 hours, respectively, P = 0.0001). Faster remission in the probiotic group was also demonstrated by a shorter time before the first episode of semisolid stool [−23.5 hours, MD −8 hours (−32 to −16), P = 0.0001] and the faster normalization of stool consistency.

In the second trial, 200 children were allocated to 2 equal groups receiving *S boulardii* (250–500 mg daily, for 5 days) in addition to ORS or ORS only. Outcome was assessed in terms of duration of diarrhea and improvement in the number of stools per day on the fifth day of presentation. Improvement was higher in the *S boulardii* group compared with the control group [92/100 (92%) vs 71/100 (71%), respectively] (29). Two other reports were comparative studies between *S boulardii* and *Lactobacillus sporogenes* or a multispecies probiotic product in children with acute gastroenteritis. Despite both studies showing superior efficacy of *S boulardii* in regard to frequency and duration of diarrhea, they were not considered because no placebo arm was included (30,31).

In addition, a recent network meta-analysis identified *S boulardii* as the most effective probiotic strain in reducing the duration of diarrhea compared to placebo, based on moderate evidence (20).

- HCPs may recommend *S boulardii** (at a dose of 250–750 mg/day, for 5–7 days) for the management of acute gastroenteritis in children, since there is evidence of reduced duration of diarrhea.
- Certainty of evidence: Low.
- Grade of recommendation: Weak.

*Note: In many trials, the strain designation of *S boulardii* was not available. However, if available, or assessed retrospectively, the strain most used was the strain recently classified as *S boulardii* CNCM I-745.

L reuteri DSM 17938

No new evidence became available after the formulation of the last recommendation. A previous meta-analysis (32) of 4 RCTs (n = 347) showed that the administration of *L reuteri* DSM 17938 compared with placebo reduced the duration of diarrhea by 0.87 days (95% CI: −1.4 to −0.3) and increased the cure rate on day 2 (3 RCTs, n = 256, RR 4.5, 95% CI: 2–10). In addition, children hospitalized for acute gastroenteritis and receiving *L reuteri* DSM 17938 showed a shorter length of stay (3 RCTs, n = 284, MD −0.5 day, 95% CI: −1.0 to 0.0). A 2020 post hoc analysis suggested a possible role for fecal metabolomics and calprotectin in the response to *L reuteri* DSM 17938 in children with acute gastroenteritis who did or did not respond to the treatment with *L reuteri* DSM 17938 (33). However, this study did not provide new evidence about the efficacy or safety of such treatment and was excluded from our analysis.

- HCPs may recommend *Limosilactobacillus reuteri (L reuteri)* DSM 17938 (at daily doses 1×10^8 to 4×10^8 CFU, for 5 days) for the management of acute gastroenteritis in children, since there is evidence of reduced duration of diarrhea.
- Certainty of evidence: Very low.
- Grade of recommendation: Weak.

Combination of *L rhamnosus* 19070-2 and *L reuteri* DSM 12246

In 2020, the WG formulated a weak recommendation on use of the combination of *L rhamnosus* 19070-2 and *L reuteri* DSM

12246, based on the findings from only 2 RCTs with a very limited number of subjects (n = 112). No additional studies were identified.

- HCPs may recommend the combination of *L rhamnosus* 19070-2 and L reuteri DSM 12246 (at a dose of 2×10^{10} CFU for each strain, for 5 days) for the management of acute gastroenteritis in children, since there is evidence of reduced duration of diarrhea.
- Certainty of evidence: Very low.
- Grade of recommendation: Weak.

Combination of *L helveticus* R0052 and *L rhamnosus* R0011

The analysis of 4 RCTs (n = 1133) performed for the previous ESPGHAN WG recommendations version of this document demonstrated that, compared with placebo or no intervention, the administration of the combination of *L helveticus* R0052 and *L rhamnosus* R0011 had no significant effect on the duration of diarrhea (MD −0.15 day, 95% CI: −0.7 to 0.4), with substantial heterogeneity (I^2 = 67%). The duration of hospitalization was not reported in any of the trials. The pooled results of 2 RCTs (n = 950) showed no significant difference between groups in the need for hospitalization in outpatients (RR 1.5, 95% CI: 0.9–2.55, no heterogeneity I^2 = 0%).

- HCPs should *not* recommend the combination of *L helveticus* R0052 and *L rhamnosus* R0011 for the management of acute gastroenteritis due to the lack of efficacy.
- Certainty of evidence: Moderate.
- Grade of recommendation: Strong.

Bacillus clausii Strains O/C, SIN, N/R, and T

In 2020, the WG provided a weak recommendation *against* the use of *Bacillus clausii* stains intrinsically resistant to chloramphenicol (O/C), novobiocin and rifampicin (N/R), tetracycline (T), or neomycin and streptomycin (SIN) for the management of acute gastroenteritis in children, due to the lack of consistent and methodologically rigorous evidence in the pediatric age group. No other RCTs were published in the last 2 years to justify a change in this recommendation. A recent in vitro study demonstrated that a commercially available mix of *B clausii* strains may be able to counteract the rotavirus-induced mucosal barrier damage and inhibit the production of reactive oxygen species and proinflammatory cytokines, providing a protective effect against enterocyte apoptosis (34). This evidence might encourage the development of further large and rigorous RCTs to investigate the efficacy of using this strain in children with acute gastroenteritis living in European countries.

- HCPs may *not* recommend *B clausii* strains O/C, SIN, N/R, and T for the management of acute gastroenteritis in children due to the lack of efficacy.
- Certainty of evidence: Very low.
- Grade of recommendation: Weak.

Prevention of AAD

The use of probiotics for preventing AAD was earlier addressed by the ESPGHAN WG on Probiotics (2). In 2016, if the use of probiotics for preventing AAD was considered because of the existence of risk factors such as class of antibiotic(s), duration of antibiotic treatment, age, need for hospitalization, comorbidities, or previous episodes of AAD, the WG recommended using *L rhamnosus* GG (moderate quality of evidence, strong recommendation) or *S boulardii* (moderate quality of evidence, strong recommendation). Other strains or combinations of strains were tested, but sufficient evidence was still lacking. If the use of probiotics for preventing *Clostridioide difficile*-associated diarrhea was considered, the ESPGHAN WG suggested using *S boulardii* (low quality of evidence, conditional recommendation).

In contrast, the AGA (2020) did not formulate any recommendations on the use of probiotics for preventing AAD. However, the AGA conditionally recommended (based on low quality of evidence) certain probiotics for the prevention of *C difficile* infection in children receiving antibiotic treatment. These included *S boulardii*; or the 2-strain combination of *L acidophilus CL1285 & L casei LBC80R*; or the 3-strain combination of *L acidophilus, L delbruekii* subsp. *bulgaricus*, and *B bifidum*; or the 4-strain combination of *L acidophilus, L delbruekii* subsp. *bulgaricus, B bifidum*, and *Streptococcus salivarius* subsp. *thermophilus* (14). No strain specification was given for the 3-strain and 4-strain combinations, which may contribute to confusion for implementation of these recommendations.

Since November 2016 (the date of the last search made by the 2016 ESPGHAN WG), evidence has consistently shown that most of the tested probiotics significantly reduce the risk of AAD, including a 2019 Cochrane review (35). The latter identified 33 RCTs involving 6352 participants. The probiotics assessed included *Bacillus* spp, *Bifidobacterium* spp, *Clostridium butyricum*, *Lactobacilli* spp, *Lactococcus* spp, *Leuconostoc cremoris*, *Saccharomyces* spp, or *Streptococcus* spp, alone or in combination. At evaluation after 5 days to 12 weeks from enrollment, a statistically significant reduction in the incidence of AAD was found in the probiotic groups compared with the control groups (8% vs 19%, respectively, RR 0.45, 95% CI: 0.36–0.56), with a number needed to treat (NNT) of 9 (95% CI: 7–13). In the high dose studies (≥5 billion CFU per day), the incidence of AAD was reduced in the probiotic groups compared with the control groups (13% vs 23%, respectively, RR 0.54, 95% CI: 0.4–0.7, NNT 6, 95% CI: 5–9).

Single-strain meta-analyses found that, compared with placebo or no intervention, probiotics such as *S boulardii* (27) or *L rhamnosus* GG (36), typically administered simultaneously or early following initiation of antibiotic therapy, reduced the risk of AAD. A 2021 systematic review of 33 RCTs confirmed the evidence-based efficacy of *S boulardii* CNCM I-745 or *L rhamnosus* GG in preventing AAD in outpatients and hospitalized children (37). However, in a scoping review performed to inform development of a core outcome set, substantial heterogeneity in the definition, duration, and severity of diarrhea as well as in outcomes was noted (38).

- If the use of probiotics for preventing AAD is considered because of the existence of risk factors such as class of antibiotic(s), duration of antibiotic treatment, age, need for hospitalization, comorbidities, or previous episodes of AAD, HCPs may recommend high doses (≥5 billion CFU per day) of *S boulardii** or *L rhamnosus* GG started simultaneously with antibiotic treatment to prevent AAD in outpatients and hospitalized children.
- Certainty of evidence: Moderate.

- Grade of recommendation: strong.

*Note: In many of the trials, the strain designation of *S boulardii* was not available. However, if available, or assessed retrospectively, the most used strain was the strain recently designated as *S boulardii* CNCM I-745.

Prevention of Nosocomial Diarrhea

Gastrointestinal infections account for the majority of hospital-acquired or healthcare-associated infections that occur more than 48 hours after the admission of children to the hospital or within 48 hours after discharge. Up to one-third of inpatient children may present with an episode of nosocomial diarrhea.

In 2018, the WG provided recommendations about the use of probiotics in the prevention of nosocomial diarrhea, based on a systematic review and meta-analysis of 8 RCTs (search date: January 2017) (3). The quality of the included studied varied, but none of the included studies had a low risk of bias. Overall, the administration of probiotics was not associated with a significant reduction in the risk of nosocomial diarrhea of any etiology, nosocomial rotaviral diarrhea, or stool shedding. However, a strain-specific analysis supported the use of selected probiotics for the duration of the hospital stay.

L rhamnosus GG

According to a 2011 meta-analysis, the administration of *L rhamnosus* GG during hospitalization may reduce the risk of nosocomial diarrhea (2 RCTs n = 823, RR 0.4, 95% CI: 0.2–0.6, NNT 12, 95% CI: 8–21) and symptomatic rotavirus gastroenteritis (3 RCTs, n = 1043, RR 0.5, 95% CI: 0.3–0.9) (39). No other RCTs using *L rhamnosus* GG as a single strain were published in recent years.

A 2016 RCT identified in the 2018 systematic review and meta-analysis demonstrated a significant reduction in the incidence of nosocomial diarrhea in children receiving a mixture of *L rhamnosus* GG, vitamin B (B1, B2, B6, B12), vitamin C and zinc compared to placebo (4% vs 24%, respectively, odds ratio OR, 0.14, 95% CI: 0.03–0.69; $P = 0.007$) (40). However, the use of such a mixture does not allow one to estimate the direct effect of *L rhamnosus* GG, so it was excluded from analysis in the 2018 review. A new RCT investigating the efficacy and tolerability of *L rhamnosus* GG for the prevention of nosocomial diarrhea in children was conducted in France between 2019 and 2020, but the results are not yet available (NCT04628819).

- HCPs may recommend *L rhamnosus* GG (at least 10^9 CFU/day) for the duration of the hospital stay for the prevention of nosocomial diarrhea in children.
- Certainty of evidence: Moderate.
- Grade of recommendation: Weak.

L reuteri DSM 17938

No new studies have been published after the publication of the previously identified 2018 meta-analysis that included 2 RCTs (n = 290) with a low risk of bias and demonstrating no effect of *L reuteri* DSM 17938 in the prevention of overall nosocomial diarrhea (RR 1.11, 95% CI: 0.68–1.81) or rotavirus-induced diarrhea infection (RR 1.14, 95% CI: 0.52–2.52).

- HCPs should *not* recommend *L reuteri* DSM 17938 for the prevention of nosocomial diarrhea in children due to the lack of efficacy.
- Certainty of evidence: High.
- Grade of recommendation: Strong.

Prevention of NEC

In 2020, both ESPGHAN (4) and AGA (14) published their recommendations on the use of probiotics for preventing NEC. While both were based on pair-wise systematic reviews and network meta-analyses, their conclusions differed.

The 2020 ESPGHAN recommendations were largely based on the systematic review and strain-specific network meta-analysis by van den Akker et al (41). ESPGHAN formulated conditional recommendations *for L rhamnosus* GG ATCC 53103 (low certainty of evidence) and the combination of *B infantis* BB-02, *B lactis* BB-12, and *Str thermophilus* TH-4 (low certainty of evidence). No recommendation *for* or *against* was formulated with regard to either *L reuteri* DSM 17938 (very low certainty of evidence) or the combination of *B bifidum NCDO 1453* & *L acidophilus NCDO 1748* (very low certainty of evidence). Conditional recommendations were formulated *against B breve* BBG-001 and *S boulardii* CNCM I-745.

The 2020 AGA recommendations (14) were based on the systematic review and network meta-analysis by Morgan et al (42), although the analyses were not strain-specific, but merely species-specific or even grouped by genus only. This approach thus differed considerably from ESPGHAN's previous position paper, which resulted in different recommendations. From evidence grading collected by AGA, the combinations of any *Lactobacillus* spp and any *Bifidobacterium* spp in general seemed most effective and were graded as high certainty of evidence. This was followed by a recommendation on the use of a *B lactis* species with moderate certainty of evidence. Another recommendation with moderate certainty of evidence was for usage of *L reuteri* species (strains DSM 17938 and ATCC 55730 were analyzed together). The positive recommendation by AGA (despite a severe risk of bias) may also be due to their inclusion of 2 very small studies (n < 60), in which a dramatically high baseline incidence of NEC was seen in the placebo groups (25% and 37% in infants weighing on average 1350 g at birth) (43,44). Also with moderate certainty of evidence is AGA's recommendation on any *L rhamnosus* species (ATCC 53103, ATCC A07FA, and LCR 35 strains were analyzed together), whereas ESPGHAN's recommendation was strain specific on the "GG" strain (ATCC 53103) only.

The baseline incidence of NEC differed, sometimes considerably, in various trials. There is no standardized universally accepted mathematical approach to take all these heterogeneities into consideration. In addition, the application of network meta-analysis techniques and inclusion criteria for meta-analyses such as language restrictions may differ. These aspects, together with ESPGHAN's approach of being strictly strain-specific, resulted in discrepancies between the 2020 recommendations of ESPGHAN (4) and AGA (14) on the use of probiotics for preventing NEC with regard to the recommended probiotic strains. Until more evidence is available, HCPs will have to decide which recommendations to follow, based on geographical considerations and evaluation of the available data.

For this document, all published systematic reviews and/or meta-analyses, as well as subsequently published RCTs that studied the use of probiotics in preterm infants, were considered if they were not considered in the 2020 ESPGHAN recommendation (4).

In addition, ClinicalTrials.gov was searched for important ongoing trials.

Whereas recently published systematic reviews (45–48) do not alter the 2020 ESPGHAN recommendations, they are discussed below. A 2020 Cochrane review provided an excellent overview (45). However, the authors did not perform strain-specific analyses (only at the genus level) and did not recommend any specific product. The authors also recognized funnel plot asymmetry suggesting publication bias. Given the low to moderate level of certainty about the effect of probiotics on the risk of NEC, the need for further, large, high-quality trials was regarded as necessary.

A 2021 network meta-analyses by Beghetti et al (46) also did not strictly adhere to a species-specific approach. Overall, *L acidophilus, B lactis* BB-12 or B94, *L reuteri* DSM 17938/ATCC 55730, and multispecies products were found to reduce all stages of NEC. Subgroup analyses focused on feeding type (exclusively human milk vs formula feeding or a mixture) were also performed, based on 13 studied probiotic categories. For *B lactis* Bb-12/B94, there was a relatively large discrepancy in effect size, so that the beneficial effect of these strains on NEC reduction was larger in exclusively human milk fed infants than in those who received preterm formula.

A 2021 network meta-analysis by Chi et al (47) included analyses across different probiotics at the genus level and also synbiotics. Their conclusion was that prebiotics in combination with *Lactobacillus* spp and *Bifidobacterium* spp were most efficacious in reducing NEC incidence, morbidity or mortality. *Lactobacilli* spp plus prebiotics performed the best, although it must be noted however that only 377 infants were randomized in the 2 trials investigating this combination. Regarding probiotic treatment only, the most efficacious treatment regarding NEC was the combination of bifidobacterial spp plus streptococci spp, which are in fact the studies investigating *B infantis* BB-02, *B lactis* BB-12, and *Str thermophilus* TH-4, also recommended in the ESPGHAN position paper.

A 2020 systematic review and meta-analysis by Gao et al (48) focused on *S boulardii* only. Based on the evidence from 10 RCTs (n = 1264), of which 7 were conducted in China, *S boulardii* was recommended for NEC prevention in preterm infants. However, due to the risk of contamination, the European Medicine Agency amended the product information with a contraindication to the use of *S boulardii* in patients (not specifically neonates) who are critically ill, immunocompromised, or in those who have a central venous catheter (49).

Three new RCTs were identified. The first RCT found no effect of *L reuteri* DSM 17938 compared with placebo on NEC stage >2 (7/68 vs 6/66, respectively, $P = 0.74$) (50). The 2 other studies, on new single and multispecies probiotics, were underpowered with regard to NEC and in addition did not find significant effects (51,52).

Overall, the 2020 ESPGHAN recommendations (4) are still valid.

For reducing the risk of NEC in preterm infants, provided all safety issues are met, HCPs may recommend:
- *L rhamnosus* GG ATCC53103 (at a dose ranging from 1×10^9 CFU to 6×10^9 CFU) (certainty of evidence: low; grade of recommendation: weak) or
- Combination of *B infantis* BB-02, *B lactis* BB-12, and *Str thermophilus* TH-4 at 3.0 to 3.5×10^8 CFU (of each strain) (certainty of evidence: low; grade of recommendation: weak).

Due to insufficient evidence, no recommendation can be made *for* or *against*
- *L reuteri* DSM 17938 (certainty of evidence: very low) or
- Combination of *B bifidum* NCDO 1453 *and L acidophilus* NCDO 1748 (certainty of evidence: very low to moderate)

Due to the lack of efficacy, HCPs may *not* recommend:
- *B breve* BBG-001 (certainty of evidence: low to moderate; grade of recommendation: weak)
- *S boulardii* (certainty of evidence: very low to moderate; grade of recommendation: weak).

H pylori Infection

Unsatisfactory *H pylori* eradication rates and therapy-associated side effects remain a problem. Several systematic reviews and network meta-analyses, focusing mainly on adults, have shown that probiotic supplementation improves eradication rates and/or reduces side effects of *H pylori* treatment (53,54). According to the 2017 ESPGHAN/NASPGHAN guidelines on the management of *H pylori* in children and adolescents (55), the routine addition of either single or combination probiotics to eradication therapy to reduce side effects and/or improve eradication rates is currently not recommended. This contrasts with the recommendations in adults (56).

For this document, 4 systematic reviews with meta-analyses, some additionally with network meta-analyses, were identified (30,57–59). However, 1 review focused on Asian children only (58). Except for *S boulardii,* the review included data on strains which were not well identified; thus, only data on *S boulardii* were considered. Two reviews focused on *S boulardii* in adults and children (30,59), thus, only pediatric data were considered. One review focused on *Lactobacillus*-supplemented triple therapy for *H pylori* infection (60). However, none of the probiotics was evaluated in more than 1 trial, thus, none met our inclusion criteria.

Overall, probiotics (as a group) and specific probiotics have been shown to be effective in increasing the *H pylori* eradication rate [however, it was still below the desired level (≥90%) of success] and in reducing gastrointestinal adverse effects associated with *H pylori* infection therapies. Most of the strains (single or in combinations) were studied in single trials only. With few exceptions, no strain specifications were given. Several of the studies were published in local (mainly Chinese) journals and were only identified through one of the meta-analyses performed by the Chinese authors (57). *S boulardii* was the only well-identified probiotic which was included in more than 2 RCTs.

For the complete list of probiotics (in alphabetical order) which were included in the reviews, and for a summary of results of the included systematic reviews, please see Table S2, Supplemental Digital Content, *http://links.lww.com/MPG/C954*. The remainder of this section is dedicated to studies providing information about use of *S boulardii* in patients with *H pylori* infection for eradication and decreasing therapy-related adverse effects.

S boulardii

Two systematic reviews with meta-analyses focused on *S boulardii* for eradication of *H pylori* infection (30,59). The first review (59) identified 11 RCTs (n = 2190), among them 2 RCTs were undertaken exclusively in children (n = 330; age range: 3–18 years) (61,62). The second review (30) identified 18 RCTs (n = 3592), among them 3 RCTs in children, including 1 trial not

included in the earlier review as it was published subsequently (63). In children, compared with placebo or no intervention, *S boulardii* given along with standard triple therapy significantly reduced the risk of overall *H pylori* therapy-related adverse effects and increased eradication rate (3 RCTs, n = 372, RR 1.14, 95% CI: 1.03–1.25) (30). While in both analyses, the addition of probiotics to standard triple therapy significantly increased the eradication rate, it was still below the desired level (≥90%) of success.

In the 2017 meta-analysis, Feng et al (57) found that, compared with placebo or no intervention, *S boulardii* given along with triple therapy significantly reduced the risk of overall *H pylori* therapy-related adverse effects (3 RCTs, n = 366, RR 0.37, 95% CI: 0.24–0.60, I^2 = 0%), particularly of diarrhea (4 RCTs, n = 576, RR 0.50, 95% CI: 0.36–0.68, I^2 = 0, and bloating (2 RCTs, n = 300, RR 0.40, 95% CI: 0.22–0.72, I^2 = 0), but had no effect on abdominal pain (2 RCTs, n = 322, RR 0.62, 95% CI: 0.26–1.46, I^2 = 67%) and nausea and vomiting (3 RCTs, n = 382, RR 0.81, 95% CI: 0.64–1.02, I^2 = 0%) (57).

Similarly, Zhou et al (30) reported that *S boulardii* reduced the incidence of total side effects (RR 0.47, 95% CI: 0.36–0.61; low quality evidence), especially diarrhea (RR 0.33, 95% CI: 0.23–0.47; low quality evidence) and constipation (RR 0.37, 95% CI: 0.23–0.57; moderate quality evidence). Reduced risk of overall *H pylori* therapy-related adverse effects, particularly diarrhea and nausea, were also reported by Szajewska et al (59). However, in both meta-analyses, children and adults were evaluated jointly. Two 2017 network meta-analyses of trials in children concluded that *S boulardii* significantly reduced bloating (*P* score = 0.76) (57,58).

- In children with *H pylori* infection, HCPs may recommend, along with *H pylori* therapy, *S boulardii** for increasing the eradication rates and decreasing therapy-related gastrointestinal adverse effects.
- Certainty of evidence: Very low.
- Grade of recommendation: Weak.

*Note: In many trials, the strain designation of *S boulardii* was not available. However, if available, or assessed retrospectively, the strain most used was the strain recently classified as *S boulardii* CNCM I-745.

Inflammatory Bowel Diseases

For this document, 2 systematic reviews and meta-analyses were included (64,65) which evaluated the combination of probiotics (*L paracasei, L plantarum, L acidophilus, L delbrueckii* subsp. *bulgaricus*, *B longum, B breve, B infantis*, *Streptococcus salivarius* subsp. *thermophilus*) (66) or *L reuteri* ATCC 55730 (67).

Ulcerative Colitis

A 2020 Cochrane review focusing on the effects of probiotics for induction of remission concluded that low-certainty evidence suggests that probiotics may induce clinical remission in patients with active ulcerative colitis when compared to placebo (64). However, specific strain(s) were not identified. Only 2 pediatric RCTs were included. A 2009 trial by Miele et al (66) randomized 29 children with newly diagnosed ulcerative colitis to receive a mixture of 8 strains (n = 14) [4 strains of Lactobacillus (*L paracasei, L plantarum, L acidophilus, L delbrueckii* subsp. *bulgaricus*), 3 strains of Bifidobacterium (*B longum, B breve, and B infantis*), and 1 strain of *Streptococcus salivarius* subsp. *thermophilus*. 900 billion viable lyophilized bacteria; weight-based dose, range: 450–1800 billion bacteria/day] combined with steroids for induction and 5-aminosalicylic acid (5-ASA) for maintenance therapy or placebo (N = 15), with placebo combined with similar medical therapy. In the probiotic group compared with the placebo group, the rate of remission was significantly higher [13 (92.8%) vs 4 (26.7%), respectively, $P < 0.001$], and fewer patients relapsed during 1 year of follow-up [3 (21.4%) vs 11 (73.3%), respectively, $P = 0.014$, RR 0.32, 95% CI: 0.025–0.773; NNT = 2]. At 6 months, 12 months, or at time of relapse, endoscopic and histological scores were significantly lower in the probiotic group than in placebo group ($P < 0.05$). There were no biochemical or clinical adverse events related to the probiotic therapy.

A 2012 trial by Oliva et al (67) randomized 40 children with mild to moderate distal ulcerative colitis to receive an enema containing 10^{10} CFU of *L reuteri* ATCC 55730 or placebo for 8 weeks, in addition to oral mesalazine. Thirty-one patients completed the trial. The Mayo score (including clinical and endoscopic features) decreased significantly in the *L reuteri* group (3.2 ± 1.3 vs 8.6 ± 0.8, $P < 0.01$) compared with the placebo group (7.1 ± 1.1 vs 8.7 ± 0.7, NS). Furthermore, the histological score significantly decreased only in the *L reuteri* group (0.6 ± 0.5 vs 4.5 ± 0.6, $P < 0.01$) (placebo: 2.9 ± 0.8 vs 4.6 ± 0.6, NS). At the post-trial evaluation of cytokine mucosal expression levels, interleukin (IL)-10 was significantly increased ($P < 0.01$), whereas IL-1b, tumor necrosis factor alpha, and IL-8 were significantly decreased ($P < 0.01$) only in the *L reuteri* group.

Another 2020 Cochrane review (65) focused on probiotics for maintenance of remission in ulcerative colitis. This review found no difference between probiotics versus placebo, probiotics versus 5-ASA, and probiotics + 5-ASA versus ASA alone. Data were limited, particularly for pediatric patients. Only 1 trial (68) intended to include children (>13 years); however, the overall mean age was 43.9 ± 14.8 years; thus, it is unclear whether children were recruited.

In addition to the 2 Cochrane reviews, other systematic reviews were identified. One of them focused on the aforementioned mixture of 8 probiotic strains (69); however, it excluded pediatric trials. A 2019 review by Astó et al (70) did not include any new studies compared with the Cochrane review. Other meta-analyses (71,72) only addressed ill-defined Chinese probiotic preparations, precluding them from evaluation in this document.

According to our methodology, at least 2 RCTs are needed to formulate a recommendation. Thus, no recommendation for the use of probiotics in the treatment of children with ulcerative colitis was formulated. This differs from the European Crohn's and Colitis Organization (ECCO) and ESPGHAN guidelines (73,74) according to which the use of the eight strain probiotic combination (*L paracasei* subsp. *paracasei* DSM 24733, *L plantarum* DSM 24730, *L acidophilus* DSM 24735, *L delbrueckii* subsp. *bulgaricus* DSM 24734, *B longum* subsp. *longum* DSM 24736, *B breve* DSM 24732, *B longum* subsp. *infantis* DSM 24737, and *S salivarius* subsp. *thermophilus* DSM 24731) or *Escherichia coli* Nissle 1917 or *L reuteri* ATCC 55730 combined with drug therapy may be considered for induction of remission of ulcerative colitis. However, the ECCO/ESPGHAN guidelines and current document are based on different methodology.

- No recommendation can be made *for* or *against* the use of probiotics studied so far in the management of children with ulcerative colitis due to insufficient evidence.

Crohn Disease

A 2020 Cochrane review concluded that evidence is vague with regard to the efficacy or safety of probiotics, when compared with placebo, for induction of remission in patients with Crohn's disease (75). No new RCTs have since been published. There is no evidence to change earlier recommendations developed by ESPGHAN (alone or in cooperation with ECCO).

- No recommendation can be made *for* or *against* the use of probiotics studied so far in the treatment of children with Crohn disease due to insufficient evidence.

Functional Gastrointestinal Disorders (Disorders of Gut–Brain Interaction)

Infant Colic

For this document, 10 systematic reviews and/or meta-analyses (76–85) focusing on infant colic were identified. For the list of probiotics (in alphabetical order) which were included in the reviews, please see Table S2, Supplemental Digital Content, *http://links.lww.com/MPG/C954*.

Treatment of Infant Colic

L reuteri DSM 17938

L reuteri DSM 17938 is the most studied probiotic for the management of infant colic (86–94). A 2018 individual participant data meta-analysis, which included data from 4 RCTs involving 345 infants with colic, documented that in breastfed infants, the administration of *L reuteri* DSM 17938 at a dose 1×10^8 CFU significantly increased the treatment success (defined as at least 50% reduction in crying time from baseline) at all time points (day 21 adjusted incidence ratio was 1.7, 95% CI: 1.4–2.2) and reduced crying and/or fussing time all time points (day 21 adjusted MD in change from baseline −25.4 minutes, 95% CI: −47.3 to −3.5). The role of *L reuteri* DSM 17938 in formula-fed infants is less clear (76). Other meta-analyses have confirmed these findings (80,82).

- HCPs may recommend *L reuteri* DSM 17938 (10^8 CFU/day for at least 21 days) for the management of infant colic in breastfed infants.
- Certainty of evidence: Moderate.
- Grade of recommendation: Weak.
- No recommendation can be made *for* or *against* the use of *L reuteri* DSM 17938 for the management of infant colic in formula-fed infants due to insufficient evidence.

Bifidobacterium animalis subsp. lactis BB-12

A 2020 RCT performed in Italy (95) in 80 breastfed infants with excessive crying and fussing (possibly related to infant colic according to the Rome III Criteria) found that compared with placebo, the administration of *B lactis* BB-12 (10^9 CFU/day, for 28 days) increased the treatment success rate, defined as a reduction in the daily crying time ≥50% (RR 2.46, 95% CI: 1.5–3.95). For crying time, the mean change from baseline was significantly higher in the probiotic group compared with the placebo group (−130 ± 44 minutes vs −85 ± 51 minutes, MD 45 minutes, 95% CI: −25 to −66).

A 2021 RCT performed in China (96) in 192 full-term infants ≤7 weeks, breastfed, with colic according to the Rome III criteria found that compared with placebo, administration of *B lactis* BB-12 (1×10^9 CFU/day) for 3 weeks significantly increased the treatment success (defined as earlier; RR 2.8, 95% CI: 1.9–4.2). There was also a significant difference between the *B lactis* BB-12 and placebo groups in mean daily crying time at the end of intervention (60.8 ± 23.4 vs 95.8 ± 26.0, MD −35 minutes, 95% CI: −42 to −28).

- HCPs may recommend *B lactis* BB-12 (10^8 CFU/day, for 21–28 days) for the management of infant colic in breastfed infants.
- Certainty of evidence: Moderate.
- Grade of recommendation: Weak.

Other Strains

Data on other probiotics, either positive or negative, are too limited to allow one to draw reliable conclusions (79,95,97,98).

Preventing Infant Colic

A 2019 Cochrane review identified 6 RCTs (involving 1886 infants) which compared probiotics with placebo for preventing infantile colic (78). The pooled results of 3 RCTs in which *L rhamnosus* GG and 2 multi-strain products (one included 4 strains of Lactobacilli, 3 strains of Bifidobacteria & *Str thermophilus* DSM 24731; and another included *L rhamnosus* GG, *L rhamnosus* LC705, *B breve* Bb99, and *Propionibacterium freudenreichii* ssp. *Shermanii*) were assessed found a similar occurrence of new cases of colic in the probiotics and placebo groups. The pooled results of 3 other RCTs found, in the probiotics group compared with the placebo group, reduced duration in crying time at study end (MD −32.6 min/day, 95% CI: −55.6 to −9.5). However, one of the included studies evaluated a prebiotic formula with added probiotic strains, thus, this was a synbiotic intervention. At the strain level, the effect was particularly evident for *L reuteri* DSM 17938 administered at a dose of 1×10^8 CFU to newborns each day for 90 days (1 RCT, n = 589) (99). Other probiotics were also studied; however, evidence is limited (100).

- No recommendation can be made *for* or *against* the use of any of the probiotics studied so far for preventing infant colic due to insufficient evidence.

Functional Abdominal Pain Disorders

Until now, there have been no specific recommendations from ESPGHAN or NASPGHAN on the use probiotics for the management of FAPD. The AGA 2020 guidelines noted with regard to irritable bowel syndrome (IBS) that there are many studies; however, significant heterogeneity in study design, outcomes, and probiotics used resulted in no recommendations for the use of probiotics in symptomatic children and adults with IBS (except in the context of a clinical trial) (14).

For this document, 3 recent systematic reviews and meta-analyses (101–103) were identified. The reviews included studies in children with disorders based on various criteria such as the

Rome II or Rome III criteria or the criteria were not mentioned, hence, thereafter we use only the term FAPD. The following probiotics (in alphabetical order) were evaluated: *Bacillus coagulans* unique IS2 (104); *B infantis* M-63, *B breve* M-16V, and *B longum* BB536 (105); *B lactis* B94 (106); *L reuteri* (strain not specified) (107); *L reuteri* DSM 17938 (6 RCTs) (108–113); *L rhamnosus* GG (5 RCTs) (114–118); *Str thermophilus* BT01, *B breve* BB02, *B longum* BL03, *B infantis* BI04, *L acidophilus* BA05, *L plantarum* BP06, *L paracasei* BP07, *L delbrueckii* subsp. *bulgaricus* BD08 [the strain designation was only given in the review, but not in the original paper (119)]. The only probiotics which were evaluated in more than 2 RCTs were *L reuteri* DSM 17938 (6 RCTs) and *L rhamnosus* GG (5 RCTs).

A 2018 systematic review concluded that there is insufficient evidence for the use of probiotics (as a group) in children with FAPD (101). Only *L rhamnosus* GG (3 RCTs) reduced the frequency and intensity of abdominal pain in children with IBS. Another review (120) also found that the use of *L rhamnosus* GG moderately increased treatment success in children with FAPD, particularly among children with IBS (3 RCTs, n = 167; RR 1.70, 95% CI: 1.27–2.27). The daily dose of *L rhamnosus* GG ranged from 10^9 CFU twice daily to 3×10^9 CFU twice daily. In children with IBS, a multicenter, crossover RCT using a mixture of 8 probiotic strains was found to be safe and more effective than placebo in ameliorating symptoms and improving quality of life; however, there was discordance between the strains listed in the original paper and in the review (119). Evidence on *L reuteri* DSM 17938 (5 RCTs using different methods of pain assessment) for treating FAPD is inconsistent. Compared with placebo, *L reuteri* DSM 17938 improved abdominal pain in 3 RCTs (108,110,121), reduced functional disability but not abdominal pain in 1 RCT (112), and was no better than placebo in 1 trial (109). Mixtures of *B infantis, B breve,* and *B longum* (1 RCT) or *B lactis* (1 RCT) were not effective in children with FAPD (105).

A 2021 systematic review and meta-analysis on the role of probiotics in the treatment of functional abdominal pain (FAP) in children found no firm evidence on the efficacy of probiotics (103). Nine RCTs (total 702 children, 506 with functional abdominal pain; 4–18 years) were identified. *L reuteri* DSM 17938 was administered in 6 RCTs (108–112,122) and *L rhamnosus* GG in 3 RCTs (114–116). Compared with placebo, in children taking *L reuteri* DSM 17938, there was significant reduction in pain intensity (6 RCTs, n = 380, MD −1.24, 95% CI: −2.35 to −0.13) and an increase in number of days without pain (2 RCTs, n = 101, MD 26.42 days, 95% CI: 22.67–30.17). For all other outcomes, there was no difference between the probiotic and placebo groups.

Another 2021 systematic review and meta-analysis evaluated the efficacy of probiotic adjuvant therapy in childhood IBS (102). Nine RCTs were included, involving 651 participants (104–107,114,115,117–119). Of note, 3 of these RCTs included mixed populations, namely subjects with IBS as well as subjects with FAP (107,114,115). There was a wide diversity in the use of the probiotic strains. *L rhamnosus* GG was investigated in 4 trials (105,114,115,118), *L reuteri* in one (107) and *Bacillus coagulans* unique IS2 in one (104). A probiotic mixture was used in 2 trials (118,119). The review concluded that probiotics are effective at treating abdominal pain caused by IBS in children. No significant correlation between abdominal pain and probiotic dose was found. However, the included studies were heterogeneous with regards to the probiotic and the placebo regimens, duration of the intervention, and the evaluation tool used. This heterogeneity makes it difficult to recommend a single probiotic strain, despite some evidence to support its use. Many studies either did not report a sample size calculation or were underpowered. These limitations would necessitate a cautious interpretation of the results.

HCPs may recommend *L reuteri* DSM 17938 (at a dose of 10^8 CFU to 2×10^8 CFU/day) for pain intensity reduction in children with FAPD.

- Certainty of evidence: Moderate.
- Grade of recommendation: Weak.

HCPs may recommend *L rhamnosus GG* (at a dose of 10^9 CFU to 3×10^9 CFU twice daily) for the reduction of pain frequency and intensity in children with IBS.

- Certainty of evidence: Moderate.
- Grade of recommendation: Weak.

Functional Constipation

According to 2014 ESPGHAN/NASPGHAN recommendations, probiotics should not be used in the treatment of functional constipation in children (123). For the current document, 3 systematic reviews were analyzed (101,124,125). For the list of probiotics which were included in the reviews, please see Table S2, Supplemental Digital Content, *http://links.lww.com/MPG/C954*.

The most recent (2022) systematic review and meta-analysis (125), which evaluated 12 studies, including 965 children (126–137), and 2 follow-up studies, including 166 children (138,139), investigated the effect of (or the addition of) probiotics versus placebo or laxative treatment. Studies were heterogeneous with respect to study design, diagnostic criteria for functional constipation, study population, study intervention, duration of treatment and follow-up, and outcome measures. Additionally, an overall high risk of bias was found across most studies. Therefore, the evidence found in this systematic review should be interpreted with caution. The authors concluded that more well-designed high-quality RCTs concerning the use of probiotics for management of children with functional constipation are needed before changes in current guidelines are indicated.

The only probiotics which were evaluated in at least 2 RCTs were *L casei rhamnosus* Lcr35 (2 RCTs) (129,140) and *L reuteri* DSM 17938 (5 RCTs) (127,130,132,133,137).

L casei rhamnosus Lcr35

Pooled results of 2 RCTs showed no significant difference between the *L casei rhamnosus* Lcr35 and placebo groups with respect to treatment success (n = 121, RR 0.27, 95% CI: 0.52–1.06) or defecation frequency per week (n = 108, SMD 0.24, 95% CI: −2.8 to 3.2).

L reuteri DSM 17938

Two RCTs concluded that *L reute*ri DSM 17938 was not successful as an additional treatment on any reported outcomes (132,137). The authors of one trial did not compare outcomes between treatment groups (*L reuteri* DSM 17938 and laxative therapy) (133).

Defecation frequency was higher in the *L reuteri* DSM 17938 group than in the placebo in one trial (130) and similar to that in the control groups in the remaining studies (132,133,137).

The findings of the systematic reviews support current ESPGHAN/NASPGHAN recommendations that probiotics should not be used in the treatment of functional constipation in children (123).

- HCPs may *not* recommend the use of probiotics evaluated so far as a single or adjuvant therapy for treatment of functional constipation in children due to the lack of efficacy.
- Certainty of evidence: Moderate.
- Grade of recommendation: Weak.

Celiac Disease

Recent literature suggests that the intestinal microbiota is altered in patients with celiac disease and may be involved in the pathogenesis as well as in the response to a gluten-free diet (141). Overall, there were no safety concerns in any of the RCTs investigating the effects of probiotics on celiac disease. However, there was no evidence of an effect on clinical outcomes, except for 1 study demonstrating that the administration of *Bifidobacterium longum CECT 7347* in children with newly diagnosed celiac disease may be associated with better short-term height gain (142). One systematic review (143) included 7 studies coming from 6 RCTs (n = 279). Two of the studies included children. The 2 studies were the 2014 Olivares study cited above (142) and another study that did not include a clinical outcome, but rather showed a significant reduction in TNF-α blood levels with administration of B *breve* (144). While in adults there was evidence for improved gastrointestinal symptoms with probiotic treatment, such findings were not reported in children.

- No recommendation can be made *for* or *against* the use of probiotics in children with celiac disease due to insufficient evidence.

Small Intestinal Bacterial Overgrowth

SIBO is a heterogenous and poorly understood entity characterized by non-specific gastrointestinal symptoms, such as abdominal distention and pain, diarrhea, flatulence, and vomiting, and sometimes by non-gastrointestinal symptoms, such as metabolic acidosis and neurological symptoms. These variable clinical features are related to the excessive growth of microorganisms within the small intestine, usually observed in children with altered gastrointestinal motility and anatomy (short bowel syndrome or previous surgery), those receiving acid-suppressive therapies, or after a recent episode of intestinal infections (post-infectious diarrhea). In those patients, probiotics are sometimes used in clinical practice, however, no RCTs are currently available to support their prescription. Only 1 RCT (145) tested the efficacy of a probiotic mixture of *L rhamnosus* R0011 (1.9×10^9 CFU) and *L acidophilus* R0052 (0.1×10^9 CFU) in preventing SIBO in a small population of children receiving proton pump inhibitors for 1 month. No difference in the incidence of SIBO, diagnosed with positive breath tests, was observed between children receiving probiotics (n = 36) and those receiving placebo (n = 34) (33% vs 26.5%; $P = 0.13$).

- No recommendation *for* or *against* the use of probiotics in the treatment or prevention of SIBO due to insufficient evidence.

Pancreatitis

In adults, a multispecies probiotic preparation increased mortality from mesenteric ischemia in patients with severe acute pancreatitis (146). No RCTs on the use of probiotics for pancreatitis in children were identified.

- As no RCT on the use of probiotics for pancreatitis in children was identified, no recommendation can be made *for* or *against* the use of probiotics for the management of pancreatitis.

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