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POSITION STATEMENT

Nutrition

Prebiotics in the management of pediatric gastrointestinal disorders: Position paper of the ESPGHAN special interest group on gut microbiota and modifications

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Abstract

Prebiotics are substrates that are selectively utilized by host microorganisms conferring a health benefit. Compared to probiotics there are few studies with prebiotics in children. Most studies have been performed using infant formula supplemented with prebiotics, while add-on prebiotic supplementation as prevention or treatment of childhood gastrointestinal disorders has rarely been reported. The aim of this position paper was to summarize evidence and make recommendations for prebiotic supplementation in children with gastrointestinal diseases. Recommendations made are based on publications up to January 1, 2023. Within the scope of the European Society for Paediatric Gastroenterology Hepatology and Nutrition Special Interest Group on Gut Microbiota and Modifications, as in our previous biotic recommendations, at least two randomized controlled clinical trials were required for recommendation. There are some studies showing benefits of prebiotics on selected

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outcomes; however, we cannot give any positive recommendations for supplementing prebiotics in children with gastrointestinal disorders.

KEYWORDS
children, gastrointestinal disease, infant, oligosaccharides

1 | BACKGROUND

The prebiotic concept was first defined in 1995 by Gibson and Roberfroid as a nondigestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria already resident in the colon.[1]

In 2004, the definition of prebiotics was changed to "selectively fermented ingredients that allow specific changes, both in the composition and/or activity in the gastrointestinal microflora that confers benefits upon host well-being and health."[2] According to this definition, a prebiotic had to meet three criteria: it had to be resistant to host digestion, it had to be fermented by intestinal microorganisms, and it had to selectively stimulate the growth and/or activity of intestinal bacteria that are good for health and well-being.[2] However, more recently, in 2017, in keeping with the latest scientific and clinical developments; the definition of a prebiotic supplement was modified by International Scientific Association for Probiotics and Prebiotics to "a substrate that is selectively utilized by host microorganisms conferring a health benefit."[3] This definition broadens the scope of prebiotics to encompass compounds other than carbohydrates, potential uses outside of the digestive tract, and several non-nutritional contexts.[3] These substances have to show specific features, which are to be tested by in vitro and in vivo experiments in different targets (i.e., animals or humans): (1) resistance to gastric acidity, hydrolysis by digestive enzymes and gastrointestinal absorption; (2) fermentation by intestinal microbiota, which can be evaluated in vitro through the addition of the respective carbohydrates to colon content suspensions, or pure or mixed bacteria cultures in an anaerobic batch or continuous culture fermentation system; and (3) growth promotion of intestinal bacteria beneficially related to health and well-being.[3,4] The most commonly-studied prebiotics are the plant-derived prebiotics, such as pectins, inulin, fructo-oligosaccharides (FOS), and the galacto-oligosaccharides (GOS), and human milk oligosaccharides (HMOs), such as the 2′-fucosyllactose (2′-FL), and the manufactured prebiotics added to infant formulas to mimic the functional characteristics of HMOs.[3]

Like all other "biotics," demonstration of health benefits is required with controlled clinical trials due to the different mechanisms of action involved in the different prebiotic substances.[3] Previously some health benefits of prebiotics have been suggested, relating to the gastrointestinal system, cardiovascular system, metabolism, and bone metabolism, in adults as well as in children.[3] The aim of this review was to evaluate evidence from randomized controlled trials on prebiotics and gastrointestinal disorders during childhood and summarize findings of randomized controlled trials and meta-analyses. Based on these, we will provide recommendations for the use of prebiotics in the management of gastrointestinal disorders.

What is Known

- Prebiotics are substrates that are selectively utilized by host microorganisms conferring a health benefit.
- Previously some health benefits of prebiotics have been suggested.

What is New

- No recommendation for the use of prebiotics to prevent morbidity in preterm infants, infantile colic, acute infectious diarrhea, Helicobacter pylori infection, functional constipation, inflammatory bowel disease, celiac disease, and allergic disorders can be made.
- In children with irritable bowel syndrome, healthcare providers may recommend psyllium supplementation (low-grade of recommendation).
- There is a need for more randomized-placebo controlled studies that would use the same type of prebiotic for a specific clinical condition in children and adolescents.

2 | METHODS

This review was conducted by the Special Interest Group on Gut Microbiota and Modifications of the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). For this review the following databases were searched: Cochrane Database of Systematic Reviews, DARE (Database of Abstracts of Reviews of Effects), CENTRAL (Cochrane Central Register of Controlled Trials), PubMed (National Library of Medicine, includes MEDLINE®), and EMBASE for systematic reviews and/or meta-analyses and subsequently published randomized controlled trials (RCTs) that compared the use of prebiotics, in all delivery vehicles and formulations, at any dose, single or multiple

prebiotics, compared with no prebiotic (i.e., placebo or no treatment or other interventions). Studies were included if they enrolled infants and children up to age 18 years. We excluded studies assessing the effect of prebiotics as a part of infant formulas in this review. ESPGHAN Special Interest Group on Gut Microbiota & Modifications is now doing a separate study of infant formula that contains biotics, including prebiotics. This evaluation is based on evidence and is intended to be published at a later date. Nonrandomized clinical trials, case reports, and abstracts from proceedings were also excluded. The reference lists from identified studies and key review articles, including previously published meta-analyses were also searched. The search was performed for publications until January 1, 2023. Only studies published in English were taken into consideration. At least two reviewers independently assessed the eligibility of each potentially relevant trial. The data extracted included baseline characteristics, inclusion criteria, experimental and control treatments, setting, dose, outcomes of interest (with definitions if available), and adverse events/side effects. Brand or trade names were not considered, as the same brands may change composition and/or manufacturing practices over time and may have a different composition in different locations. Studies that evaluated prebiotics together with other biotics were not included in this review. The recommendations were formulated only if at least two well-designed RCTs that used a given prebiotic were available; if there was only one RCT, regardless of whether it showed a benefit, no recommendation was formulated (Figure 1).

Initially, it was planned to use the system developed by the Grading of Recommendations, Assessment Development, and Evaluations Working Group, and to categorize the certainty of evidence (quality of the evidence) and the strength of recommendations, which were previously used for synbiotics and probiotics.[5,6] However, due to lack of evidence this could not be performed. A modified Delphi process was used to establish consensus on the statements.[5,6] The draft document containing the list of statements formulated by the core group was circulated by email to all group members. Each member was asked to vote by marking "agree" or "disagree" beside each statement. Each member was given the opportunity to provide comments and suggest different wording. Anonymity was retained. Eighty percent agreement from the group was required to accept or omit a statement during

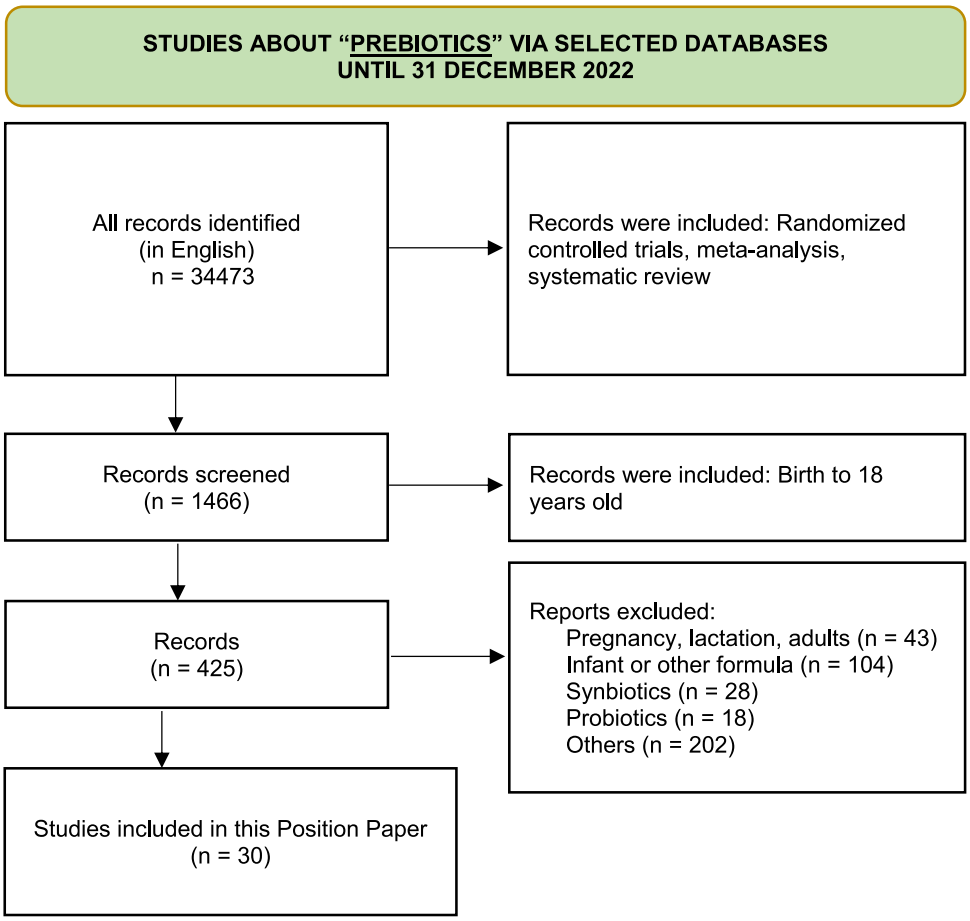

FIGURE 1 Flowchart: studies about "prebiotics" via selected databases until December 31, 2022.

development of the final document. Statements not meeting 80% agreement were modified according to feedback provided by the group members and sent to the group for Round 2. The list of statements that did not meet consensus from Round 1 was emailed to all the members. In Round 2, the group used the same voting method as described for Round 1, but with the knowledge of the group scores and comments. Thus, everyone could reflect upon the group results and change their mind, while preserving the anonymity of their responses. Round 3 was a face-to-face meeting. Eighty percent agreement was used to determine acceptance or rejection of a statement. Anonymity was not retained. The discussion continued until agreement was reached to retain, modify, or eliminate the statement from the final document. Once full consensus was reached, the statements were included in the final document.[5,6] The level of agreement is presented next to each statement/recommendation.

Country, publication year, study type, age group and number of children, disease or condition, prebiotic type, and duration of intervention are shown in Table 1.

3 | RESULTS

3.1 | Prebiotics to prevent morbidity in preterm infants

In 2019, Chi et al. published a meta-analysis on the use of prebiotics in preterm newborns to prevent morbidity and mortality.[35] The aim of this systematic review with meta-analysis was to summarize the findings of 17 RCTs where in a total of 1322 preterm infants were randomized to either a prebiotic or control group. The review found an overall reduction in sepsis and mortality rates in children receiving prebiotic supplements, but not in necrotizing enterocolitis rate. Also, time to full enteral nutrition was reduced if infants received prebiotics.[35] However, we found significant shortcomings in the meta-analysis carried out by Chi et al.[35] that compromise the accuracy of the reported findings.

A significant constraint of the meta-analysis performed by Chin et al. in 2019[35] is the inclusion of specific RCTs in different subgroup analyses, potentially leading to an overinterpretation of the results. A total of 11 distinct RCTs were identified in this research, with some lacking comprehensive data on sepsis and mortality outcomes. Also, many outcomes were misreported in the analyses. For example, in the paper by Luoto et al.,[36] who studied the effects of GOS in moderately preterm infants on the incidence, severity, and duration of respiratory tract infections during the first year of life, the incidence of viral infections was incorrectly counted as neonatal sepsis cases.

Furthermore, the authors of the meta-analysis also included data on clinically suspected sepsis contrary to the scientific standard of culture-verified sepsis, e.g., from the largest of the included studies.[16] In addition, one of these included RCT did not study a prebiotic supplement, but a fermented postbiotic formula instead.[37] The other RCTs investigated GOS,[36] short-chain GOS (scGOS) with long-chain fructo-oligosaccharides (lcFOS),[33] scGOS with lcFOS and acidic oligosaccharides,[34] inulin,[16] or lactulose.[17] Five other studies from Chi's systematic review also investigated a prebiotic intervention (mostly scGOS/lcFOS) but these were part of the formula that was provided. Following our methods, these studies were thus excluded from our position paper here. After a thorough analysis of the two trials assessing the effects of scGOS/lcFOS with or without acidic oligosaccharides,[33,34] it is clear that only 80 preterm newborns, with an average gestational age of around 30 weeks, received the prebiotic treatment. Both trials did not show an effect on necrotizing enterocolitis (stage ≥2) or mortality rates, and only found trend toward a lower sepsis incidence. Dilli et al.[16] compared inulin versus placebo and found no effects on morbidity and mortality rates. However, the median time to full enteral nutrition was shorter in the prebiotic group than in the placebo group, but with 17 and 25 days, respectively, longer than currently observed in most neonatal intensive care units in both groups.[36]

In the pilot RCT conducted by Riskin et al.,[17] with a total of 28 participants, no clear benefits were observed from the administration of lactulose to infants. Only one additional RCT was identified by databases searches following the publication of the meta-analysis by Chi et al.[6,7] In this trial, a total of 86 preterm newborns, born between 27 and 33 weeks' gestation, were randomly assigned to receive either a placebo or a mixture of two human milk-like oligosaccharides (HMLOs), specifically 2′ FL and lacto-N-neotetraose (LNnT) during their hospitalization. The authors reported no differences in morbidity or mortality, except for a nonsignificant trend in reducing time to full enteral feeding (12.2 days in HMLOs group vs. 14.4 days in placebo group). In addition, head circumferences of infants who had received the HMLOs were significantly larger than those in the control group, although a clear hypothesis for this finding is lacking.[7]

In summary, the number of included studies investigating the use of prebiotic supplements in preterm infants is low. None of the studies showed clear benefits on outcomes. Moreover, there were not two studies that investigated the same product. Taken together, currently, we cannot form any positive recommendations for supplementing prebiotics in preterm infants.

There is no recommendation for the use of prebiotics in preterm infants.

TABLE 1 Country, publication year, study type, age group, disease or condition, prebiotic type, and duration of intervention.

Prebiotic	Study site	Study design	Condition	Aim/end points	Inclusion criteria	Intervention	Control group(s)
2′-fucosyllactose (2′FL) and lacto-N-neotetraose (LNnT)[7]	France	Randomized, double-blind, placebo-controlled trial	Preterm infants	The effects of HMO supplementation on feeding tolerance, growth, and safety	Preterm infants (27–33 weeks' gestation, birth weight <1700 g)	HMO supplement ($n = 43$) (2′-fucosyllactose [2′FL] and lacto-N-neotetraose [LNnT] in a 10:1 ratio [0.374 g/kg body weight/day])	Isocaloric placebo ($n = 43$)
Dietary fiber mixture[8]	Brazil	Randomized, double-blind, placebo-controlled trial	Chronic constipation	Clinical efficacy and effect of dietary fibers on colonic transit time in children with controlled chronic constipation	Children with chronic constipation, aged 4–12 years ($n = 54$)	Dietary fiber mixture	Placebo (maltodextrin)
Dietary fibers[9]	The Netherlands	Randomized, double-blind, placebo-controlled trial	Constipation	Effects of dietary fibers on defecation frequency, incontinence frequency, stool consistency, presence of abdominal pain and flatulence, necessity for step-up medication, and dry weight of feces were recorded	Children with functional constipation ($n = 135$)	Fiber mixture in a yogurt drink	Lactulose
Dietary fiber[10]	United Kingdom		Functional constipation	Effect of dietary fiber intakes of children with constipation with specifically designed behavior modification technique with a self-monitoring and reward system	Forty-three children, aged 2–14 years, with functional constipation	receiving general advice on increasing dietary fiber intake	
FOS and xilooligosaccharides[11]	Italy	Prospective, randomized, single-blind controlled trial	Acute infectious diarrhea	The rate of resolution of diarrhea 72 h after treatment	Children aged between 3 and 36 months, with acute diarrhea ($n = 119$)	Hypotonic ORS containing zinc and FOS plus xylooligosaccharides	Hypotonic ORS
Fructooligosaccharides[12]	Brazil	Randomized, double-blind, placebo-controlled parallel clinical trial	Constipation	The effect of FOS in the treatment of infants with constipation	Infants with Constipation ($n = 36$)	FOS was added to the infant formula	Placebo was added to the infant formula

(Continues)

TABLE 1 (Continued)

Prebiotic	Study site	Study design	Condition	Aim/end points	Inclusion criteria	Intervention	Control group(s)
Glucomannan (GNN)[13]	Poland	Randomized, double-blind, placebo-controlled trial	Abdominal pain-related functional gastrointestinal disorders (FGIDs)	The efficacy of glucomannan (GNN) as the sole treatment for abdominal pain-related FGIDs	Children aged 7–17 years with abdominal pain-related FGIDs classified according to the Rome III diagnostic criteria ($n = 84$)	GNN, a polysaccharide of 1,4-D-glucose and D-mannose, a soluble fiber at a dosage of 2.52 g/d (one sachet of 1.26 g two times a day)	Placebo (maltodextrin)
GNN[14]	Italy	Double-blind, randomized, crossover study	Constipation	Effects of fiber supplementation (glucomannan) in the treatment of children with functional constipation with or without encopresis	Children with chronic functional constipation with and without encopresis ($n = 31$)	Fiber (glucomannan, a fiber gel polysaccharide from the tubers of the Japanese Konjac plant) given as 100 mg/kg body weight daily (maximal 5 g/day) with 50 mL fluid/500 mg	Placebo given as 100 mg/kg body weight daily (maximal 5 g/day) with 50 mL fluid/500 mg
GNN[15]	Poland	Randomized, double-blind, placebo-controlled trial	Functional constipation	Treatment success (≥3 stools per week with no soiling), stool consistency score, stool frequency, abdominal pain episodes	Children aged 3–16 years with functional constipation according to Rome III criteria ($n = 80$)	GNN (2.52 g/d)	Placebo
Inulin[16]	Turkiye	Prospective Randomized controlled clinical trial	NEC	Effects of probiotics and inulin alone or combined on NEC in VLBW infants	VLBW infants ($n = 400$)	Inulin added to breastmilk or formula	Probiotic (*Bifidobacterium lactis*), or synbiotic (*B. lactis* plus inulin) added to breastmilk or formula
Lactulose[17]	Israel	Prospective, double-blinded, placebo-controlled, single-center study	Preterm infants	The safety and prebiotic effects of lactulose in preterm infants	Preterm newborns (23–34 weeks; $n = 28$)	1% lactulose in all feeds (human milk or formula)	1% dextrose in all feeds (human milk or formula)
Mixture of acacia fiber, psyllium fiber, and fructose[18]	Italy	Randomized, open-label, prospective, controlled,	Children with chronic functional constipation	Effectiveness of a mixture of acacia fiber, psyllium fiber, and fructose with polyethylene glycol 3350	Children with chronic functional	Mixture of acacia fiber, psyllium fiber, and fructose (16.8 g daily) with polyethylene glycol	Polyethylene glycol 3350 combined with electrolytes

TABLE 1 (Continued)

Prebiotic	Study site	Study design	Condition	Aim/end points	Inclusion criteria	Intervention	Control group(s)
		parallel-group study		combined with electrolytes on the frequency of bowel movements, stool consistency, fecal incontinence, and improvement of other associated gastrointestinal symptoms and safety	constipation ($n = 100$)	3350 combined with electrolytes	
Mixture of galacto-oligosaccharide and polydextrose (1:1)[19]			Preterm infants	Infants were categorized based on the extent of crying and irritability during the first 2 months of life, and their gut microbiota was investigated	Ninety-four preterm infants (gestational age 32–36 weeks and birth weight >1500 g)	Mixture of GOSand polydextrose 1:1	Probiotics (*Lactobacillus rhamnosus* GG) or placebo
Nondigestible carbohydrates (NDC)[20]	Egypt, Greece, Israel, Italy, The Netherlands, Poland, Portugal, and Slovenia	Randomized, double-blind, placebo-controlled multicenter study	Acute infectious diarrhea in children with mild to moderate dehydration	Efficacy and safety of a mixture of nondigestible carbohydrates on acute infectious diarrhea	144 boys aged 1–36 months with acute infectious diarrhea	NDC; soy polysaccharide 25%, alpha-cellulose 9%, gum arabic 19%, FOS 18.5%, inulin 21.5%, resistant starch 7%) as an adjunct to oral rehydration therapy	Placebo
Oligofructose-enriched inulin[21–28]	Poland	Randomized controlled study	Celiac disease	Intestinal permeability measurements, zonulin, sugar absorption test in children with celiac disease; the effect on bone metabolism and immune response; the effect on the concentration of volatile organic compounds in the urine; quantitative gut microbiota characteristics and short-chain fatty acids concentration, effect of on fat-soluble vitamins status, parathormone, and calcium-related element; plasma profile	Children with celiac disease ($n = 34$)	10 g of oligofructose-enriched inulin with a strict gluten-free diet	Placebo (maltodextrin) with a strict gluten-free diet

(Continues)

TABLE 1 (Continued)

Prebiotic	Study site	Study design	Condition	Aim/end points	Inclusion criteria	Intervention	Control group(s)
				and urine excretion of amino acids, effect on iron homeostasis			
Partially hydrolyzed guar gum (PHGG)[29]	Turkiye	Randomized prospective controlled study	Constipation	Effect of partially hydrolyzed guar gum or lactulose on standardized bowel diary, defecation frequency, stool consistency, and presence of flatulence and abdominal pain	Children with constipation ($n = 61$)	Partially hydrolyzed guar gum	Lactulose
Polyphenol-based prebiotic[30]	Nicaragua	Randomized, double-blinded, placebo-controlled clinical study	Acute infectious diarrhea	Efficacy and durability of a polyphenol-based prebiotic treatment for acute gastroenteritis	Acute gastroenteritis ($n = 300$)	A single titrated 0.5–2 ounce liquid dose of a novel polyphenol-based prebiotic (Aliva) diluted with two to eight ounces of oral rehydration solution (ORS)	Placebo
Psyllium[31]	United States	Randomized, double-blind, placebo-controlled trial	Irritable bowel syndrome (IBS)	The efficacy of psyllium fiber treatment on abdominal pain and stool patterns in children with IBS	IBS ($n = 103$)	Psyllium	Placebo
Psyllium[32]	India	Randomized, double-blind, placebo-controlled trial	IBS	Assess the IBS severity scoring scale (IBS-SSS) at baseline and after 4 weeks	Eighty-one children with IBS	Psyllium	Placebo
scGOS/lcFOS; 9:1[33]	Iran	Single-center RCT	NEC in preterm infants	Efficacy and safety of enteral supplementation of scGOS/lcFOS on incidence of NEC in preterm infants	Seventy-five preterm infants birth weight (BW) ≤1500 g, gestational age ≤34 weeks and were not fed with formula	30 mL/kg/day volume of breast milk was randomly allocated to have enteral supplementation with a (scGOS/lcFOS; 9:1)	Not receive any prebiotic
scGOS/lcFOS/pAOS[34]	The Netherlands	Randomized, double-blind, placebo-controlled trial	Premature infants	The effect of enteral supplementation of a prebiotic mixture on serious infectious morbidity in preterm infants	Preterm infants with gestational age <32 weeks and/or birth weight <1500 g received ($n = 113$)	Enteral supplementation of scGOS/lcFOS/pAOS	Placebo (maltodextrin)

Abbreviations: FOS, fructo-oligosaccharide; HMO, human milk oligosaccharide; NDC, nondigestible carbohydrates; NEC, necrotizing enterocolitis; ORS, oral rehydration solution; RCT, randomized controlled trial; scGOS/lcFOS/pAOS, short-chain GOS/long-chain fructo-oligosaccharides/pectin-derived acidic oligosaccharides; VLBW, very low birth weight.

3.1 | Prebiotics and infantile colic

The available literature on prebiotic treatment of infant colic is limited compared with previous research on probiotics and synbiotics. In a Finnish randomized double-blind study, 94 moderate or late preterm infants were randomized to receive a prebiotic mixture of GOS and polydextrose or probiotic (*Lactobacillus rhamnosus* GG ATCC 53103) or placebo during the first 2 months of life, and followed-up for 1 year. Excessive crying was found in 27 of 94 infants (29%), with a significantly lower frequency in the prebiotic and probiotic groups than in the placebo group (19% vs. 19% vs. 47%, respectively; $p = 0.02$).[19]

No general recommendations on the use of any specific prebiotic in infancy as a prophylactic or therapeutic measure for infantile colic can be given at this time.

There is no recommendation for the use of prebiotics as prophylactic or therapeutic for infantile colic.

3.1 | Prebiotics and acute infectious diarrhea

There is limited information available for the prebiotic treatment of acute infectious diarrhea in children when compared to prior experience/studies with probiotics/synbiotics. There are three RCTs investigating the role of prebiotics in diarrheal disease.

Hoekstra et al.[20] conducted an RCT in 144 boys aged 1–36 months in Egypt, Greece, Israel, Italy, Holland, Poland, Portugal, and Slovenia, with mild to moderate dehydration associated with diarrhea, to assess the effectiveness and safety of a combination of nondigestible carbohydrates (including soy polysaccharide 25%, alpha-cellulose 9%, gum arabic 19%, FOS 18.5%, inulin 21.5%, and resistant starch). They showed no difference for 48 h stool volume, duration of diarrhea, and length of hospital stay between the placebo and prebiotic groups.[20]

Noguera et al.[30] performed a double-blinded RCT in Nicaragua to assess the effects of a polyphenol-based prebiotic in 111 children and 133 adults, presenting symptoms of acute gastroenteritis, specifically mild to moderate diarrhea. The primary objective of this study was the duration until the last unformed stool. The present study observed that individuals who were administered prebiotic treatment had considerably reduced durations until their final unformed bowel movement at various time intervals, including 30 min, 2 h, 24 h, 48 h, 72 h, and 5 days. In addition, a notable decrease in symptoms associated with acute gastroenteritis was found. However, it is important to note that no subgroup analysis was conducted specifically for children, and the trial excluded all participants under the age of 12 due to safety concerns.[30]

Passariello and colleagues[11] conducted a single-blind, prospective, controlled RCT in 119 children (aged 3–36 months) with acute diarrhea in Italy. They tested the effectiveness of a zinc and prebiotic (FOS and xylooligosaccharide)-containing hypotonic oral rehydration solution (ORS) for treating acute diarrhea in children. In children taking ORS together with zinc and prebiotics, the resolution of diarrhea at 72 h was significantly higher. Although the outcomes of this study are encouraging, the effect of zinc in the prebiotic arm cannot be excluded.[11]

Because there were not at least two RCTs that evaluated the same prebiotic preparation, it was impossible to determine whether the intervention was effective and to make a recommendation.

There is no recommendation for the use of prebiotics for the treatment of acute infectious diarrhea.

3.1 | Prebiotics and *Helicobacter pylori* infection

H. pylori treatment protocol includes antibiotic and proton pump inhibitors and these treatments might be related with dysbiosis. There may be theoretical reasons to target intestinal microbiota with long-term approaches, such as prebiotic administration, to prevent complications. In addition, the use of selected probiotics may potentially increase *H. pylori* eradication rates and prevent antibiotic-induced diarrhea.[6] However, prebiotics as such have not been investigated in randomized controlled trials, neither in children nor in adults with *H. pylori* infection. No mention of prebiotics was included in a recent review on the management of *H. pylori* infection in European children by the *H. pylori* Special Interest Group of ESPGHAN.[38]

We are unable to make any recommendations about the use of prebiotics as an additional treatment or prevention in *H. pylori* infection.

There is no recommendation for the use of prebiotics in prevention or treatment in *Helicobacter pylori* infection.

3.1 | Prebiotics and functional abdominal pain disorders (FAPD)

A 2022 systematic review and meta-analysis identified six studies evaluating the role of prebiotics in the management of FAPD in children.[39] Three trials examined children diagnosed with irritable bowel syndrome (IBS) according to the Rome II, III, and IV criteria.[31,32,40] In the randomized, double-blind, controlled, and prospective study from Turkiye, included 71 children between the ages of 4 and 16 years who were diagnosed with IBS according to the Rome III criteria. Administration of synbiotics and probiotics resulted in significant improvements for belching-abdominal fullness, bloating after meals, and constipation when compared to prebiotics.[40] The second study is a double-blinded RCT from the United States, demonstrating the efficacy of psyllium supplementation for 4 weeks with a reduction in the mean number of pain episodes compared to placebo (8.2 ± 1.2 vs. 4.1 ± 1.3, $p = 0.03$). While the reduction of mean number of pain episodes was found, the level of pain intensity, the absolute number of episodes and other parameters did not differ between the groups.[31] An additional double-blinded RCT from India investigated the effect of 4 weeks of prebiotic supplementation (psyllium) on IBS severity scoring scale (IBS-SSS). There was a significant reduction in IBS-SSS in the psyllium group versus the placebo group ($p < 0.001$) at 4 weeks. Similarly, 43.9% in the psyllium group versus 9.7% in the placebo group attained remission.[32] While there are some interesting results, studies about psyllium are limited, and further better-designed randomized controlled trials are needed.

Three other studies relate to FAPD. The first RCT study was carried out in 1985 in Canada, before the Rome Criteria era. Therefore, the diagnosis of FAPD was based on Apley's criteria.[41] Subjects supplemented for 2 weeks with two corn fiber cookies per day ($n = 26$) were compared to a placebo group ($n = 26$). The fiber group demonstrated more children who had a 50% decrease in the frequency of attacks, compared to placebo ($p = 0.04$).[42] Another RCT from Poland evaluated the effect of supplementing glucomannan for 4 weeks in 84 subjects with abdominal pain-related functional gastrointestinal disorders (FGIDs). They concluded that glucomannan was no more effective than placebo in achieving therapeutic success in the management of FGIDs in children.[13] An RCT, studying 60 children, the effect of partially hydrolyzed sugar gum supplementation on FAP as well as IBS, was evaluated when compared to placebo in Italy. The supplemented group presented a higher level of efficacy in IBS, compared to placebo ($p = 0.025$) in reducing clinical symptoms with improvement of the Birmingham IBS score ($p = 0.025$). In FAPD, intensity of abdominal pain, assessed with the Wong–Baker Face Pain Rating Score, pain was improved (40% vs. 13.3%, $p = 0.025$). This analysis did not include two further studies that examined the impact of prebiotics on functional gastrointestinal complaints in healthy children and autistic individuals, without a particular diagnosis of either FAPD or IBS.[43,44]

In conclusion, we identified two RCTs demonstrating clinical efficacy of psyllium supplementation in children with IBS.

> In children with irritable bowel syndrome, healthcare providers may recommend psyllium supplementation.
> Certainty of evidence: Low.
> Grade of recommendation: Low.

3.1 | Prebiotics and functional constipation

Regarding the impact of fiber/prebiotics in children with functional constipation, 11 studies, with 808 children recruited, investigated the effect of seven different fibers and/or prebiotics isolated or added to infant formula, compared to placebo or active control treatments.[8–10,12,14,15,18,29,45–47] A definition of treatment success was documented in five out of 11 studies. Among these, one study assessed the efficacy of a combination of acacia fiber, psyllium fiber, and fructose, which was found to be as effective as laxative treatment.[18] Another study evaluated glucomannan and reported more effectiveness compared to placebo.[14] Three studies examined various combinations of glucomannan, FOS, inulin, gum arabic, resistant starch, soy polysaccharide, and cellulose, but did not demonstrate superiority over placebo.[8,12,15] Other authors did not define treatment success; however, they reported that the studied treatment (dietary fiber, prebiotic mixtures of transgalacto-oligosaccharides, inulin, soy fiber, or resistant starch) was as effective as lactulose on fecal incontinence, abdominal pain, defecation frequency, consistency of stools, or abdominal pain.[9,10,29,46] The frequency of defecation was documented in all 11 investigations, and there were no statistically significant variations seen between the investigational products and laxative treatment,[31–34] as well as placebo or other control treatment.[8,10,12,14,15,45,47] Regarding safety, adverse events were reported by eight of the 11 studies, and four observed mild side effects in the experimental group, such as diarrhea, abdominal distention, flatulence, and vomiting.[9,12,15,18]

The quality of evidence does not allow to establish a robust and significant impact of prebiotics as adjuvants

in the comprehensive treatment of functional constipation.

There is no recommendation for the use of prebiotics in functional constipation.

3.1 | Prebiotics and inflammatory bowel disease (IBD)

Diets rich in fiber, fruits, and vegetables, containing lots of compounds with prebiotic properties, were found to have a protective role in IBD.[48] Hence, prebiotics have the potential to serve as an effective supplementary treatment for inducing and sustaining remission in individuals with IBD. Nevertheless, there have been limited publications on the use of prebiotics in patients with IBD, specifically in the adult population.[49–56] No pediatric studies were found. Therefore, no conclusion about the usefulness of prebiotics in children with IBD patients can be made.

There is no recommendation for the use of prebiotics in patients with inflammatory bowel disease.

3.1 | Prebiotics and celiac disease (CD)

Limited information is available on the prebiotic use in children with CD. A single RCT was performed using the prebiotic oligofructose-enriched inulin (10 g per day) as compared to placebo (maltodextrin) for a period of 12 weeks. This trial was designed to assess the impact of the oligofructose-enriched inulin on children with CD following a gluten-free diet (GFD). A total of 34 children were subjected to randomization to assign them to either the prebiotic group or the placebo group for the duration of a 12-week intervention.[21,57] Selected biochemical parameters, analysis of vitamins and amino acids concentration, nutritional status, bone metabolism, and the gut microbiota were analyzed and results were reported in different research papers.[21–28,57] The authors concluded that the supplementation with oligofructose-enriched inulin had no significant effect on barrier integrity. The only positive finding was an increase in mannitol excretion, suggesting a possible increase in the epithelial surface secondary to prebiotic supplementation.[22] In another study, the authors found that children in the prebiotic group exhibited a noteworthy rise in the number of *Bifidobacterium* and the overall concentration of short-chain fatty acids (a 31% increase; specifically, levels of fecal acetate and butyrate).[27] This study provides an initial understanding of the prospective health advantages associated with the use of prebiotics in children diagnosed with CD who strictly follow a GFD. The findings presented in this study are based on a single RCT including a limited sample size of 34 individuals. However, these results provide some indications that the inclusion of oligofructose-enriched inulin in the diet may have potential benefits in enhancing the composition of fecal microbiota and promoting the synthesis of bacterial metabolites. In addition, it may contribute to the improvement of intestinal barrier function and the absorption of minerals and vitamins. However, the lack of effect on the primary outcome, the numerous secondary outcomes, excessively variable participants' characteristics (i.e., wide age span, different clinical presentation, and differences in GFD duration), and the use of just one prebiotic mixture severely limit the possibility of drawing conclusions and generalizing efficacy of prebiotic. Future studies based on the presented results are needed to further explore the efficacy of prebiotics in CD.

There is no recommendation for the use in prebiotics for patients with celiac disease.

3.1 | Prebiotics and allergy

The high prevalence of allergic diseases in Western countries and the limited possibilities of causal therapy make evidence-based recommendations for primary prevention necessary.[58] The increasingly recognized role of early nutrition and gut microbiome in modulating optimal development and function of the immune system is driving the attention on the potential role of prebiotics as effective strategy for allergy prevention.[59] Preclinical and clinical studies reported that some prebiotics could exert a preventive action against the occurrence of allergic diseases not only through a beneficial modulation of gut microbiome structure and function, but also, through a direct interaction with epithelial and immune cells, regulating the gut barrier structure and function, as well the immune response toward tolerance to environmental antigens.[60] Most of the preclinical evidence indicated that these prebiotic supplementations may prevent allergic response and induce immune tolerance in murine models.[61] Clinical evidence is based on studies evaluating subjects with allergy risk, and still limited studies on prebiotic supplementation in pregnant and lactating women. Furthermore, most clinical studies evaluating the

preventive action of prebiotics against allergy have been mainly performed on the occurrence of atopic dermatitis (AD), whereas other allergic diseases were much less investigated.[62] In 2011, the Committee on Nutrition of ESPGHAN reported insufficient evidence to recommend supplementing infant formulas with prebiotics to prevent allergy.[63] In 2013, a Cochrane review reported a potential benefit of prebiotics during infancy in the prevention of AD, but no conclusive evidence was found regarding whether the use of prebiotics should be restricted to infants at high risk of allergy or whether it may influence the occurrence of other allergic diseases, including food allergy and asthma.[64] In 2016, the World Allergy Organization (WAO), using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach, was in favor of using prebiotic supplementation in not-exclusively breastfed infants for allergy prevention, but reporting very low certainty of evidence. In addition, the WAO guideline panel opted not to offer a recommendation on the use of prebiotic supplements during pregnancy or when breastfeeding.[65] The 2021 guidelines from the European Academy of Allergy and Clinical Immunology (EAACI) did not provide a specific recommendation regarding the use of prebiotics in pregnant and/or breastfeeding women and/or infants, either alone or in combination with other methods, for the prevention of food allergies in infants and young children.[66] Subsequent data published until now from partly large-scale, randomized, double-blinded intervention studies consistently show no preventive effects of prebiotics in allergic rhinitis, bronchial asthma, and atopic eczema. Finally, based on the EAACI guideline, the current guidelines do not recommend the use of prebiotics in infants for the purpose of allergy prevention, not even as part of infant formula.[58] Nonetheless, the overall safety profile of the prebiotic intervention is good, and many trials evaluating their preventive effects against allergy did not report adverse events. In an intervention study describing the allergy-preventive effect in AD by prebiotics, a significantly higher rate of allergic rhinitis was found as an adverse effect.[58]

Allergies are multifactorial diseases with a concomitant role of several environmental factors interacting with the genetic background.[67] Consequently, future effective actions against allergies should consider the concomitant application of different strategies starting early in life, most probably at the beginning of the first 1000 days.[68]

There is no recommendation for the use of prebiotics for the prevention of food allergy, allergic rhinitis, asthma, and atopic dermatitis.

Overall, there are limitations on prebiotic supplementation for the management of children with gastrointestinal disorders. There is scarcity of data, underpowered and heterogeneous studies, assessing prebiotic effect on gastrointestinal conditions. Existing studies may be underpowered and are highly heterogenous so not amenable to meta-analysis. It is necessary to carry out a greater number of studies, taking care of the type and size of population selected, as well as the adequate dose and type of prebiotics, to establish recommendations based on evidence of adequate quality.

4 | CONCLUSION

Published studies using prebiotics are characterized by a high degree of heterogeneity regarding the intervention (type of prebiotic, preparation, dose, duration, and time of supplementation), the studied population, the diagnostic criteria, and the time at which individual endpoints were recorded. The clinical efficacy and safety of a specific prebiotic or a combination of prebiotics cannot be generalized to other prebiotics. Due to limited data, it is not feasible to offer a recommendation regarding the utilization of prebiotics to prevent morbidity in preterm infants or treatment of infantile colic, acute infectious diarrhea, *H. pylori* infection, functional constipation, inflammatory bowel disease, celiac disease, and allergic disorders. Healthcare providers may suggest the use of psyllium supplementation for children with IBS, specifically for abdominal pain episodes. There is a requirement for an increased number of randomized, placebo-controlled studies that use a consistent prebiotic intervention for a specific clinical condition in children and adolescents.

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

CONFLICT OF INTEREST STATEMENT

Flavia Indrio has participated as an advisory board member, consultant, and/or speaker for, BioGaia, Danone NNI. Ener Cagri Dinleyici has participated as an advisory board member, consultant, and/or speaker for Biocodex, BioGaia, Nutricia, and Nestle Health Science. Chris H. P. Van den Akker reports receipt of speakers and consultancy honoraria from Nestlé Nutrition Institute, Nutricia Early Life Nutrition, and Baxter. The remaining authors declare no conflict of interest.

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