

REVIEW ARTICLE

Guidance on the use of probiotics in clinical practice in children with selected clinical conditions and in specific vulnerable groups

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ABSTRACT

Aim: The use of probiotics has been covered by many guidelines, position papers and evidence-based recommendations, but few have referred to specific patient groups or clinical indications. This review summarises recommendations and scientifically credited guidelines on the use of probiotics for children with selected clinical conditions and provides practice points.

Methods: An expert panel was convened by the European Paediatric Association in June 2017 to define the relevant clinical questions for using probiotics in paediatric health care and review and summarise the guidelines, recommendations, position papers and high-quality evidence.

Results: The panel found that specific probiotic strains were effective in preventing antibiotic-associated and nosocomial diarrhoea, treating acute gastroenteritis and treating infantile colic in breastfed infants. However, special caution is indicated for premature infants, immunocompromised and critically ill patients and those with central venous catheters, cardiac valvular disease and short-gut syndrome. This review discusses the safety of using probiotics in selected groups of paediatric patients and the quality of the available products providing practice points based on proved findings.

Conclusion: Efficacy of probiotics is strain specific. Their benefits are currently scientifically proven for their use in selected clinical conditions in children and not recommended for certain patient groups.

INTRODUCTION

Knowledge on the role of gut microbiota in health and disease is developing rapidly, and the number of published scientific papers on the benefits of its modifications is increasing exponentially. It is, therefore, of no surprise that the medical community and the general public are asking for evidence-based answers on when and how to modify gut microbiota in order to improve health in general or to treat or prevent specific diseases.

The ability to manipulate the composition and metabolic footprints of our gut microbiota has been well known for decades, namely through the use of probiotics, prebiotics

Abbreviations

AAD, Antibiotic-associated diarrhoea; AGE, Acute gastroenteritis; EPA, European Paediatric Association; ESPGHAN, The European Society for Paediatric Gastroenterology, Hepatology and Nutrition; LGG, *Lactobacillus rhamnosus* GG; RCT, Randomised controlled trial; RTI, Respiratory tract infections; UNEPSA, Union of National European Paediatric Societies and Associations; URTI, Upper respiratory tract infections.

Key notes

- This European review summarises recommendations and scientifically credited guidelines on the use of probiotics for children with selected clinical conditions and provides practice points.
- An expert panel convened by the European Paediatric Association found that specific probiotic strains were effective in preventing antibiotic-associated and nosocomial diarrhoea, treating acute gastroenteritis and treating infantile colic in breastfed infants.
- However, special caution is indicated for certain groups, including premature infants, immunocompromised and critically ill patients.

and the combination of these two, known as synbiotics (1). Since 2014, the currently valid definition of probiotics, from the WHO and the International Scientific Association for Probiotics and Prebiotics, has been: 'live microorganisms that, when administered in adequate amounts, confer a health benefit on the host' (2).

Discussions about how to use probiotics for various clinical indications have been advanced by many different guidelines, position papers and evidence-based recommendations. There has been a more limited number with regard to specific population groups and fewer on the roles of prebiotics and synbiotics. However, their use in vulnerable populations such as in infants and children, and in defined clinical conditions, should be more rigorously controlled. In addition, their use in clinical practice should follow evidence-based recommendations whenever they are available.

That is why the European Paediatric Association, the Union of the National European Paediatric Societies and Associations (EPA/UNEPSA), convened a panel of independent European experts to examine probiotic supplementation. The panel was chosen based on their scientific profile and publication history and all members were active participants in the work and activities of the Association.

The aim of this review was to summarise the scientifically credited guidelines and recommendations that were currently available on the use of probiotics in paediatric healthcare practice (3) and recommend points for use in clinical practice in selected clinical conditions. The panel decided not to include foods containing probiotics, prebiotics and synbiotics, because it is out of the scope of this paper. We also excluded the use of live bacteria to prevent necrotising enterocolitis in premature babies.

METHODS

The panel of experts organised by EPA/UNEPSA, who are the co-authors of the present review, met in person in June 2017. The aim of that meeting was to define the clinical questions of special relevance for the use of probiotics in paediatric health care, to propose the scope of the paper on the review and the outline what would be included, to discuss the research methods and to set the time limits. The document was further developed and discussed by email from June to October 2017, and the final recommendations for clinical practice, called practice points, were agreed on by all the panel members and finally approved during a teleconference in November 2017.

We searched the PubMed and Cochrane Library databases up to September 2017 for any relevant guidelines, recommendations and position papers covering the paediatric clinical indications that were selected and retrieved the most recent high-quality evidence. The searches were limited to documents published in English. If any of the guidelines were unavailable, outdated or inappropriate, and high-quality evidence existed, such as at least two prospective randomised placebo-controlled trials with the same

outcome (4), the expert panel used those to formulate its recommendations for paediatric clinical practice.

Probiotics for preventing common infections

Description of the problem

Common acute infections in children are a significant burden for health care, especially for children attending day care centres, who have a two to three times higher chance of acquiring common infections than children who stay at home (5). Most common infections include upper respiratory tract infections (URTI) and acute gastroenteritis (AGE). They also make more outpatient doctor and emergency care visits and higher antibiotic use (6). All that presents a substantial economic burden for the family and the healthcare system in general, with an estimated cost of around 1.8 billion US Dollars per year in the United States (6).

Current preventive measures are of limited effectiveness, and therefore, an increasing number of randomised controlled trials (RCTs) have investigated the role of probiotics in the prevention of common infections in children.

Current recommendations

Currently, there are no recommendations from relevant authorities on the use of probiotics in the prevention of common infections in children attending day care centres.

There are systematic reviews which have evaluated the available literature, and the most recent one, which included a meta-analysis, was published in 2016 (7). That meta-analysis found that probiotics in general reduced the risk of a respiratory tract infection (RTI) by a relative risk (RR) of 0.89 and a 95% confidence interval (95% CI) of 0.82–0.96. However, this meta-analysis had several limitations: age groups were evaluated together and there was no strain-specific analysis. Therefore, it is difficult to extrapolate these results into clinical practice.

Summary of the latest evidence

With respect to the prevention of RTI in general, studies have found an overall positive effect in children beyond infancy (8–15). Most of the studies found reductions in URTIs, but questions remain unanswered about the strains to use and when to recommend them.

There were two probiotic strains examined in more than two well-designed RCTs, and they were *Lactobacillus rhamnosus* GG (LGG) and *Bifidobacterium (B). animalis* subsp. *lactis* (BB-12). LGG was examined in three studies (8,11,13) covering a total of 1375 children receiving doses from 10^8 to 10^9 CFU/day, and all the studies reported positive effects on lowering the incidence of RTIs (16). The other strain investigated in four RCTs (17–20) was *B. animalis* subsp. *lactis* BB-12, and in contrast to LGG, all the results were negative (16). There were no more probiotic strains, or their combinations, evaluated in more than two RCTs.

Most of the studies that investigated probiotic use to prevent URTIs also investigated the risk of acquiring gastrointestinal infections, but the evidence on preventing

gastrointestinal infections was even weaker (16). There were no meta-analyses that assessed the overall effect, and based on literature search, there were no two RCTs that investigated the same probiotic strain and yielded positive results (16). Moreover, both studies that investigated LGG found no effect (8,11) and the similar results were on *B. animalis* subsp. *lactis* (BB-12) (18,19). All these results should be interpreted with caution because most of them were performed in the winter period when the incidence of gastrointestinal infections was lower, and therefore, the valid argument could be that the sample size was not sufficiently powered to assess gastrointestinal risk (16).

Practice points

- If probiotics are considered for the prevention of URTIs in children attending day care centres during the winter months, only LGG should be considered. However, the evidence is limited and meta-analyses confirming its efficacy are lacking.
- There is no convincing evidence to recommend the use of probiotics for preventing gastrointestinal infections in day care centres.

Prevention of nosocomial infections

Description of the problem

Nosocomial or hospital-acquired or health care-associated infections develop during a hospital stay, and they are not present or incubating at admission (21). The incidence of nosocomial infections on paediatric wards is still high, even in developed countries, and ranges from 5% to 10% (22). Gastrointestinal and RTIs account for the most of them. Nosocomial infections have several negative impacts: they worsen outcome of the treatment, prolong hospital stays and increase hospital expenses (10). Current standard preventive measures, such as increased hygiene, have a positive effect and decrease infections spreading, but cannot successfully prevent all of them (23,24).

Current recommendations

The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Working Group on Prebiotics and Probiotics recommends that if probiotics for preventing nosocomial diarrhoea are considered, LGG should be used at a dose of least 10^9 CFU/day, for the duration of hospital stay (25). There are no recommendations for preventing RTIs in children hospitalised on paediatric wards.

Summary of the latest evidence

The systematic review from the ESPGHAN Working Group on Prebiotics and Probiotics identified eight RCTs, out of which the majority ($n = 3$) investigated LGG (25). Analysis of the two RCTs, involving 823 subjects, showed that children provided with LGG during their hospital stay had a reduced risk of nosocomial diarrhoea from 13.9% to 5.2% (RR 0.35, 95% CI 0.19–0.65) (25). *L. reuteri* DSM 17938

was investigated by two RCTs at two different doses and both of them – 10^8 CFU/day (26) and 10^9 CFU/day (27) – were not effective (RR 1.11, 95% CI 0.68–1.81) (25).

There is only limited evidence on the role of probiotics in the prevention of nosocomial URTIs outside intensive care units, and this comprised two, albeit big, RCTs (16). One RCT investigated LGG given to 742 children at a dose of 10^9 CFU and found that it reduced the risk of URTI (25). The other study, performed at the same centre, used *B. animalis* subsp. *lactis* (BB-12) at the same dose and was not able to prove positive effect (28). In conclusion, although there is evidence that some probiotic strains could have been effective in preventing RTIs, the evidence is insufficient to recommend their routine use.

Practice points

- If the use of probiotics for the prevention of nosocomial diarrhoea is considered, only LGG can be recommended and the patient should receive least 10^9 CFU/day for the duration of the hospital stay.
- There is insufficient evidence to recommend probiotic use for the prevention of nosocomial respiratory tract infections.

Prevention of allergy

Description of the problem

Allergic diseases are one of the main health problems in children. The current prevalence varies between 5% and 10% and is still increasing (29). The World Allergy Organization reports that approximately one in five people suffers from some form of allergic disease, such as allergic rhinitis, asthma, conjunctivitis, eczema, food allergies, drug allergies and other severe allergic reactions (30). In the United States, allergies are the sixth leading cause of chronic illness, with an annual cost for health care of 18 billion US Dollars (31). Furthermore, in the last 25 years, admissions for food allergies have increased by 500%, and for anaphylaxis, they have increased by 615% (32,33). The increasing incidence and high burden of allergies on families and on the health system and society, in general, prompts the use of effective preventive strategies, including probiotics, especially for children at high risk of atopic diseases.

Current recommendations

The World Allergy Organization recommends the use of probiotics (i) in pregnant women who are carrying a child with a high risk of allergy, (ii) in breastfeeding women when the infant faces a high risk of allergy and (iii) in infants with atopic predisposition (34).

These recommendations do not address the role of specific strains or their combinations, the dose of probiotics that should be offered or the duration of the treatment. In contrast to The World Allergy Organization, other guidelines do not recommend the use of probiotics in the prevention of atopic diseases due to high variations in the evidence obtained (35–37).

Summary of the latest evidence

There have been numerous RCTs that have investigated the role of probiotics in preventing allergies, mainly atopic dermatitis and sensitisation. Unfortunately, the study protocols differed in respect to probiotic species and strains, in respect to doses and duration of treatment and, most importantly, in respect to the timing of the application, such as only during pregnancy (38,39), during pregnancy and maternal administration during breastfeeding (40–42), during pregnancy and in infants (43–54) and only in infants (55–58).

The most recent meta-analysis comprised 17 RCTs covering 4755 children and showed that the use of probiotics, in general, decreased the risk of atopic dermatitis (RR 0.78, 95% CI 0.69–0.89), especially if a combination of probiotics was used (RR 0.54, 95% CI 0.43–0.68) (59). However, no significant difference in terms of preventing asthma, wheezing or rhinoconjunctivitis was found (59). Other meta-analyses focused on the time when probiotics were administered (60). Pooled analysis showed that probiotics could reduce the risk of atopy most efficiently if administered prenatally to pregnant mother and postnatally to the child (RR 0.71, 95% CI 0.57–0.89) (60). That protocol was, as previously stated, used in the majority of studies. Furthermore, some of these studies followed children for longer periods of time (46–48,52,53). Follow-up studies revealed that, although risk for atopic dermatitis remained reduced over time, the risk for other allergic diseases, such as wheezing and allergic rhinoconjunctivitis, was increased in the probiotic group (47, S61). This provides additional complications for the decision to recommend probiotics. In conclusion, the evidence to recommend specific probiotic strains or combinations for the prevention of atopy is insufficient (35–37).

Practice points

- Based on the currently available evidence, probiotics cannot be recommended for the prevention of atopic diseases.

Probiotics for the prevention of antibiotic-associated diarrhoea

Description of the problem

Antibiotic-associated diarrhoea (AAD) is defined as diarrhoea that occurs in relation to an antibiotic treatment and is attributed to the drugs after the exclusion of other possible aetiologies (S62). AAD is common in children and may affect up to a third of patients treated with antibiotics, especially in the case of broad-spectrum anti-infective drugs (S63). Treatment with probiotics relies on the hypothesis that AAD is due to changes in gut microbiota caused by antibiotics. Younger or immunocompromised children, as well as hospitalised children, may benefit most from a reduction in AAD episodes (S62). In addition to preventing episodes of AAD, further benefits that could be achieved with the probiotics are a decreased duration of hospital

stays, reduced medical costs and decreased rates of comorbidity (S62).

Current recommendations

The ESPGHAN Working Group on Prebiotics and Probiotics (S64) recommends the use of LGG or *Saccharomyces (S). boulardii* for the prevention of AAD. Similarly, a 2017 recommendation for Asia-Pacific region children supported the use of LGG or *S. boulardii* for the prevention of AAD (S65).

Summary of the latest evidence

A 2015 Cochrane review (S66) found that the incidence of AAD in the probiotic group was 8% (163/1992) compared to 19% (364/1906) in the control group (RR 0.46, 95% CI 0.35–0.61; $I^2 = 55%$) based on a total number of 3898 participants. In the ESPGHAN Working Group for Prebiotics and Probiotics Clinical Guidelines (S64), the pooled results of all the available RCTs, namely five studies covering 445 children, showed that, compared with placebo or no treatment, LGG administration reduced the risk of AAD from 23% to 9.6% (RR 0.48, 95% CI 0.26–0.89) and that the number needed to treat was eight (95% CI 6–40). The administration of *S. boulardii* reduced the risk from 20.9% to 8.8% in six RCTs covering 1653 children (RR 0.43, 95% CI 0.30–0.60) and the number needed to treat was nine (95% CI 7–12). Furthermore, *S. boulardii* reduced the risk of diarrhoea associated with *Clostridium difficile* in two RCTs covering 579 children (RR 0.25, 95% CI 0.08–0.73).

Practice points

- In order to prevent AAD, LGG or *S. boulardii* should to be considered.
- *S. boulardii* should also to be considered to prevent *C. difficile*-associated diarrhoea.
- Other strains of probiotics, either single strains or in combination, are not currently recommended.
- No safety data on the use of probiotics for preventing AAD in severely ill children are available, and therefore, their use should be subjected to special scrutiny.

Probiotics for the treatment of acute gastroenteritis

Description of the problem

AGE is a very common disease in children. In Western industrialised countries, it accounts for millions of visits to primary care practices and to emergency department, as well as hospital admissions in developing countries. It still represents one of the major causes of deaths (S67). ESPGHAN has defined AGE as a decrease in consistency of stools – loose or liquid – and, or an increase in the frequency of evacuations, at least three in 24 hours, with or without fever or vomiting (S68). The mainstay of the treatment for AGE is rehydration using oral rehydrating solutions, while drugs are considered unnecessary in the majority of cases (S68). As an adjunct to oral rehydrating solution, administering probiotics could further diminish

the duration of the disease and the severity of the clinical symptoms. That is why it was investigated by several RCTs.

Current recommendations

The position paper by the ESPGHAN Working Group on Prebiotics and Probiotics (S68) summarised all the relevant evidence on the use of probiotics in the treatment of AGE, it recommended that only two live microorganisms, LGG and *S. boulardii*, should be considered in the treatment of AGE in children as an adjunct to oral rehydrating solution (S68). Recommendations for children in the Asia-Pacific region have also strongly supported the use of LGG and *S. boulardii* as adjunct treatments to oral rehydration therapy for gastroenteritis (S65).

Summary of the latest evidence

Combined data from 11 RCTs on 2,444 children (S69) showed that LGG significantly reduced the duration of diarrhoea compared with placebos or no treatment (mean difference -1.05 days, 95% CI -1.7 to -0.4). This was particularly valid for children treated in Europe, as shown in five RCTs involving 744 participants (mean difference -1.3 days, 95% CI -2.0 to -0.5) (S69).

In a review published in 2012, the use of *S. boulardii* at a daily dose of between 250 and 750 mg, compared with placebos or no intervention, significantly reduced both the duration of diarrhoea in 11 RCTs covering 306 subjects (mean difference -0.99 days, 95% CI -1.4 to -0.6) and the risk of diarrhoea on day three in nine RCTs covering 1,128 (RR 0.52, 95% CI 0.4–0.65) (S70). In hospitalised children, the use of *S. boulardii* also reduced the duration of hospitalisation in 449 subjects (mean difference -0.8 days, 95% CI -1.1 to -0.5) (S70).

Practice points

- When treating AGE in children, LGG and *S. boulardii* may be considered as an adjunct to the oral rehydration therapy.
- LGG should be administered for 5 to 7 days, at a dose of $\geq 10^{10}$ CFU/day, and *S. boulardii* should be administered for 5 to 7 days, at a dose of 250–750 mg/day. There are currently no recommendations for other strains or products containing single or multiple strains of probiotics.
- Probiotics should ideally be initiated early in the course of diarrhoea.

Treatment of functional pain disorders

Description of the problem

In respect to functional disorders associated with abdominal pain, probiotics have been investigated for treatment of irritable bowel syndrome and for functional abdominal pain not otherwise specified (S71). According to the last Rome IV criteria (S71), irritable bowel syndrome should be considered if abdominal pain occurs during at least 4 days per month and is associated with a

change in frequency of defecation and/or a change in the appearance of stools. Functional abdominal pain is defined as a pain that appears at least four times per month and includes episodic or continuous abdominal pain that does not occur solely during physiologic events and which, after appropriate evaluation, cannot be fully explained by another medical condition (S71). Both conditions are very frequent and affect up to one-third of school-aged children (S72). Furthermore, due to mainly unexplained aetiology, there is no causal treatment. As one of the findings has been altered intestinal microbiota, probiotics were proposed as one of the treatment modalities (S73).

Current recommendations

This review did not find relevant guidelines for the use of probiotics in children with functional abdominal pain disorders.

Summary of the latest evidence

A 2017 meta-analysis showed that probiotics, in general, significantly reduced the frequency of abdominal pain compared to placebos, with a standardised mean difference of -0.55 (95% CI -0.98 to -0.12) (S74). Unfortunately, this meta-analysis did not perform strain-specific analysis. Moreover, the protocols differed in respect to primary outcomes, duration of interventions and type of functional abdominal pain disorders. As a result, clinically relevant recommendations cannot be provided. The only strain-specific meta-analysis evaluated the role of LGG for abdominal pain-related gastrointestinal disorders in children (S75). This meta-analysis included three RCTs and found that the use of LGG moderately decreased pain in the overall population with abdominal pain-related functional gastrointestinal disorders (RR 1.31, 95% CI 1.08–1.59) and in the irritable bowel syndrome subgroup (RR 1.70, 95% CI 1.27–2.27), but not for functional abdominal pain and dyspepsia. However, as this meta-analysis was from 2011, five RCTs were subsequently published, all involving *L. reuteri* DSM 17938 (S76–S80). Of those, three found more pronounced pain reductions in probiotic group (S77–S79). Interestingly, placebos were able to significantly reduce pain intensity as well (S79,S81,S82).

In conclusion, there is some evidence that probiotics could decrease the pain intensity in children with functional abdominal pain disorders and only two strains (LGG and *L. reuteri* DSM 17 938) were proven to be effective in more than two RCTs. However, it was difficult to interpret the results as they included different study protocols, durations of interventions, primary outcomes and type of pain.

Practice points

- Due to the limitations of the available evidence and lack of current guidelines, no recommendation can be provided on the use of probiotics for treating functional abdominal pain disorders.

Probiotics for the prevention and treatment of infantile colic

Description of the problem

Infantile colic is a common problem affecting 10% to 30% of healthy, thriving infants (S83). According to the Rome IV criteria, infantile colic may be diagnosed in an infant who is less than 5 months of age when their symptoms start and stop, they present with recurrent and prolonged periods of crying, fussing or irritability that occur without an obvious cause that cannot be prevented or resolved by caregivers, and in whom there is no evidence of failure to thrive, fever or illness (S84). The aetiology is still undefined, but intestinal dysbiosis has been hypothesised as a possible underlying condition, implying that probiotics could be useful in prevention and/or treatment.

Current recommendations

Currently, no statements and recommendations have been issued by the relevant European Societies and Institutions for the use of probiotics in infant colic. However, Latin-American Guidelines were published in 2015 (S85), and there are recommendations covering children in the Asia-Pacific region (S65), both supporting the use of the strain of *L. reuteri* DSM 17938 for the prevention and treatment of infantile colic.

Summary of the latest evidence

As far as prevention is concerned, although some promising results have been shown with *L. reuteri* DSM 17938, data are scarce (S86). The evidence is stronger for treatment. A review by Szajewska et al. identified four RCTs that showed that the use of *L. reuteri* DSM 17938 reduced crying times in breastfed infants with infantile colic (S87). In contrast, one RCT that recruited both breastfed and formula-fed infants did not confirm this effect (S88). A meta-analysis from 2014 included three RCTs and found that, compared with placebos, administration of *L. reuteri* DSM 17938 reduced crying times on day 21 by 43 minutes (mean difference -43 min/day, 95% CI -68 to -19), but mainly in exclusively or predominantly breastfed infants (mean difference -57 min/day, 95% CI -67 to -46) (S89). Other studied strains (LGG) and mixtures of probiotics did not have an effect (S87).

Practice points

- If the use of probiotic is considered, *L. reuteri* DSM 17938 is the only strain shown to be effective in treating infantile colic in breastfed infants.
- If administered, the dose of *L. reuteri* DSM 17938 should be at least 10^8 CFU/day, provided for 21–30 days.
- Limited evidence on the use of *L. reuteri* DSM 17938 in the prevention of infantile colic precludes specific recommendation.
- There is no evidence for other strains of probiotics or products containing probiotic mixtures.

Safety of probiotic use

Description of the problem

In the recent years, the use of probiotics has increased worldwide, and therefore, it is particularly important that the risks of probiotic treatments are discussed and acknowledged (S90). The most commonly used microbiota are species or strains of *Bifidobacterium*, of *Lactobacillus* and of *Saccharomyces*. The safety issues that are most commonly described in the literature for those three genera, in particular for the LGG (S91) and for *S. boulardii*, are more as a consequence of their frequent use and not a marker of their impaired safety (S92). There are also increased safety concerns on the use of probiotics if other species that belong to the same genera are pathogenic (*Streptococcus*, *Bacillus* and *Enterococcus*). As each probiotic strain is expected to have a specific clinical effect, the safety profile could possibly be different for each probiotic (S93). However, the safety issues have not been established for most of them and the data have only been generated as secondary outcomes. It is important to note that there are a lack of studies assessing the safety of probiotics as the primary study outcome (S94).

In general, the side effects of probiotic use could be systemic infections, deleterious metabolic activities, immune stimulation in susceptible populations, gastrointestinal symptoms and the transfer of genes coding for potentially dangerous bacterial features, such as antimicrobial resistance (S95). Other possible safety risks include metabolic effects, such as the production of D-lactate with lactic acidosis, deconjugation of bile salt, and short- and long-term immunomodulating effects. The latter are particularly relevant for neonatal use and the transfer of genetic material such as plasmids coding for antimicrobial resistance from probiotic bacteria to more pathogenic bacteria (S90,S91,S94,S95). Finally, there are also adverse effects limited to mild gastrointestinal symptoms, such as abdominal cramping, nausea, diarrhoea, flatulence and of taste alteration, but the studies described no difference compared to the placebo (S94).

Current recommendations

This review could not find relevant recommendations or guidelines related to the safety issues of probiotics. Most of the reported adverse effects were based on case reports or case series and further properly designed RCTs to assess this issue as a primary outcome should be undertaken.

In 2011, the US Agency for Healthcare Research and Quality published a report on the safety of probiotics, based on a systematic review of 622 RCTs (S94). There were four main conclusions to this report. The first referred to the Generally Recognised as Safe Status and said that the evidence that properly addressed the safety of probiotics was limited, but the majority of probiotic strains that were studied should be generally regarded as safe. Secondly, the report stated that there were no safety issues in specific populations and that the case reports suggested that the adverse effects were more frequent in patients with compromised health. Another key finding was that there was no

conclusive evidence that using a mixture of different probiotic strains had more adverse events than using one probiotic strain. The final finding was that the long-term effects of probiotic strains use were unknown (S94).

Summary of the latest evidence

Sepsis. The risk for fungaemia associated with *S. boulardii* is increased in critically ill patients, those in intensive care units, those using mechanical ventilation or fitted with central venous catheters, those treated with broad-spectrum antibiotics and those who are immunosuppressed or premature neonates (S92,S96,S97). Clinical practice guidelines do not recommend the use of *S. boulardii* in patients with *C. difficile* infections who are critically ill (S98). In children, sepsis with *Lactobacillus* strains has been reported in association with prematurity, short-gut syndrome, cardiac surgery, immunosuppression and cerebral palsy (S99–S104).

Various studies have shown that patients who are potentially at a major risk for septic dissemination are immunocompromised patients, including those in a debilitated state or with a malignancy, and premature infants. Minor risk factors are the presence of a central venous catheter, impaired intestinal barrier, short-gut syndrome, administration of probiotics by jejunostomy, concomitant administration of broad-spectrum antibiotics (probiotics resistance), high mucosal adhesion or the known pathogenicity of probiotic strains and cardiac valvular disease (S64,S90,S105).

Metabolic effects. The Probiotics in Pancreatitis Trial, a multicentre, double-blind, placebo-controlled clinical trial, demonstrated a higher mortality rate in adult patients with severe pancreatitis who were treated with multispecies probiotic preparation in most of the cases due to bowel ischaemia. These were *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus salivarius*, *Lactococcus lactis*, *Bifidobacterium bifidum* and *Bifidobacterium lactis*. The study conclusion was that in patients with severe pancreatitis the probiotics should not be administered (S106, S107). However, this study has been seriously criticised in respect of a number of factors, including its design, choice of patients and outcome variables, and therefore, the final results should be treated with caution.

Effect on immune system development. There are no long-term studies to prove the immunological adverse reactions due to probiotic use in human subjects (S90,S91,S105). However, there are many RCTs where probiotics were given to patients to prevent allergic disease very early in life, including prenatally in pregnant women, and for a long period of time (S46–S48,S52,S53). Follow-ups of these studies revealed that, although the risk for atopic dermatitis remained reduced over time, the risk for other allergic diseases, namely wheezing and allergic rhinoconjunctivitis, was increased in the probiotic group (S47,S61). Those findings imply that probiotics could have a long-term effect on the immune system, but the exact mechanisms and the long-term outcomes are yet to be determined.

The transfer of antimicrobial resistance. The transfer of antimicrobial resistance has been demonstrated for *Lactobacillus*, which is naturally resistant to vancomycin (S90, S91). LGG has no plasmids that contain transferable or other antibiotic resistance (S91). *Lactobacillus reuteri* ATCC 55730 had a transferable resistance trait for tetracycline and lincomycin and therefore was replaced by a new strain, *L. reuteri* DSM 17938 (S108). The use of *Enterococcus faecium* SF68 strain in acute gastroenteritis was not recommended for children due to the possible transfer of vancomycin-resistant genes (S109).

Practice points

- The use of probiotics in children seems to be safe in general, even when provided in high doses.
- Probiotics should be used with caution in special situations, such as prematurity, immunocompromised patients, critically ill patients, those with central venous catheter, cardiac valvular disease and short-gut syndrome.
- Some probiotic strains are not recommended for use in children, such as *Enterococcus faecium* SF68, due to the possible transfer of vancomycin-resistance genes.
- In children with the *C. difficile* infection, *S. boulardii* is proven to be efficacious; however, due to the potential infectious spread, special caution is required in critically ill patients.

Quality of the commercial probiotic products

Description of the problem

Increased awareness and knowledge of the potential benefits of probiotics have resulted in the exponential growth in number of commercial products, making it one of the fastest growing global markets with the best forecast for further growth up to 2020 (S110). Probiotic products are coming onto the market in a wide range of different forms. For example, they are being added to foods or provided as supplements packed into capsules, pills, suspensions, powder sachets, sprays and granulates. However, because they are categorised as dietary, food supplements (S111), foods for specific health use (S112) or as natural health products (S113), probiotic products have to comply with significantly less stringent criteria than medicinal products or drugs. This raises doubts about their quality and that is why the ESPGHAN Working Group for Prebiotics and Probiotics performed a literature search and provided recommendations (S114). Based on their review of the literature, the authors concluded that the majority of studies reported on more than one labelling inconsistency in most of the tested products. The strains were frequently misidentified and misclassified, the products were occasionally contaminated with facultative or even obligatory pathogens, strains were not viable, and the number of colonies was diminished to the extent that precluded health benefit. Probiotic products licensed as drugs were also affected, although not to the same extent (S114).

Table 1 Summary of proposed practice points for every reported clinical indication

Clinical indication	Practice points
Prevention of common infections	<ul style="list-style-type: none"> If probiotics are considered for prevention of upper respiratory tract infections in children attending day care centres during winter months, only LGG could be considered. However, evidence is limited and meta-analyses confirming its efficacy are lacking. There is no convincing evidence to recommend the use of probiotic for the prevention of gastrointestinal infections in day care centres.
Prevention of nosocomial infections	<ul style="list-style-type: none"> If the use of probiotic for prevention of nosocomial diarrhoea is considered, only LGG (at least 10^9 CFU/day, for the duration of hospital stay) can be recommended. The evidence to recommend probiotic use in the prevention of nosocomial respiratory tract infections is insufficient.
Prevention of allergy	<ul style="list-style-type: none"> Based on the currently available evidence, probiotics cannot be recommended for prevention of atopic diseases.
Prevention of antibiotic-associated diarrhoea	<ul style="list-style-type: none"> In prevention of AAD, LGG or <i>S. boulardii</i> should be considered. <i>S. boulardii</i> is also to be considered in the prevention of <i>C. difficile</i>-associated diarrhoea. Other strains of probiotics, single or in combination, are currently not recommended. No safety data on the use of probiotics for prevention of AAD in severely ill children are available; thus, their use should be subjected to special scrutiny.
Treatment of acute gastroenteritis	<ul style="list-style-type: none"> In the treatment of AGE in children, LGG and <i>S. boulardii</i> may be considered as an adjunct to the oral rehydration therapy. LGG should be administered for 5–7 days, at dose $\geq 10^{10}$ CFU/day. <i>S. boulardii</i> should be administered for 5–7 days, at dose 250–750 mg/day. Other strains or products containing single or multiple strains of probiotics have currently no recommendation. Probiotic should ideally be initiated early in the course of diarrhoea.
Treatment of functional abdominal pain disorders	<ul style="list-style-type: none"> Due to limitations of the available evidence and lack of current guidelines, no recommendation can be provided on the use of probiotics in the treatment of functional abdominal pain disorders.
Probiotics for prevention and treatment of infantile colic	<ul style="list-style-type: none"> If the use of probiotic is considered, <i>L. reuteri</i> DSM 17938 is the only strain shown to be effective in the treatment of infantile colic in breastfed infants. If administered, the dose of <i>L. reuteri</i> DSM 17938 is to be at least 10^8 CFU/day, provided for 21–30 days. Limited evidence on the use of <i>L. reuteri</i> DSM 17938 in the prevention of infantile colic precludes specific recommendation. Other strains of probiotics or products containing probiotic mixtures have currently no evidence.
Safety of probiotic use	<ul style="list-style-type: none"> The use of probiotics in children seems to be safe in general, even when provided in high doses. Probiotics should be used with caution in special situations such as prematurity, immunocompromised patients, critically ill patients, central venous catheter, cardiac valvular disease and short-gut syndrome. Some probiotic strains are not recommended to be used in children, such as <i>Enterococcus faecium</i> SF68, due to the possible transfer of vancomycin-resistance genes. In children with <i>C. difficile</i> infection <i>S. boulardii</i> is proven to be efficacious, however due to potential infectious spread, a special caution is required in critically ill patients.
Quality of the commercial probiotic products	<ul style="list-style-type: none"> To secure that the patient will receive a probiotic product that meets the required quality cannot be solved by the health practitioner, and therefore, this paper does not provide practice points on this issue.

AAAD = antibiotic-associated diarrhoea; LGG = *Lactobacillus rhamnosus* GG.

Current recommendations

Due to the important quality issues listed above, and to establish the documented effect on health, the ESPGHAN Working Group recommended the following (S114): (i) a precise identification of the microorganisms to strain level; (ii) products prescribed for specific clinical indications and situations to be subjected to rigorous clinical trials; (iii) systematic quality controls by the respective authorities to confirm the viability- and strain-level identification of the active ingredients; (iv) adverse events, potentially related to probiotic products should be reported and a register of those events should be maintained by health authorities (S114).

Summary of the latest evidence

Since the publication of the ESPGHAN Position Paper (S114), one further paper provided a consumer's guide for

the use of probiotics (S115). However, neither of them can solve the problem of quality issues and should be considered as calls for improvement of the regulatory control mechanisms.

Practice points

- The health practitioner cannot ensure, on his or her own, that the patient receives a probiotic product that meets the required quality. For that reason, this paper does not provide practice points on this issue. This issue needs to be resolved by the respected regulatory agencies, including the European Pharmacopoeia which proposed, in a paper published 2017, actions to harmonise quality standards for live biotherapeutic products used in human health care (S116).

CONCLUSION

Probiotics have been prescribed to children since birth with increased frequency, in order to either prevent or treat various clinical conditions. Therefore, the EPA-UNEPSA expert panel defined the clinical conditions that have special relevance for the use of probiotics in paediatric health care. Based on the current guidelines and recent high-quality evidence, they have provided instructions for their use in paediatric health care in Europe.

Positive instructions on the use of strictly defined strains are suggested for (i) the prevention of upper respiratory tract infections in children attending day care centres; (ii) the prevention of nosocomial diarrhoea; (iii) the prevention of antibiotic-associated diarrhoea; (iv) the treatment of acute gastroenteritis; and (v) the treatment of infantile colic in breastfed babies (Table 1).

Probiotics are not recommended for (i) the prevention of gastrointestinal infections in day care centres; (ii) the prevention of nosocomial respiratory tract infections; (iii) the prevention of atopic diseases; (iv) the prevention of infantile colic; and (v) the treatment of functional abdominal pain disorders (Table 1).

All the practice points, listed in Table 1, are based on the current literature. However, the knowledge of probiotics is developing and future studies may reveal positive effects for other clinical conditions and for other probiotic strains.

Although probiotics are generally regarded as safe, there are clinical conditions in which their use requires special caution, such as prematurity, immunocompromised patients, critically ill patients, those with a central venous catheter, cardiac valvular disease and short-gut syndrome.

Improved control mechanisms by the respective regulatory agencies are advocated to ensure that patients receive commercial probiotic products that meet the required quality.

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CONFLICTS OF INTEREST

Iva Hojsak has been a clinical investigator and, or, speaker for Biogaia, Chr Hansen, Biogaia, Medisadria, Nutricia, Pharmas. Olivier Goulet has been a clinical investigator and/or speaker for Fresenius Kabi, Danone and Biocodex. Fugen Cullu Çokuğraş has been a speaker for Abbott and Danone. Sanja Kolaček has been a clinical investigator and/or speaker for Abbott, Abbvie, Biogaia, Chr Hansen, Danone, MEDIS, Nestle, Nutricia and MSD. The other authors have no conflict of interest to declare.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Appendix S1 Supplementary References.