

Use of Probiotics for Management of Acute Gastroenteritis: A Position Paper by the ESPGHAN Working Group for Probiotics and Prebiotics

*Hania Szajewska, †Alfredo Guarino, ‡Iva Hojsak, §Flavia Indrio, ‡Sanja Kolacek,
 ||Raanan Shamir, ¶Yvan Vandenas, and #Zvi Weizman,
 on Behalf of the ESPGHAN Working Group for Probiotics and Prebiotics

ABSTRACT

The use of probiotics has been suggested in the treatment of acute gastroenteritis (AGE) in addition to early rehydration and avoidance of dietary restrictions. This document provides recommendations for the use of probiotics for the treatment of AGE in previously healthy infants and children based on a systematic review of previously completed systematic reviews and of randomized controlled trials (RCTs) published subsequently to these reviews. The recommendations were formulated only if at least 2 RCTs that used a given probiotic (with strain specification) were available.

Received January 14, 2014; accepted January 21, 2014.

From the *Medical University of Warsaw, Department of Paediatrics, Warsaw, Poland, the †Department of Translational Medicine, Section of Pediatrics, University of Naples Federico II, Naples, Italy, the ‡Department of Paediatrics, Children's Hospital Zagreb, University of Zagreb School of Medicine, Zagreb, Croatia, the §Department of Pediatrics, University Hospital Policlinico, University of Bari, Italy, the ||Institute of Gastroenterology, Nutrition and Liver Diseases, Schneider Children's Medical Center of Israel, Sackler Faculty of Medicine, Tel-Aviv University, Israel, the ¶Department of Pediatrics, UZ Brussel, Vrije Universiteit Brussel, Brussels, Belgium, and the #Pediatric Gastroenterology and Nutrition Unit, Soroka Medical Center, Ben-Gurion University, Beer-Sheva, Israel.

Address correspondence and reprint requests to Hania Szajewska, MD, Department of Paediatrics, Medical University of Warsaw, 01-184 Warsaw, Dzialdowska 1, Poland (e-mail: hania@ipgate.pl).

H.S. has participated as a clinical investigator, and/or advisory board member, and/or consultant, and/or speaker for Arla, Biogaia, Biocodex, Danone, Dicoform, HiPP, Nestlé, Nestlé Nutrition Institute, Nutricia, Mead Johnson, Merck, and Sequoia. A.G. has participated in basic research supported by Biocodex and Dicoform and in clinical trials and/or advisory boards and/or conference grant by Nutricia, Humana, Malesci, and Mead Johnson. I.H. has participated as a clinical investigator for Biogaia and Chr Hansen. F.I. has participated as a clinical investigator and/or consultant and/or speaker for Arla Food, Biogaia, Noos, Nestlé, and Nestlé Nutrition Institute. S.K. has participated as a clinical investigator, and/or speaker for Abbott, Arla, Biogaia, Chr Hansen, Danone, Dukat, Nestlé, Nutricia, and Merck-Sharpe-Dohme. R.S. has participated as a clinical investigator, and/or advisory board member, and/or consultant, and/or speaker for Abbott, Danone Institute International, Danone, Enzymotec, Nestlé, Nestlé Nutrition Institute, and Nutricia. Y.V. is a consultant for Biocodex and United Pharmaceuticals. Z.W. has participated as a clinical investigator, and/or consultant and/or speaker for BioCodex, BioGaia, HiPP, Materna, Mead Johnson, Nestlé, Nutricia, and Sensus.

Copyright © 2014 by European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

DOI: 10.1097/MPG.0000000000000320

The GRADE system developed by the Grading of Recommendations, Assessment, Development, and Evaluations Working Group, was used to grade the strength of evidence and grades of recommendations used in these guidelines. It offers 4 categories of the quality of the evidence (high, moderate, low, and very low) and 2 categories of the strength of recommendation (strong or weak). The use of the following probiotics (in alphabetical order) may be considered in the management of children with AGE in addition to rehydration therapy: *Lactobacillus rhamnosus* GG (low quality of evidence, strong recommendation) and *Saccharomyces boulardii* (low quality of evidence, strong recommendation). Less compelling evidence is available for *Lactobacillus reuteri* DSM 17938 (very low quality of evidence, weak recommendation) and heat-inactivated *Lactobacillus acidophilus* LB (very low quality of evidence, weak recommendation). The latter, although traditionally discussed with other probiotics, does not fit with the definition of probiotics. Other strains or combinations of strains have been tested, but evidence of their efficacy is weak or preliminary.

Key Words: diarrhea, guideline, infants, microbiota, probiotics, RCT, systematic review

(JPGN 2014;58: 531–539)

INTRODUCTION

Acute gastroenteritis (AGE) has been defined by the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) as a decrease in the consistency of stools (loose or liquid) and/or an increase in the frequency of evacuations (typically ≥ 3 in 24 hours), with or without fever or vomiting (1a). Diarrhea typically lasts < 7 days and not longer than 14 days. In Europe, it is estimated that the incidence of AGE ranges from 0.5 to 1.9 episodes per child per year in children up to 3 years of age (1a). Rehydration is the key treatment and should be applied as soon as possible. Regular feeding should not be interrupted and should be carried on immediately after initial rehydration. Drugs are generally not necessary, although some have an impact on the duration and symptoms of AGE. Apart from drugs, certain probiotics, usually defined as “live microorganisms which when administered in adequate amounts confer a health benefit on the host” (1), may reduce the duration and intensity of symptoms. These guidelines developed by the ESPGHAN Working Group (WG) on Probiotics and Prebiotics provide recommendations for the use of probiotics for the treatment of AGE in previously healthy infants and children. Children with at-risk conditions, such as chronic

disorders or immunodeficiency, are not covered. This document supplements the update of the guidelines on the management of AGE in Europe to be published elsewhere (1a).

METHODS FOR GUIDELINES DEVELOPMENT

This document provides a systematic review of previously completed systematic reviews and of randomized controlled trials (RCTs) published subsequently to these reviews. For systematic reviews and meta-analyses, we preferentially report the findings of the most recent and methodologically unbiased one. If an individual trial was reported in a systematic review or meta-analysis, we refrained from reporting the same trial twice. Three systematic reviews, published elsewhere (2–4), were performed specifically by the members of the WG to assist the development of these guidelines. To appraise the evidence for subsequently published RCTs not included in the systematic review(s), the Cochrane Collaboration's tool for assessing risk of bias was used, which includes the following criteria: adequacy of sequence generation, allocation concealment, and blinding of participants, personnel, and outcome assessors; incomplete outcome data are addressed (5).

The focus was on 6 taxonomic groups (*Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Streptococcus*, *Enterococcus*, and/or *Bacillus*). Because hundreds of different probiotics (single or combinations) are available, some of them only locally, the decision on the inclusion of a specific probiotic was based on whether it is commonly used in European countries, and thus, of interest to the users of this document. For the same reason, *Lactobacillus acidophilus* LB, a heat-killed microorganism, was included, even though it does not fit with the widely used definition of probiotics. While working on this document, the WG found that the same brand may have a different composition in different locations. Considering the above, the WG made the decision to deal with strain(s) only rather than brands or commercial names. Moreover, the WG is aware that taxonomically equivalent probiotic microorganisms may be supplied by different manufacturers. At least 1 study indicated that the manufacturing process may influence properties of probiotic bacteria. In that study, it was demonstrated that the differences in the *in vitro* properties of *Lactobacillus rhamnosus* GG (LGG) isolates, in particular pathogen exclusion by inhibition and competition, depended on the product source (matrix) as well as the production processes and conditions (6); however, at present, whether or not these manufacturing differences translate into differences *in vivo*, as well as clinical outcomes, remain unclear. Consequently, the taxonomically equivalent probiotics are presented jointly, regardless of the manufacturer. Finally, depending on the country, the same probiotic microorganism(s) may be available as food supplements, available as registered pharmaceutical products, and/or incorporated into foods (7). In general, the microbiological quality and labeling of products sold for medicinal purposes tend to be of higher quality than those for probiotics used in dairy foods or available as probiotic supplements (8–12). In this document, the effectiveness of probiotics was analyzed regardless of the registration status. Health care professionals and consumers should, however, be aware of possible variations.

The primary outcome measures were stool output and duration of diarrhea (time until permanent cessation); however, other outcomes typically considered when evaluating interventions for treating AGE (13), such as admission to the hospital, duration of hospital stay, weight gain after rehydration, and episodes of vomiting, were also taken into account. The WG abstained from evaluating the safety of probiotics, as this issue was recently

thoroughly reviewed by the US Agency for Healthcare Research and Quality (for review, see reference (14)).

For reporting the effect, if feasible, for dichotomous outcomes, the results for individual studies and pooled statistics are reported as the risk ratio (RR) between the experimental and control groups with 95% confidence intervals (95% CI); for the continuous outcomes, the results are reported as the mean difference (MD) with 95% CI. In other circumstances, we report the findings as reported by the authors of the included studies.

When synthesizing the evidence, each section presents a summary of the evidence followed by the key recommendations. The GRADE system, developed by the Grading of Recommendations, Assessment, Development, and Evaluations Working Group (15), was used to grade the strength of evidence and grades of recommendations used in these guidelines. In brief, the GRADE system offers 4 categories of the quality of the evidence (high, moderate, low, and very low) and 2 categories of the strength of recommendation (strong or weak). With regard to the quality of evidence, the content of these guidelines was restricted to evidence from RCTs or systematic reviews of RCTs. Thus, at the start, the quality of evidence was high. It was, however, “downgraded” if there were any of the following problems: methodological limitations, important inconsistencies among studies, uncertainty with regard to the directness of the evidence (ie, the generalizability of the findings to the population of interest), sparse or imprecise data, or a high probability of reporting bias. The quality of evidence was “upgraded” if there was a large effect size (eg, relative risk <0.5 or >2). The strength of a recommendation was graded as “strong” when the evidence showed that the benefit of the intervention clearly outweighs the undesirable effects. The strength of a recommendation was graded as “weak” when the tradeoffs were less certain (either because of the low quality of evidence or because the evidence suggested that desirable and undesirable effects are closely balanced). The highest grade of recommendation does not always correspond to the highest evidence level. Recommendations were formulated and graded, and a consensus was reached. Any disagreement was resolved by discussion until a consensus was reached.

The WG adopted the position of the US Food and Drug Administration Guidance for Industry (16) that at least 2 adequate and well-controlled studies, each convincing on its own, are needed to establish the effectiveness of an intervention. Consequently, the recommendations were formulated only if at least 2 RCTs that used a given probiotic were available. If there was only 1 RCT, regardless of whether or not it showed a benefit, no recommendation was formulated. Moreover, if the strain specification was not given and/or the probiotic product was not otherwise identifiable, no recommendation was made.

It is known that various probiotic strains differ in their effects; thus, pooling data on different probiotics has been repeatedly questioned (17,18). This concern is fully supported by the WG; however, for the sake of completeness, we report the pooled data (meta-analysis) of all probiotic trials to estimate the extent to which the use of a variety of probiotics strains, as a group, influences AGE. No recommendation on the use of probiotics in general was, however, made. Instead, preference was given to reporting evidence and recommendations related to a specific probiotic strain or their combinations separately (17).

Having considered all of the above, the probiotics discussed in this document fit into 1 of the following categories (Table 1):

1. Probiotics with a positive recommendation
2. Probiotics with a negative recommendation
3. Probiotics with insufficient evidence to make a recommendation

TABLE 1. Probiotics for treating acute gastroenteritis

| Probiotics with a positive recommendation | QoE | Recommendation | Dose |
|---|----------------|----------------|--|
| <i>Lactobacillus</i> GG | Low | Strong | $\geq 10^{10}$ CFU/day (typically 5–7 days) |
| <i>Saccharomyces boulardii</i> | Low | Strong | 250–750 mg/day (typically 5–7 days) |
| <i>L reuteri</i> DSM 17938 | Very low | Weak | 10^8 to 4×10^8 (typically 5–7 days) |
| <i>L acidophilus</i> LB (heat-inactivated) | Very low | Weak | Min 5 doses of 10^{10} CFU >48 h; max 9 doses of 10^{10} CFU for 4.5 days |
| Probiotics with a negative recommendation | QoE | Recommendation | Reason |
| <i>Enterococcus faecium</i> (SF68 strain) | Low | Strong | Safety issues (a possible recipient of the vancomycin-resistant genes) |
| Probiotics with insufficient evidence to make a recommendation | QoE | | |
| Lack of data | | | |
| <i>Bifidobacterium lactis</i> Bb12 | Not applicable | | |
| Methodological issues | | | |
| <i>Escherichia coli</i> Nissle 1917 | Very low | | |
| No strain specification | | | |
| <i>L acidophilus</i> | Very low | | |
| <i>L acidophilus</i> and <i>B bifidum</i> | Very low | | |
| <i>L acidophilus</i> and <i>B infantis</i> | Very low | | |
| Only 1 RCT available | | | |
| <i>Bacillus clausii</i> (strains O/C84, N/R84, T84, SIN84) | Very low | | |
| <i>B lactis</i> Bb12 and <i>S thermophilus</i> TH4 | Very low | | |
| <i>L acidophilus rhamnosus</i> 573L/1, 573L/2, 573L/3 | Moderate | | |
| <i>L helveticus</i> R0052 and <i>L rhamnosus</i> R0011 | Very low | | |
| <i>L paracasei</i> strain ST11 | Moderate | | |
| <i>L delbrueckii</i> var <i>bulgaricus</i> , <i>L acidophilus</i> , <i>S thermophilus</i> , <i>B bifidum</i> (strains LMG-P17550, LMG-P 17549, LMG-P 17503, and LMG-P 17500) | Very low | | |
| Only 1 RCT available, no strain identification | | | |
| <i>Bacillus mesentericus</i> and <i>Clostridium butyricum</i> and <i>E faecalis</i> | Very low | | |
| <i>L acidophilus</i> , <i>L paracasei</i> , <i>L bulgaricus</i> , <i>L plantarum</i> , <i>B breve</i> , <i>B infantis</i> , <i>B longum</i> , <i>S thermophilus</i> | Very low | | |
| <i>L acidophilus</i> and <i>L rhamnosus</i> and <i>B longum</i> and <i>S boulardii</i> | Moderate | | |

CRF = colony-forming units; RCT = randomized controlled trial; QoE = quality of evidence.

A draft of the guidelines was sent to the WG members for review and further comments. All critical feedback was discussed during the meeting held in Rome (September 2013), and changes were incorporated as necessary. The conclusions of this document may require revision in the future as new information becomes available. It is the intention of the WG to revise the recommendations not later than in 5 years and produce an updated document.

PROBIOTICS OVERALL

A number of meta-analyses have evaluated the effects of probiotics for the treatment of AGE. One of the most recent is an update to a published Cochrane review (search date: July 2010) (19). This review collected data from 63 RCTs ($n = 8014$) that evaluated the efficacy of probiotics for the treatment of acute infectious diarrhea in subjects of all ages. Probiotics, as a group, reduced the duration of diarrhea by approximately 1 day (35 RCTs, $n = 4555$, MD -25 hours, 95% CI 16–34) and the risk of diarrhea lasting ≥ 4 days (29 RCTs, $n = 2853$, RR 0.41, 95% CI 0.32–0.53). The majority of the trials (56 RCTs) were carried out in

infants and young children. Forty-six RCTs tested a single probiotic, and 17 RCTs tested a combination of 2 to 8 probiotics. The 3 most commonly studied probiotics were *Lactobacillus* GG (13 RCTs), *Saccharomyces boulardii* (10 RCTs), and *Enterococcus* lactic acid bacteria SF68 (5 RCTs). The remaining probiotics, or their combinations, were evaluated in 3 or fewer studies.

Overall, the quality of evidence was low. The methodological limitations include unclear randomization, no or unclear allocation concealment, no or unclear blinding, and no intention-to-treat (ITT) analysis in many of the included RCTs. There were no placebo groups in some trials. Included trials used different definitions of diarrhea and reported outcomes, namely the duration of diarrhea. Moreover, significant heterogeneity between trials for both primary and secondary outcomes was detected.

Probiotics With Positive Recommendations

LGG

The Cochrane review (search date: July 2010) found that use of LGG reduced the duration of diarrhea (11 RCTs, $n = 2072$,

MD -27 hours, 95% CI -41 to -13), mean stool frequency on day 2 (6 RCTs, n = 1335, MD -0.8, 95% CI -1.3 to -0.2), and the risk of diarrhea lasting ≥ 4 days (4 RCTs, n = 572, RR 0.6, 95% CI 0.4-0.9) (19).

A more recent systematic review (search date: May 2013) focused on studies on the use of LGG to treat AGE in children (2). Fifteen RCTs involving 2963 children were identified. Compared with controls, LGG had no effect on the total stool volume (2 RCTs, n = 303, MD 8.97 mL/g, 95% CI -86.26 to 104.2). Combined data from 11 RCTs (n = 2444), however, showed that LGG significantly reduced the duration of diarrhea compared with placebo or no treatment (MD -1.05 days, 95% CI -1.7 to -0.4). LGG was more effective when used at a daily dose of $\geq 10^{10}$ colony-forming units (CFU) (8 RCTs, n = 1488, MD -1.1 days, 95% CI -1.9 to -0.3) than when used at a daily dose of $< 10^{10}$ CFU (3 RCTs, n = 956, MD -0.9 day, 95% CI -2.5 to 0.7). LGG was effective in children treated in Europe (5 RCTs, n = 744, MD -1.3 days, 95% CI -2.0 to -0.5); in the non-European setting, the difference between the LGG group and the control group was of a borderline statistical significance (6 RCTs, n = 1700, MD -0.9, 95% CI -1.8 to 0.08). It was concluded that LGG reduces the duration of diarrhea. A subset of patients who are more likely to benefit includes subjects treated with a high daily dose of LGG ($\geq 10^{10}$ CFU/day) who are both inpatients and outpatients from geographic Europe.

The quality of evidence was downgraded for the methodological limitations of many of the included trials. The major limitations were unclear randomization, no or unclear allocation concealment, and no or unclear blinding. Moreover, there were no placebo groups in some trials. Included trials used different definitions of diarrhea and reported outcomes, namely the duration of diarrhea. Consistency points were deducted for significant heterogeneity between trials for both primary and secondary outcomes.

Recommendation. The use of *Lactobacillus* GG may be considered in the management of children with AGE as an adjunct to rehydration therapy.

QUALITY OF EVIDENCE: Low

RECOMMENDATION: Strong recommendation

S. boulardii

One meta-analysis (search date: August 2009) of 9 RCTs (n = 1117) concluded that in otherwise healthy infants and children, the use of *S. boulardii* reduces the duration of diarrhea by approximately 1 day (20). The Cochrane review (search date: July 2010) documented that the use of *S. boulardii* reduced the risk of diarrhea lasting ≥ 4 days (6 RCTs, n = 606, RR 0.37, 95% CI 0.2-0.65, NNT 3, 95% CI 2-3) (19). Finally, the authors of the most recent review (search date: October 2011) included 13 RCTs carried out in Europe (mainly in Turkey, 1 study in Italy) and in some non-European countries (Argentina, Bolivia, Cuba, India, Mexico, Myanmar, and Pakistan). The daily dose of *S. boulardii* varied between 250 and 750 mg. None of the studies evaluated the effect of *S. boulardii* on stool volume. Compared with the placebo or no intervention groups, the use of *S. boulardii* significantly reduced both the duration of diarrhea (11 RCTs, n = 1306, MD -0.99 days, 95% CI -1.4 to -0.6) and the risk of diarrhea on day 3 (9 RCTs, n = 1128, RR 0.52, 95% CI 0.4-0.65). For both outcomes, significant heterogeneity was observed ($I^2 = 83\%$ and 63%, respectively). In hospitalized children, the use of *S. boulardii*

reduced the duration of hospitalization (n = 449, MD -0.8 days, 95% CI -1.1 to -0.5) (21).

The quality of evidence was downgraded for the methodological limitations, such as unclear randomization, unclear or no allocation concealment, lack of blinding, and no ITT analysis in many RCTs. There were no placebo groups in some trials. Included trials used different definitions of diarrhea and reported outcomes, namely the duration of diarrhea. Consistency points were deducted for significant heterogeneity between trials.

Recommendation. The use of *S. boulardii* may be considered in the management of children with AGE as an adjunct to rehydration therapy.

QUALITY OF EVIDENCE: Low

RECOMMENDATION: Strong recommendation

Lactobacillus reuteri Strain DSM 17938 (and the Original Strain ATCC 55730)

It was documented in the past that *L. reuteri* ATCC 55730 had a moderate clinical effect in treating AGE in children (22). Because *L. reuteri* ATCC 55730 strain was found to carry transferable resistance traits for tetracycline and lincomycin, it was replaced by a new strain, *L. reuteri* DSM 17938, with no unwanted plasmid-borne resistances (23). Bioequivalence of *L. reuteri* ATCC 55730 and *L. reuteri* DSM 17938 has been evaluated in vitro studies. Similarities with regard to the chromosomal genes, colony and cell morphology, fermentation pattern, mucin binding, and reuterin production were shown (22). Another study documented similarities in the characteristics of temporary colonization (24). Overall, these studies suggested bioequivalence of the 2 strains.

A recent systematic review (search date: August 2013) (4), developed specifically for these guidelines, evaluated data on the effectiveness of *L. reuteri* DSM 17938 (presently commercially available) and the original strain, *L. reuteri* ATCC 55730, in the treatment of AGE in children. Two RCTs (n = 196) that evaluated *L. reuteri* DSM 17938 (25,26) and 3 RCTs (n = 156) (27-29) that evaluated *L. reuteri* ATCC 55730, which involved hospitalized children ages 3 to 60 months, met the inclusion criteria. None of the studies evaluated the effect of any of *L. reuteri* on stool volume. Compared with placebo or no treatment, DSM 17938 significantly reduced the duration of diarrhea (MD -32 hours, 95% CI -41 to -24) and increased the chance of cure on day 3 (RR 3.5, 95% CI 1.2-10.8, random effects model). Similar results were obtained with the original strain, *L. reuteri* ATCC 55730. In summary, this systematic review and meta-analysis of RCTs shows that *L. reuteri* DSM 17938, similar to its original strain *L. reuteri* ATCC 55730, may have a role in the management of children with AGE. The findings apply to hospitalized children. Data from outpatients and country-specific cost-effectiveness analyses are needed.

The quality of evidence was downgraded for the methodological limitations of the included trials (unclear or inadequate allocation concealment, no blinding in 1 trial, no or unclear ITT analysis) and for sparse data. Furthermore, bioequivalence remains questionable.

Recommendation. The use of *L. reuteri* DSM 17938 may be considered in the management of children with AGE as an adjunct to rehydration therapy.

QUALITY OF EVIDENCE: Very low

RECOMMENDATION: Weak recommendation

Heat-Killed *L acidophilus* LB

The efficacy of a heat-killed *L acidophilus* strain LB was evaluated in 1 systematic review (search date: August 2013) developed specifically for these guidelines (3). Four RCTs involving 305 children ages 1 to 48 months, treated as inpatients or outpatients, were identified. The daily intake of *L acidophilus* LB ranged from a total of 5 doses of 10^{10} CFU >48 hours to 8 doses of 10^{10} CFU >3 days to 9 doses of 10^{10} CFU for a maximum of 4.5 days. One study was performed in Europe (France), and the remaining studies were performed outside Europe (Ecuador, Peru, and Thailand). None of the studies evaluated the effect of *L acidophilus* LB on stool volume. The pooled results from 3 RCTs (n = 224), all carried out in hospitalized children, showed that *L acidophilus* LB significantly reduced the duration of diarrhea compared with placebo (MD -21.6 hours, 95% CI -26.5 to -16.6, random effects model). One study carried out in outpatients showed no effect of *L acidophilus* LB on the duration of diarrhea. The chance of cure on day 3 was similar in both groups (2 RCTs, n = 144, RR 1.03, 95% CI 0.88–1.2); however, use of *L acidophilus* LB increased the chance of cure on day 4 (2 RCTs, n = 153, RR 1.44, 95% CI 1.20–1.73). The authors concluded that there is limited evidence to recommend LB for treating diarrhea in children.

The quality of evidence was downgraded for the methodological limitations of the trials (unclear or inadequate allocation concealment), for uncertainty with regard to the directness of the evidence, and for sparse data.

Recommendation. The use of heat-inactivated *L acidophilus* LB may be considered in the management of children with AGE as an adjunct to rehydration therapy.
 QUALITY OF EVIDENCE: Very low
 RECOMMENDATION: Weak recommendation

Note: Health care professionals should be aware that *L acidophilus* LB, being a heat-killed microorganism, although traditionally discussed with other probiotics, does not fit with the definition of probiotics.

Probiotics With a Negative Recommendation

Enterococcus faecium (SF68 Strain)

A number of RCTs have evaluated the effect of *E faecium* SF68 (30–36). The subgroup analysis performed within a Cochrane review (search date: July 2010) found that *Enterococcus* LAB SF68 reduced the risk of diarrhea lasting ≥ 4 days (4 RCTs, n = 333, RR 0.21, 95% CI 0.08–0.52) (19); however, in vitro studies have documented that the *E faecium* SF68 strain is a possible recipient of the vancomycin-resistance genes (37). Considering that the risk for in vivo conjugation cannot be ruled out, the WG agreed that probiotics with safety issues should not be used in children.

The quality of evidence was downgraded for the methodological limitations of the included trials (unclear or inadequate allocation concealment, no blinding in some trials, and no or unclear ITT analysis).

Recommendation. *E faecium* SF68 should not be considered in the management of children with AGE because of safety issues. (Negative recommendation originates from in vitro data.)
 QUALITY OF EVIDENCE: Low
 RECOMMENDATION: Strong recommendation

Probiotics With Insufficient Evidence to Make a Recommendation

Lack of Data

Bifidobacterium lactis Bb12

No RCT evaluated the effect of exclusively administered *B lactis* Bb12.

Methodological Issues

Escherichia coli Nissle 1917

Two RCTs involving use of *E coli* Nissle 1917 were identified. In the first multicenter (Russia, Ukraine) trial, the efficacy and safety of *E coli* Nissle 1917 were evaluated in 113 children aged 2 to 47 months with acute diarrhea lasting <3 days, with no/mild dehydration, who were treated as outpatients. The use of *E coli* Nissle 1917 reduced the duration of diarrhea compared with placebo by 2.3 days (median 2.5 vs 4.8 days, respectively; $P < 0.05$). There was a higher responder rate within 10 days (defined as a reduction in stool frequency to ≤ 3 watery or loose stools in 24 hours for at least 2 days) in the *E coli* Nissle 1917 group than in the placebo group (52/55 vs 39/58, respectively; RR 1.4, 95% CI 1.16–1.7) (38). The findings were promising; however, there were some methodological limitations to the study, including unclear allocation concealment, unclear ITT analysis, and unclear sample size calculations. Moreover, in the results, there were a number of discrepancies in what is reported in the text and in the figures. Overall, these limitations call for caution when interpreting the findings.

The second RCT was also a multicenter study (Russia, Ukraine). The study involved 151 children ages 1 to 47 months with acute diarrhea, which persisted for >4 consecutive days but <14 days, and moderate dehydration. The use of *E coli* Nissle 1917 reduced the duration of diarrhea compared with placebo by 3.3 days (median: 2.4 vs 5.7 days, respectively; $P < 0.05$); there was a similar response rate on day 7 (59/75 vs 45/76, respectively), but the response rate was higher in the *E coli* Nissle 1917 group than in the placebo group on day 14 (70/75 vs 50/76, respectively; $P < 0.05$) and on day 21 (74/75 vs 54/76, respectively; $P < 0.05$) (39). Some issues that were not adequately addressed in the article raised concern. For example, 14.5% of the children in the placebo group were still dehydrated moderately on day 21, and there was a very low (71%) response rate in the placebo group.

Taken collectively, the findings may not be reliable; hence, a lack of recommendation. *E coli* Nissle 1917 may or may not reduce the severity and the duration of AGE. The WG assessed the quality of evidence as very low. The quality of evidence was downgraded for the methodological limitations described above.

QUALITY OF EVIDENCE: Very low

No Strain Specification

L acidophilus

One RCT conducted in 98 Indian children ages 6 months to 12 years found no significant difference in the duration of diarrhea between the group treated with heat-killed *L acidophilus* (strain not specified) and the placebo group (2.26 ± 0.06 vs 2.32 ± 0.06 hours, respectively; MD 0.04 days, 95% CI 0.03–0.05). There were also no significant differences between groups in any of the secondary outcomes (oral rehydration solution [ORS] consumed, frequency of stools, time for rehydration, hospital stay, weight gain, and need for intravenous [IV] rehydration) (40).

One RCT conducted in 80 Iranian children found no significant difference between the group treated with an *L acidophilus* (strain not specified) supplement at a dose of 10×10^9 CFU (strain not specified, unclear if live or killed, $n = 40$) and the placebo group in mean stool frequency on day 2 (4.0 ± 3.2 vs 4.0 ± 3.6 , respectively; MD 0.0, 95% CI -1.49 to 1.49) and on day 3 (1.4 ± 2.6 vs 2.3 ± 2.6 , respectively; MD -0.90 , 95% CI -2.04 to 0.24). In the experimental group compared with the placebo group, there was a significantly reduced duration of hospital stay (3.4 ± 0.9 vs 3.9 ± 1.2 days, respectively; MD -0.6 , 95% CI -1.04 to -0.16). The authors reported a significantly shorter duration of diarrhea in the *L acidophilus* group ($P = 0.037$), but no data were presented (41).

The WG assessed the quality of evidence as very low. It was downgraded for the methodological limitations of the trials (unclear allocation concealment and unclear blinding in one trial). Additionally, it was downgraded for sparse data and uncertainty with regard to the directness of the evidence (both studies were carried out outside of Europe). Although 2 RCTs were available, the strain was not specified; hence, a lack of recommendation.

QUALITY OF EVIDENCE: Very low

L acidophilus and *B bifidum*

The efficacy of *L acidophilus* and *B bifidum* was evaluated in 2 RCTs. The first study was carried out in 62 inpatients ages 6 to 36 months with acute nonbloody, nonbacterial diarrhea of <2 days duration. Compared with the placebo group, the administration of *L acidophilus* and *B bifidum* (strain specification not given), at a dose of 3×10^9 CFU of each organism for 5 days, reduced the duration of diarrhea (mean \pm standard error, 4.5 ± 0.8 vs 3.4 ± 0.8 days, respectively; $P = 0.027$), defecation frequency ($P = 0.042$), and duration of hospital stay (2.7 ± 0.6 vs 2.1 ± 0.7 days, respectively; $P = 0.033$) (42).

The second double-blind RCT conducted in 67 Thai children ages 2 months to 7 years with acute diarrhea found that compared with placebo, administration of *L acidophilus* and *B bifidum* (no strain specification) stored either at 4°C or at room temperature shortened the duration of diarrhea (median [interquartile range, IQR] 51.5 (43) vs 28 (30) vs 26.5 (38), respectively; $P < 0.01$) and reduced the number of stools ($P < 0.01$). The secondary outcomes, in particular the total volume of fluid therapy and duration of hospitalization, were not significantly different between the groups. The originality of this study was that equal efficacy was shown for the probiotic independent of storage temperature (4°C vs room temperature). Unfortunately, no analysis of viable strains was performed (43).

The quality of evidence was downgraded for the methodological limitations of the trials (unclear sequence generation, unclear allocation concealment, no ITT analysis), for uncertainty with regard to the directness of the evidence, and for sparse data. Although 2 RCTs were available, the strain was not specified, hence, a lack of recommendation.

QUALITY OF EVIDENCE: Very low

L acidophilus and *B infantis*

Two open RCTs were identified. In the first study, carried out in Taiwan, the efficacy of lyophilized *L acidophilus* and *B infantis* (no strain specifications were given) at a dose of 3×10^9 CFU of each organism for 4 days was evaluated in 100 children ages 6 to

60 months hospitalized because of AGE. Compared with the nontreated control group, in the probiotic group there was a significant reduction in the duration of diarrhea (86.4 ± 19.2 vs 74.4 ± 16.8 hours, respectively; MD -12 hours, 95% CI -19 to -5) and in the frequency of diarrhea on the first and second days of hospitalization ($P < 0.01$) (44).

The second trial was carried out in Thailand in 71 children ages 1 to 24 months with acute watery diarrhea. Compared with the no additional treatment group, the administration of the live *L acidophilus* and *B infantis* (no strain specifications were provided, 6×10^9 CFU/day for 2 days) significantly reduced the duration of diarrhea (69.6 ± 41 vs 38.4 ± 17 hours, respectively; MD -31.2 hours, 95% CI -46 to -17); however, it had no effect on the stool frequency and duration of hospitalization (45).

The WG assessed the quality of evidence as very low. The quality of evidence was downgraded for the methodological limitations of the trials (unclear sequence generation, unclear allocation concealment, and no blinding) and for uncertainty with regard to the directness of the evidence. Although 2 RCTs were available, the strains were not specified; hence, a lack of recommendation.

QUALITY OF EVIDENCE: Very low

ONLY 1 RCT AVAILABLE

Bacillus clausii

Spore-forming bacteria, primarily of the genus *Bacillus*, are commercialized as probiotics (46). One open RCT evaluated the efficacy of treatment with *B clausii* (strains O/C84, N/R84, T84, SIN84) at a dose of 10^9 CFU in Italian children ages 3 to 36 months visiting a family pediatrician for acute diarrhea. Administration of *B clausii* in addition to ORS ($n = 100$) compared with ORS only (control group, $n = 92$) had no effect on the duration of diarrhea (median 4.9 days; IQR 3.97–5.4 vs 4.8 days, IQR 3.97–5.3, respectively; $P = 0.76$) (36).

The WG assessed the quality of evidence as low. It was downgraded for no allocation concealment, single blinding, and for sparse data. Only 1 RCT was available; hence, a lack of recommendation.

QUALITY OF EVIDENCE: Very low

B lactis B12 and *S thermophilus* TH4

One RCT conducted in 224 Chinese children ages 6 to 36 months evaluated the effect of a lactose-free formula supplemented with 2 doses of a mixture of *B lactis* B12 and *S thermophilus* TH4 compared with unsupplemented formula. Regardless of the dose used, the duration of diarrhea was the same in both groups (2.8 ± 1.7 vs 2.8 ± 1.7 days; MD 0.0 hours, 95% CI -0.55 to 0.55) (47).

The WG assessed the quality of evidence as very low. It was downgraded for unclear randomization sequence generation, unclear allocation concealment, unclear blinding, sparse data, and uncertainty with regard to the directness of the evidence. Only 1 RCT was available, hence, a lack of recommendation.

QUALITY OF EVIDENCE: Very low

***L rhamnosus* 573L/1, 573L/2, 573L/3**

One double-blind, placebo-controlled RCT conducted in 87 Polish children ages 2 months to 6 years found that administration of *L rhamnosus* 573L/1, 573L/2, 573L/3 (dose 1.2×10^{10} CFU twice daily, for 5 days) compared with placebo had no effect on the duration of diarrhea of any etiology (3.5 ± 2.3 vs 4 ± 3 days, respectively; MD -0.5 day, 95% CI -1.65 to 0.6 , $P=0.36$); however, in a subset of children with rotavirus infection, there was significant reduction in the duration of diarrhea of rotavirus etiology in the experimental group compared with the placebo group ($n=39$; 3.2 ± 1.45 vs 4.8 ± 2.8 days, respectively; MD -1.6 days, 95% CI -3.0 to -0.1 , $P=0.03$) (48). The WG assessed the quality of evidence as moderate. It was downgraded for sparse data. Only 1 RCT was available; hence, a lack of recommendation.

QUALITY OF EVIDENCE: Moderate

***Lactobacillus helveticus* R0052 and *L rhamnosus* R0011**

One RCT conducted in Czech children ages 12 to 72 months with AGE treated as outpatients was found. Children receiving *L helveticus* R0052 and *L rhamnosus* R0011 (previously known as *L acidophilus* Rosell-11 and *L rhamnosus* Rosell-11 (49)) ($n=38$) compared with placebo ($n=33$) had a significantly shorter duration of diarrhea (4.0 ± 2.0 vs 5.45 ± 2.2 days, MD 1.45 days, 95% CI -2.5 to -0.4) (50).

The WG assessed the quality of evidence as very low. It was downgraded for the methodological limitations of the trial (unclear sequence generation, unclear allocation concealment, unclear blinding of outcome assessors, and no ITT analysis) and for sparse data. Only 1 RCT was available; hence, a lack of recommendation.

QUALITY OF EVIDENCE: Very low

***Lactobacillus paracasei* Strain ST11**

The effect of *L paracasei* strain ST11 (10^{10} CFU/day) was investigated in Bangladesh in 230 boys ages 4 to 24 months with diarrhea of <2 days duration. Compared with placebo, *L paracasei* ST11 had no effect on the duration of diarrhea, the total stool output, the total ORS solution intake, the number of children without diarrhea by the end of the study, or the number of children requiring IV fluids; however, a clinical benefit was found in a subset of children ($n=63$) with nonrotavirus diarrhea (51).

The WG assessed the quality of evidence as moderate. It was downgraded for sparse data and uncertainty with regard to the directness of the evidence. Only 1 RCT was available; hence, a lack of recommendation.

QUALITY OF EVIDENCE: Moderate

L delbrueckii* var *bulgaricus*, *L acidophilus*, *S thermophilus*, *B bifidum

One open RCT evaluated the efficacy of treatment with *L delbrueckii* var *bulgaricus*, *L acidophilus*, *Streptococcus*

thermophilus, and *B bifidum* (strains LMG-P17550, LMG-P 17549, LMG-P 17503, and LMG-P 17500) at doses of 10^9 CFU, 10^9 CFU, 10^9 CFU, and 5×10^8 CFU, respectively, in Italian children ages 3 to 36 months visiting a family pediatrician for acute diarrhea. The administration of the mixture of probiotics in addition to ORS ($n=97$) compared with ORS only (control group, $n=92$) significantly reduced the duration of diarrhea (median 70 hours, IQR 49–101 vs 115.5 hours, IQR 95.2–127, respectively), estimated difference (-37 hours, IQR -47 to -25 , $P<0.001$) (36).

The WG assessed the quality of evidence as very low. It was downgraded for no allocation concealment, single blinding, and sparse data. Only 1 RCT was available; hence, a lack of recommendation.

QUALITY OF EVIDENCE: Very low

NO STRAIN SPECIFICATION AND ONLY 1 RCT AVAILABLE***Bacillus mesentericus* and *Clostridium butyricum* and *Enterococcus faecalis***

One open RCT evaluated the efficacy of treatment with *B mesentericus* (1.1×10^7 CFU), *C butyricum* (2.0×10^7 CFU), and *E faecalis* (3.17×10^8 CFU) (no strain specifications given) in Taiwanese children ages 3 months to 14 years (mean age 39 months) hospitalized for AGE. The administration of the mixture of probiotics in addition to standard therapy ($n=82$) compared with standard therapy only (control group, $n=77$) significantly reduced the duration of diarrhea (1.8 ± 1.6 vs 2.9 ± 1.4 days, respectively; MD -1.1 days, 95% CI -1.7 to -0.5) (52).

The WG assessed the quality of evidence as very low. It was downgraded for the methodological limitations of the trial (lack of blinding, no ITT analysis), for uncertainty with regard to the directness of the evidence, and for sparse data. Only 1 RCT was available; hence, a lack of recommendation.

QUALITY OF EVIDENCE: Very low

L acidophilus*, *L paracasei*, *L bulgaricus*, *L plantarum*, *B breve*, *B infantis*, *B longum*, and *S thermophilus

One double-blind placebo-controlled RCT conducted in 224 Indian children ages 6 months to 2 years with acute rotavirus diarrhea lasting <72 hours reported on the effects of the use of the combination of *L acidophilus*, *L paracasei*, *L bulgaricus*, *L plantarum*, *B breve*, *B infantis*, *B longum*, and *S thermophilus* (commercially available as VSL#3). Baseline characteristics of the study population were not presented. Compared with the placebo group, in the VSL#3 group the frequency of loose stools on days 2 to 4 was reduced; however, no P values were reported. There was also a significant difference in the recovery on day 4 (final evaluation) in the VSL#3 group compared with the placebo group (101/113 vs 44/111, respectively; $P<0.001$) (53).

The WG assessed the quality of evidence as very low. It was downgraded for the methodological limitations of the trial (unclear randomization sequence generation, unclear allocation concealment, unclear blinding, and no ITT analysis). Additionally, it was downgraded for sparse data and uncertainty with regard to the

directness of the evidence. Only 1 RCT was available; hence, a lack of recommendation.

QUALITY OF EVIDENCE: Very low

L acidophilus* and *L rhamnosus* and *B longum* and *S boulardii

One RCT carried out in 64 Bolivian hospitalized children ages 1 to 23 months with rotavirus diarrhea was found. Children receiving, in addition to oral rehydration, *S boulardii* alone (n = 21) compared with placebo (n = 20) had a significantly shorter duration of diarrhea (median 58 vs 84.5 hours, respectively; $P = 0.04$). Children receiving the mixture of probiotics (*L acidophilus* and *L rhamnosus* and *B longum* and *S boulardii*) (strain identifications not given) (n = 23) compared with placebo also had a reduced duration of diarrhea; however, the difference between groups was not statistically significant (median 60 vs 84.5 hours, respectively; $P = 0.06$). There was no difference between the group treated with *S boulardii* and that treated with the mixture of probiotics. Only *S boulardii* reduced the duration of fever. The duration of hospitalization was similar in all 3 groups ($P = 0.31$) (54).

The WG assessed the quality of evidence as moderate. It was downgraded for sparse data and uncertainty with regard to the directness of the evidence. Only 1 RCT was available, hence, a lack of recommendation.

QUALITY OF EVIDENCE: Moderate

SUMMARY

General Comments

1. Rehydration is the key treatment for AGE and should be applied as soon as possible.
2. Overall, probiotics (as a group) as an adjunct to rehydration therapy reduced the duration of diarrhea by approximately 1 day; however, the WG questions pooling different probiotic strains together in a meta-analysis.
3. Probiotic effects are strain specific; thus, the efficacy and safety of each should be established and recommendations for using these strains should be made accordingly.
4. The safety and clinical effects of 1 probiotic microorganism should not be extrapolated to other probiotic microorganisms.
5. A lack of evidence regarding the efficacy of a certain probiotic(s) does not mean that future studies will not establish health benefit(s).
6. The WG recommends choosing a probiotic, the efficacy of which has been confirmed in well-conducted RCTs, from a manufacturer who has a regulated quality control of factors including the composition and content of the probiotic agent.
7. Studies that documented the efficacy of specific strains at a specific dosage in a specific setting are not sufficient evidence to support the presence of health effects at a lower dosage and in a different setting.

Specific Recommendations

1. The use of the following probiotics may be considered in the management of children with AGE as an adjunct to rehydration therapy:

- a. low quality of evidence; strong recommendation: LGG, *S boulardii*
 - b. very low quality of evidence, weak recommendation: *L reuteri* DSM 17938, and heat-inactivated *L acidophilus* LB (the latter, however, although traditionally discussed with other probiotics, does not fit with the definition of probiotics)
2. *E faecium* SF68 should not be considered in the management of children with AGE because this strain is a possible recipient of the vancomycin-resistance genes.

Future Research

1. Country-specific studies to examine the cost-effectiveness of using probiotics with documented safety and efficacy are needed.
2. The role of probiotics in the treatment of AGE in the era of rotavirus vaccination has yet to be established.
3. Because norovirus, at least in some settings (55), has become the leading cause of medically attended AGE, the efficacy of probiotics in treating norovirus AGE needs to be confirmed.

REFERENCES

1. Guarino A, Albano F, Ashkenazi S, et al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition/European Society for Paediatric Infectious Diseases evidence-based guidelines for the management of acute gastroenteritis in children in Europe. *J Pediatr Gastroenterol Nutr* 2008;46(Suppl 2):S81–122.
1. Food and Agriculture Organization of the United Nations. Health and nutritional properties of probiotics in food including powder milk with live lactic acid bacteria. http://www.who.int/foodsafety/publications/fs_management/en/probiotics.pdf. Accessed March 10, 2014.
2. Szajewska H, Skórka A, Ruszczyński M, et al. Meta-analysis: *Lactobacillus* GG for treating acute gastroenteritis in children—updated analysis of randomised controlled trials. *Aliment Pharmacol Ther* 2013;38:467–76.
3. Szajewska H, Ruszczyński M, Kolaček S. Meta-analysis shows limited for using *Lactobacillus acidophilus* LB to treat acute gastroenteritis in children. *Acta Paediatr* 2014;103:249–55.
4. Szajewska H, Urbańska M, Chmielewska A, et al. Meta-analysis: *Lactobacillus reuteri* strain DSM 17938 (and the original strain ATCC 55730) for treating acute gastroenteritis in children. *Benef Microbes* 2014;Jan 24:1–9.
5. Higgins JPT, Altman DG, Sterne AC. Assessing risk of bias in included studies. In: Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]*. www.cochrane-handbook.org. Accessed March 10, 2013.
6. Grześkowiak Ł, Isolauri E, Salminen S, et al. Manufacturing process influences properties of probiotic bacteria. *Br J Nutr* 2011;105:887–94.
7. Sanders ME, Guarner F, Guerrant R, et al. An update on the use and investigation of probiotics in health and disease. *Gut* 2013;62:787–96.
8. Szajewska H, Fordymacka A, Bardowski J, et al. Microbiological and genetic analysis of probiotic products licensed for medicinal purposes. *Med Sci Monit* 2004;10:BR346–50.
9. Hamilton-Miller JM, Shah S, Winkler JT. Public health issues arising from microbiological and labelling quality of foods and supplements containing probiotic microorganisms. *Public Health Nutr* 1999;2:223–9.
10. Hamilton-Miller JM, Shah S, Smith CT. “Probiotic” remedies are not what they seem. *BMJ* 1996;312:55–6.
11. Marcobal A, Underwood MA, Mills DA. Rapid determination of the bacterial composition of commercial probiotic products by terminal restriction fragment length polymorphism analysis. *J Pediatr Gastroenterol Nutr* 2008;46:608–11.
12. Masco L, Huys G, De Brandt E, et al. Culture-dependent and culture-independent qualitative analysis of probiotic products claimed to contain bifidobacteria. *Int J Food Microbiol* 2005;102:221–30.
13. Dalby-Payne JR, Elliott EJ. Gastroenteritis in children. *Clin Evid (Online)* 2011;2011:pii: 0314.

14. Hempel S, Newberry S, Ruelaz A, et al. Safety of probiotics used to reduce risk and prevent or treat disease. *Evid Rep Technol Assess (Full Rep)* 2011;1–645.
15. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–6.
16. Center for Drug Evaluation and Research; Center for Biologics Evaluation and Research. Guidance for industry: providing clinical evidence of effectiveness for human drug and biological products. <http://www.fda.gov/downloads/Drugs/20/GuidanceComplianceRegulatoryInformation/Guidances/ucm078749.pdf>. Published May 1998. Accessed August 2013.
17. Szajewska H. Advances and limitations of evidence-based medicine—impact for probiotics. *Ann Nutr Metab* 2010;57 (suppl):6–9.
18. Rijkers GT, Bengmark S, Enck P, et al. Guidance for substantiating the evidence for beneficial effects of probiotics: current status and recommendations for future research. *J Nutr* 2010;140:S671–6.
19. Allen SJ, Martinez EG, Gregorio GV, et al. Probiotics for treating acute infectious diarrhoea. *Cochrane Database Syst Rev* 2010CD003048.
20. Szajewska H, Skórka A. *Saccharomyces boulardii* for treating acute gastroenteritis in children: updated meta-analysis of randomized controlled trials. *Aliment Pharmacol Ther* 2009;30:955–63.
21. Dinleyici EC, Eren M, Ozen M, et al. Effectiveness and safety of *Saccharomyces boulardii* for acute infectious diarrhea. *Expert Opin Biol Ther* 2012;12:395–410.
22. Chmielewska A, Ruzczyński M, Szajewska H. *Lactobacillus reuteri* strain ATCC 55730 for the treatment of acute infectious diarrhoea in children: a meta-analysis of randomized controlled trials [Polish]. *Pediatrics Współczesna* 2008;10:32–6.
23. Rosander A, Connolly E, Roos S. Removal of antibiotic resistance plasmids from *Lactobacillus reuteri* ATCC 55 730 and characterization of the resulting daughter strain, *L reuteri* DSM 17 938. *Appl Environ Microbiol* 2008;74:6032–40.
24. Egervärn M, Lindmark H, Olsson J, et al. Transferability of a tetracycline resistance gene from probiotic *Lactobacillus reuteri* to bacteria in the gastrointestinal tract of humans. *Antonie Van Leeuwenhoek* 2010;97:189–200.
25. Francavilla R, Lionetti E, Castellana S, et al. Randomised clinical trial: *Lactobacillus reuteri* DSM 17938 vs. placebo in children with acute diarrhoea—a double-blind study. *Aliment Pharmacol Ther* 2012;36:363–9.
26. Dinleyici EC, Dalgic N, Guven S, et al. The effect of a *Lactobacillus reuteri* on the duration of diarrhea and length of hospital stay in children with acute diarrhea in Turkey: prospective, single blind, randomized controlled trial. <http://www.esphghan2013.org/docs/conference-files/46th-annual-meeting-of-espghan-abstracts>. Accessed July 1, 2013.
27. Shornikova AV, Casas IA, Isolauri E, et al. *Lactobacillus reuteri* as a therapeutic agent in acute diarrhea in young children. *J Pediatr Gastroenterol Nutr* 1997;24:399–404.
28. Shornikova AV, Casas IA, Mykkänen H, et al. Bacteriotherapy with *Lactobacillus reuteri* in rotavirus gastroenteritis. *Pediatr Infect Dis J* 1997;16:1103–7.
29. Eom TH, Oh EY, Kim YH, et al. The therapeutic effect of *Lactobacillus reuteri* in acute diarrhea in infants and toddlers [Korean]. *Korean J Pediatr* 2005;48:986–90.
30. Bellomo G, Mangiagale A, Nicastro L, et al. A controlled double-blind study of SF68 strain as a new biological preparation for the treatment of diarrhoea in pediatrics. *Curr Ther Res* 1980;28:927–35.
31. Bellomo G, Finocchiaro C, Frigerio G, et al. Controlled study of Enterococcus LAB strain SF68 in acute enteritis in children with concomitant respiratory infection [Studio controllato sull'enterococco L.A.B. ceppo SF 68 nelle enteriti acute del bambino concomitanti ad infezioni delle vie respiratorie]. *Clin Pediatr* 1982;64:219–27.
32. Bruno F, Frigerio G. A new therapeutic alternative for the treatment of enteritis—controlled double-blind tests with the strain SF 68 [Eine neuartige möglichkeit zur behandlung der enteritis—kontrollierte doppel-blindversuche mit dem Stamm SF 68]. *Schweizerische Rundschau für Medizin Praxis* 1981;70:1717–20.
33. Bruno F, Nastasi A, Bruno M. Double-blind controlled study of the effect of the lactogenic enterococcus SF68 strain on various enterocolitis associated manifestations and on salmonella infections [Studio controllato doppio-cieco sull'effetto dell'enterococco lattoprodotto ceppo SF 68 su manifestazione associate a forme enterocolitiche varree a salmonellosi]. *Clin Ter* 1983;105:203–7.
34. Buydens P, Debeuckelaere S. Efficacy of SF68 in the treatment of acute diarrhoea. A placebo-controlled trial. *Scand J Gastroenterol* 1996;31:887–91.
35. Wunderlich PF, Braun L, Fumagalli I, et al. Double-blind report of the efficacy of lactic acid-producing Enterococcus SF68 in the prevention of antibiotic-associated diarrhoea and in the treatment of acute diarrhoea. *J Int Med Res* 1989;17:333–8.
36. Canani RB, Cirillo P, Terrin G, et al. Probiotics for treatment of acute diarrhoea in children: randomised clinical trial of five different preparations. *BMJ* 2007;335:340.
37. Lund B, Edlund C. Probiotic *Enterococcus faecium* strain is a possible recipient of the vanA gene cluster. *Clin Infect Dis* 2001;32:1384–5.
38. Henker J, Laass M, Blokhin BM, et al. The probiotic *Escherichia coli* strain Nissle 1917 (EcN) stops acute diarrhoea in infants and toddlers. *Eur J Pediatr* 2007;166:311–8.
39. Henker J, Laass MW, Blokhin BM, et al. Probiotic *Escherichia coli* Nissle 1917 versus placebo for treating diarrhea of greater than 4 days duration in infants and toddlers. *Pediatr Infect Dis J* 2008;27:494–9.
40. Khanna V, Alam S, Malik A, et al. The efficacy of tyndalized *Lactobacillus acidophilus* in acute diarrhea. *Indian J Pediatr* 2005;72:935–8.
41. Rafeey M, Ostadrahimi A, Boniadi M, et al. *Lactobacillus acidophilus* yogurt and supplement in children with acute diarrhea: a clinical trial. *Res J Med Sci* 2008;2:13–8.
42. Kianifar HR, Farid R, Ahanchian H, et al. Probiotics in the treatment of acute diarrhea in young children. *Iranian J Med Sci* 2009;34:204–7.
43. Rerksuppaphol S, Rerksuppaphol L. *Lactobacillus acidophilus* and *Bifidobacterium bifidum* stored at ambient temperature are effective in the treatment of acute diarrhoea. *Ann Trop Paediatr* 2010;30:299–304.
44. Lee MC, Lin LH, Hung KL, et al. Oral bacterial therapy promotes recovery from acute diarrhea in children. *Acta Paediatr Taiwan* 2001;42:301–5.
45. Vivatvakin B, Kowitdamrong E. Randomized control trial of live *Lactobacillus acidophilus* plus *Bifidobacterium infantis* in treatment of infantile acute watery diarrhea. *J Med Assoc Thai* 2006;89 (suppl 3):S126–33.
46. Sanders ME, Morelli L, Tompkins TA. Sporeformers as human probiotics: Bacillus, Sporolactobacillus, and Brevibacillus. *Comp Rev Food Sci Food Saf* 2003;2:101–10.
47. Mao M, Yu T, Xiong Y, et al. Effect of a lactose-free milk formula supplemented with bifidobacteria and streptococci on the recovery from acute diarrhoea. *Asia Pac J Clin Nutr* 2008;17:30–4.
48. Szymański H, Pejcz J, Jawień M, et al. Treatment of acute infectious diarrhoea in infants and children with a mixture of three *Lactobacillus rhamnosus* strains—a randomized, double-blind, placebo-controlled trial. *Aliment Pharmacol Ther* 2006;23:247–53.
49. Foster LM, Tompkins TA, Dahl WJ. A comprehensive post-market review of studies on a probiotic product containing *Lactobacillus helveticus* R0052 and *Lactobacillus rhamnosus* R0011. *Benef Microbes* 2011;2:319–34.
50. Tlaskal P, Schramlova J, Kokesova A, et al. Probiotics in the treatment of diarrheal disease of children. *NAFAS* 2005;3:25–8.
51. Sarker SA, Sultana S, Fuchs GJ, et al. *Lactobacillus paracasei* strain ST11 has no effect on rotavirus but ameliorates the outcome of nonrotavirus diarrhea in children from Bangladesh. *Pediatrics* 2005;116:e221–8.
52. Huang YF, Liu PY, Chen YY, et al. Three-combination probiotics therapy in children with salmonella and rotavirus gastroenteritis. *J Clin Gastroenterol* 2014;48:37–42.
53. Dubey AP, Rajeshwari K, Chakravarty A, et al. Use of VSL#3 in the treatment of rotavirus diarrhea in children: preliminary results. *J Clin Gastroenterol* 2008;42 (suppl 3 pt 1):S126–9.
54. Grandy G, Medina M, Soria R, et al. Probiotics in the treatment of acute rotavirus diarrhoea. A randomized, double-blind, controlled trial using two different probiotic preparations in Bolivian children. *BMC Infect Dis* 2010;10:253.
55. Payne DC, Vinjé J, Szilagyi PG, et al. Norovirus and medically attended gastroenteritis in U.S. children. *N Engl J Med* 2013;368:1121–30.

All rights reserved. © 2014 by European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

No part of this publication may be reproduced, transmitted or stored in any form or by any means either mechanical or electronic, including photocopying, recording or through an information storage and retrieval system, without the written permission of the copyright holder.

While the advice and information in this publication is believed to be true and accurate at the date of its publication, neither the authors, the editors nor the publisher can accept any legal responsibility for any errors or omissions. The data and opinions appearing in the publication and any advertisements are the responsibility of the contributor or advertiser, and the mention of any product, service or therapy should not be construed as an endorsement. Please consult the latest prescribing information from the manufacturer before issuing prescriptions for any products mentioned in this publication.



Springer Healthcare

Springer Science+Business Media France Sarl.

22, rue de Palestro - 75002 Paris - France

Tel : +33 (0) 1 53 00 98 60 - Fax : +33 (0) 1 53 00 98 61