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Evidence-based use of Probiotics in Children

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ABSTRACT

The use of Probiotics is exploding for many ailments. Though considered generally harmless, probiotics can transmit Antibiotic-Resistant Genes (ARG), cause infection in immunocompromised hosts, and run the risk of unintended consequences by disrupting the dynamic equilibrium of the gut microbiome. So, evidence-based use of probiotics is recommended.

We reviewed the available evidence in probiotics and microbiome research, and present the probable conclusions for the clinician to decide on their use.

***Conclusions: Structural defect in research:** The biological effect of the microbiome is likely to be due to the microbiome in contact with the mucosa. It has been shown that this is different from the intraluminal (fecal) microbiome commonly analyzed in most studies. These studies also do not stratify according to genetic predisposition and native microbiome, both of which can affect colonization of the gut by probiotics.*

***Study Design:** There is a lack of case control design, adequate sample size, and selection of specific probiotic species.*

***Diarrhea:** LGG and Saccharomyces Boulardi were recommended in acute diarrhea based on low-quality evidence. Studies done in the US and Canada did not support their use. For prevention of antibiotic-associated diarrhea, LGG and Saccharomyces Boulardi were useful, but only S Boulardi reduced C Diff diarrhea.*

***Constipation:** No consistent beneficial effect of probiotics reported.*

***Infantile Colic:** L. reuteri DSM 17938 reduced colic duration only in breastfed babies.*

***Regurgitation:** There is insufficient data to recommend L. reuteri DSM 17938.*

***Functional Abdominal Pain/IBS:** The studies' limitations, especially the inadequate sample size, prevent an evidence-based recommendation of probiotics.*

***Necrotizing Enterocolitis:** Though Lactobacillus subsp. and Bifidobacterium subsp administration has shown better prevention, the American Academy of Pediatrics didn't support routine use in view of the chance of infection, especially in Very Low Birth Weight (VLBW) babies.*

***Pouchitis:** Despite low quality of evidence, AGA has recommended an 8-strain proprietary probiotic mix to prevent and treat pouchitis.*

***Cow's Milk Protein Allergy and Other Allergies:** Though L. rhamnosus GG has shown some promise, high-quality studies are required for a firm recommendation.*

***Probiotics in Infant formula:** No overwhelming consistent benefit has been shown. There is a chance of transmitting ARG through the indiscriminate use of probiotics in babies.*

Keywords
Pediatric probiotics, Gut microbiota, Lactobacillus, Gastrointestinal.

Introduction

Probiotics have gained widespread popularity, from general consumer use to clinical applications. The global probiotics market, valued at $87.7 billion in 2023, is projected to reach $131 billion by 2032. The number of scientific papers on probiotics and the microbiome has surged, from approximately 7,000 in 2014 to over 10,000 in 2024, reflecting both consumer popularity and growing scientific curiosity [1].

Though promoted as safe, probiotics can transmit antibiotic-resistant genes (ARG) and can cause infection in rare cases. Most importantly, disrupting the delicate balance among the colonic microbiome can lead to unintended consequences such as chronic diseases.

Hence, probiotic use should be guided by scientific evidence. Critical questions about their efficacy and mechanisms of action remain unanswered. One reason may be the significant gaps in probiotics/microbiome research methodology.

One of the most debated issues is whether oral probiotic supplementation truly alters the gut microbiome. Most studies on probiotic impact are based on stool microbiome analysis. However, research suggests that this method fails to capture the microbial ecosystem in direct contact with the gastrointestinal (GI) mucosa [2]. Studies have revealed that the microbiome associated with GI mucosal surfaces, as examined by analyzing mucosal biopsies, differs from the microbiota found in feces [3] (Figure 1). It is logical to assume that most of the effects of probiotics and microbiome on the gut mucosa will be from those in contact with the epithelium, not those present in the stool. Orally administered probiotics have been recovered from stool without colonization of the colon [3]. This raises the debate about whether oral probiotic supplementation alters the gut microbiome. Studies with appropriate methodology (biopsies) have shown confusing results, indicating that probiotics are the least effective in recolonizing the gut with a healthy microbiome after the native microbiome is destroyed by antibiotics [2].

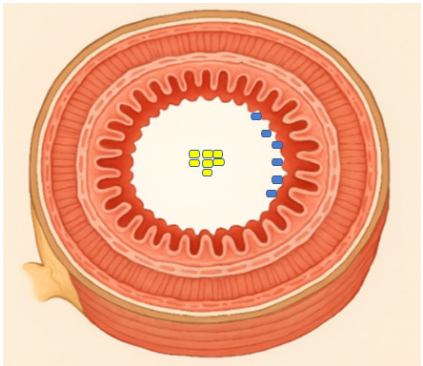

Figure 1: Schematic Cross Section of Colon with Mucosal (Blue) and Luminal (Yellow) Microbiomes.

Other factors, such as an individual's genetics and native microbiome population, influence whether probiotics successfully colonize the gut (acceptors and refusers) [3,4]. Unfortunately, most studies fail to stratify participants based on these variables, leaving gaps in understanding. Furthermore, limitations such as small sample sizes, inconsistent use of multiple probiotic species, and a lack of robust double-blind trials with standardized methodologies continue to hinder the reliability of current findings [5,6]. *In vitro* studies hint at probiotic-derived metabolites affecting microbial metabolism, but robust human trials are needed to validate these findings.

In light of these limitations, the conclusions drawn from existing probiotic and microbiome research should be interpreted with caution. The intricate dynamics between administered probiotics, native microbiota, and host factors demand deeper exploration to develop more definitive therapeutic strategies.

Gut microbiota and Probiotics

The human body is home to billions of microorganisms, forming symbiotic relationships that sustain growth and health. The gut microbiota—a dense community of bacteria, archaea, viruses, and eukaryotes within the gastrointestinal system—plays essential roles in metabolism, nutrition, and immunity [7]. This microbial population evolves over an individual's lifetime, influenced by diet, genetics, and lifestyle, resulting in unique gut flora for each person [8].

Dysbiosis, or microbial imbalance, disrupts gut homeostasis and may contribute to health issues. Probiotics—live microorganisms administered to restore microbial balance—offer potential benefits in maintaining a healthy gastrointestinal environment [9]. An expert panel convened by the Food and Agriculture Organization (FAO) and World Health Organization (WHO) defined probiotics in 2001, later refined by the International Scientific Association for Probiotics and Prebiotics (ISAPP) in 2013 as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host [10]."

Despite claims of efficacy in treating a broad spectrum of diseases, many probiotics are marketed as food supplements, subject to less stringent regulation compared to pharmaceuticals. This poses safety concerns, particularly for children. Rigorous, unbiased trials focusing on pediatric populations are necessary to substantiate these claims and ensure safety.

Methods

We searched PubMed and other known databases for relevant scientific trials, observational studies, recommendations, position papers, and consensus guidelines related to use of Probiotics among pediatric population. The evidences published in English or having a reliably published English transcript were only considered in this review.

Probiotics in Diarrhoea

Acute diarrhoea is one of the leading causes of childhood mortality

worldwide, especially in developed countries. The pathogenic organisms usually attack the intestinal mucosa and disrupt the gut integrity, leading to a large amount of water loss in the gut lumen that ultimately causes diarrhoea. It is thought that the Probiotics compete with the enteric pathogens for available nutrients and mucosal binding sites; thus produce a specific immune response against the organisms. Most of the acute infectious gastroenteritis (AGE) in children is viral-induced and self-limiting. Therefore, any causal treatment is not recommended unless indicated, and rehydration with oral rehydration solution (ORS) remains the mainstay of treatment. Still, there are a number of Probiotics available commercially in the market.

There is a clear conflict between data on the role of Probiotics as well as the specific strain in treating gastroenteritis in children. Lactobacillus rhamnosus GG (LGG) is probably the most studied probiotic in pediatric AGE. A Cochrane review of 11 RCTs (n=2072) investigating LGG found that it reduced the duration of diarrhoea by a mean of 27 hours (95% CI, −41 to −13). Subsequent follow-up review at 2013 reported reduced diarrheal duration, but LGG had no effect on stool volume (Mean duration, 8.97 mL/g; 95% CI, −86.26 to 104.2) [11].

A meta-analysis including 29 RCTs by Szajewska et al. revealed a reduction of duration of diarrhoea (mean difference -1.06 day, 95% CI -1.32 TO -0.79) when 250-750 mg/day of *Saccharomyces boulardii* was used for 5 days in acute gastroenteritis compared to placebo or no treatment [5]. Eight RCTs (n=999) considered duration of hospitalization and found a mean difference of -0.85 day (95% CI -1.3 to -3.4). But both the groups were unreliable due to very high heterogeneity (I^2=90% and 91% respectively). Moreover, only one of the trials was double blinded, and 38% followed proper randomization of the samples.

The third known probiotic used in acute childhood diarrhoea was Lactobacillus reuteri strain ATCC 55730. Though previous trials have shown significant clinical effect in AGE, this strain was replaced with a new strain L reuteri DSM 17938, as the ATCC 55730 strain was responsible for the transfer of resistance traits for tetracycline and Lincomycin [12]. Two RCTs involving 196 hospitalized children with acute diarrhoea found DSM 17938 significantly reduces the duration of diarrhoea (MD −32 hours, 95% CI −41 to −24) and facilitates discharge by day 3 (RR 3.5, 95% CI 1.2–10.8) [13,14]. The stool volume weren't considered in any of the studies. Notably, the studies included only the hospitalized children, and the study sample allocations were questionable due to inadequate randomization and blinding. Clinical trials involving a larger number of children visiting the outpatient departments are needed to get a clearer and scientifically sounder picture regarding the role of Lactobacillus reuteri strain DSM 17938.

In a nutshell, there is a few clinical trials conducted supporting the use of probiotics in treatment of acute childhood diarrhoea. But most of the clinical have issues in sample selection, randomization, and the results are inconsistent across different trials. Therefore, the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) working group has recommended only 2 strains as an adjunct to rehydration therapy in acute gastroenteritis, though the quality of evidence is low: LGG, and S. Boulardii [15]. For L. reuteri DSM 17938 the recommendation is weak as the quality of evidence is very low. The claims couldn't be supported by enough pieces of evidence in form of systemic review or meta-analysis to recommend other probiotics like *L acidophilus* strain LB [16]. Interestingly, most of the trials investigating the role of probiotics were conducted in Italy, India, Turkey, Pakistan, and Poland. RCTs in the North American region found a gross contradiction in the results of similar trials. The Pediatric Emergency Care Applied Research Network conducted a large, multicenter, double blind placebo-controlled trial including 943 children from 10 different centres of the United States and they reported that *L rhamnosus* ATCC 53103, given at a dose of 1×10^{10} CFU twice daily for 5 days, couldn't decrease the occurrence of moderate-to-severe gastroenteritis among children [17]. A similar study by Pediatric Emergency Research Canada showed identical results when they administered a 2-strain combination of *L rhamnosus* R0011 and *L helveticus* R0052 in a 95:5 ratio at a total dose of 4×10^9 CFU twice daily for 5 days [18]. Therefore, the American Gastroenterological Association (AGA) has recommended against the use of probiotics in acute infectious gastroenteritis [19].

Enterococcus faecium SF68 is another studied probiotic to have efficacy in acute diarrhoea [20]. A Cochrane review has reported that this strain reduce the risk of diarrhea (RR 0.21, 95% CI 0.08–0.52) lasting >4 days in 4 RCTs (n=333). Most of these trials are open-labelled and therefore, not considered a strong evidence for recommendation. Moreover, in vitro studies have demonstrated the possibility of transfer of the vancomycin-resistance genes associated with E. faecium SF68 strain. Therefore, the use of E. faecium SF68 strain hasn't been recommended in any clinical guideline.

Certain probiotics have shown positive evidence in the prevention of diarrhoea, especially in antibiotic-associated diarrhoea (AAD). Antibiotic-induced destruction of the normal gut microbiome results in such diarrhoea, which, in general, presents as mild diarrhoea. But in some instances, it leads to severe fatal pseudomembranous colitis, caused by Clostridium difficile infection. Now an obvious query arises whether probiotics get killed by the bacteria if co-administered. There is no scientific evidence to support the claim, moreover, certain strains like S. Boulardii are resistant to antibiotics used for bacterial infections [11].

Evidences showed some strains of probiotics can be useful to prevent antibiotic associated diarrhoea. Lactobacillus rhamnosus GG significantly reduces the risk of AAD (RR 0.48; 95% CI, 0.26-0.89) as per data from 5 different RCTs (n=445). Similar results were found when the effect of S. Boulardii (RR 0.43, 95% CI, 0.30-0.60) was investigated based on 6 RCTs. So, LGG and S. Boulardii have proven efficacy in preventing AAD, regardless of the antibiotic use indication. When C. Difficile-associated diarrhoea was considered, LGG had no significant effect in

prevention [21]. On the contrary, the role of S. Boulardii in risk reduction of C. difficile-induced diarrhea was supported in 2 RCTs (n=579; RR, 0.25; 95% CI, 0.08 to 0.73) [15]. A systemic review and meta-analysis by ESPGHAN WG recommended 2 probiotic strains, LGG and S. Boulardii in preventing AAD, but only S. Boulardii has been suggested for prevention of C. difficile diarrhoea (Conditional recommendation) [22].

Certain groups have advocated routine use of probiotics along with antibiotics, as certain probiotics have proven efficacy, and it can prevent serious and fatal AAD. On the contrary, commercially available probiotics are costlier. Considering both the risks and rewards, probiotic might be beneficial with antibiotics in hospitalized children, younger age groups, and children with at-risk or previous history of C. difficile diarrhoea [23].

Probiotics in Constipation

Constipation is a common problem in children, with a prevalence varying from 0.007% to 29.6% across different studies [24]. Only 10% of them have detectable underlying causes, rest are considered as functional constipation. Functional constipation (FC) is defined as two or fewer defecations per week with at least one episode of fecal incontinence per week, a history of stool retention, or retentive posturing, a history of painful or hard bowel movement, the presence of a large fecal mass in the rectum [25]. FC causes significant dysfunction of both mental and physical health of the children with a cumulative burden of 9.5% globally [26]. Organic constipation requires treatment of the causative conditions, whereas conventional treatment for FC includes non-pharmacological interventions (toilet training, family support, high fibre diet) and pharmacological measures such as laxatives. Studies have shown, 40% of children with FC remain symptomatic despite using laxatives [27], and after initial recovery, 50% have at least one relapse within the first 5 years [28]. Therefore, probiotics are receiving increasing attention as newer modalities in the treatment of childhood functional constipation.

Various probiotics alone, as mixture forms, or with conventional therapy have been investigated in the treatment of childhood FC. A systemic review and meta-analysis of 6 RCTs showed a significant decrease in stool frequency among the Asian children [29]. But the stool consistency didn't show any significant improvement; heterogeneity between the included trials was another limitation worth mentioning. Some isolated studies supported the positive role of various probiotics mixtures on improving defaecation frequency [30-32]. But the sample size of any of the trials wasn't large enough; secondly, the allocation, randomization measures were at fault in most of the studies. Therefore, the results are inconsistent with the findings of systemic reviews and meta-analyses. A systemic review of 16 RCTs investigated the effects of pre-, pro-, synbiotics in treating pediatric FC. It failed to establish any significant improvement in the outcome measures like fecal inconsistency, defecation frequency, and painful defecation [33].

A recent network meta-analysis of 9 RCTs revealed that laxatives co-administered with certain probiotic products show significant improvement in bowel movement and stool frequency compared to placebo. The probiotic products showing some positive effects were: Protexin® (highest improvement; contains Lactobacillus casei PXN 37, Lactobacillus rhamnosus PXN 54, Streptococcus thermophiles PXN 66, Bifidobacterium breve PXN 25, Lactobacillus acidophilus PXN 35, Bifidobacterium infantis PXN 27, and Lactobacillus bulgaricus PXN 39, TVC: 1 billion CFU TVC: 1×10^9), Lactobacillus rhamnosus GG ATCC 53103, Lactobacillus reuteri DSM 17938, Lactobacillus casei rhamnosus Lcr35, Lactobacillus reuteri DSM 17938, and probiotic mixture (Bifidobacteria breve+longum) [34]. But when the efficacy of specific probiotics was individually compared versus the placebo or laxative, only Lactobacillus rhamnosus Lcr35 (mean difference 1.37, 95%CIs=0.32 to 2.43) provided significant improvement in bowel movement or stool frequency. Similarly, the probiotics failed to show any beneficial effects on abdominal pain or stool incontinence [35]. Overall, L. rhamnosus Lcr35, B. longum and L. reuteri DSM17938 showed some positive results whereas *L. rhamnosus GG, B. lactis* strain DN-173 010 were reported to have negative results in FC. Based on such pieces of evidence, no probiotics have been advocated to use in the treatment of childhood functional constipation in the clinical recommendations developed by ESPGHAN and NASPGHAN [27].

Probiotics in Infantile Colic

Infant colic or excessive crying is a physiological phenomenon in infants, affecting around 10–30% of healthy infants and their families worldwide. As per Wessel's criteria, colic is defined as crying or fussing for three hours or more a day, for three days or more per week, for three weeks in infants aged less than three months [36]. Infantile colic is a self-limiting condition, as the symptoms get resolved spontaneously within 3-4 months after birth.

The most studied probiotic in treating infantile colic is *Lactobacillus reuteri* DSM 17938 strain. Evidences suggest that it can reduce the mean crying time of 56 minutes/day in exclusively breastfed infants at the age of 3 weeks [37]. A Cochrane analysis included 5 RCTs which administered 10^8 CFU of *Lactobacillus reuteri* DSM 17938 in breastfed infants (n=388) once daily for 21-18 days, and found that the probiotic can cause 2.3 fold increases in the chance of reduction of daily crying time by at least 50% (p-=0.01) [38]. Similar findings were reported in a larger systemic review including 15 RCTs and five meta-analyses [39]. It involved only term infants with no postnatal complications or major congenital abnormalities, and found to have reduced infantile crying and fussing with *L. reuteri* DSM 17938. However, a trial enrolling predominantly formula-fed infants with abdominal colic couldn't prove the beneficial effects of *L. reuteri* DSM 17938 at a daily dose of 1×10^8 CFU [40].

Some researcher have investigated role of *L. reuteri* DSM 17938 in prevention of infantile colic. This probiotic could show a reduction of crying time of 45 minutes per day, but there was no or little difference in the prevention of colic compared to placebo [41]. *Bifidobacterium breve* BR03 and B632 were administered in

formula-fed infants and showed improvement in crying time, but such supplements showed no differences in the breast-fed children [42]. Interestingly, the results were different in another study with B. Brevis [43].

In a nutshell, *L. reuteri* DSM 17938 can effectively reduce infant colic in breastfed infants. But more evidence is required in formula-fed infants.

Probiotics in Regurgitation

Gastroesophageal reflux (GER) is common in children; about 60% of them have reflux symptoms once a year, 20-30% once a week [44]. Almost all premature babies and most newborns have 2-3 reflux episodes per hour [45]. When the reflux affects the lifestyle of the person, it transitions into gastroesophageal reflux disease (GERD). Symptoms such as, heartburn, upper abdominal pain, food regurgitation, and retching are common in paediatric primary care settings. It is a clinical diagnosis. Montreal Definition and Classification provides the clinical framework for diagnosing gastroesophageal reflux disease (GERD) [46]. The available diagnostic tests are not meant for diagnosing gastroesophageal reflux, but to aid in the management of specific patient.

Studies based on genomic sequencing have focused on the role of the esophageal microbiome in GERD. Some investigators have put more importance on microbial dysbiosis than gastric acid secretion in the development of esophageal mucosal diseases in adults [47]. Emerging evidences suggest that the esophageal microbiome (EM) plays a major role by its interaction with the host immune system [48]. Various factors like, age, diet, use of antibiotics and other medications, oral hygiene, smoking etc. can disrupt the EM. It results in persistent esophageal dysbiosis which generates a host of immunogenic response and ultimately propagates the inflammatory cascade. Researchers have evidence that non-erosive reflux disease is associated with a shift of EM away from *Fusobacteria, Actinobacter spp*., towards *Proteobacteria and bacteroidetes* [47].

L. reuteri DSM 17938 prevents regurgitation during the first month of life in breast-fed term infants. An RCT compared 40 infants who received probiotic supplementation or placebo and showed, when treated with *L. reuteri* DSM 17938, 10^8 CFU daily for four weeks, a decrease in the number of regurgitation episodes a day [49]. Another RCT in 2014 studied the impact of *L. reuteri* DSM 17938 during the first 3 months of life on the onset of colic, reflux and constipation in term children. The study showed a statistical significant difference for regurgitation episodes a day, 2.9 versus 4.6 ($p < 0.01$), in the probiotic and the placebo group, respectively [50].

In a RCT, 42 children with regurgitation were included and divided in a probiotic group and a placebo group. Patients in the probiotic group received 10^8 CFU of *L. reuteri* DSM 17938 per day for 30 days. Parents noted the frequency of regurgitation at home, and gastric emptying time was calculated by an ultrasound at the beginning and the end of the study. The study showed a statistically significant difference in reducing gastric distension, accelerating gastric emptying, and thereby diminishing episodes of regurgitation in patients receiving the probiotic strain [51].

In summary, there is insufficient evidence to recommend a specific strain in the management of regurgitation, although there are some promising data for *L. reuteri* DSM 17938.

Probiotics in Functional abdominal pain and IBS

Functional abdominal pain syndrome (FAPS) is a newly proposed term for recurrent abdominal pain syndrome. FAPS is one of the first recognized functional gastrointestinal disorders in children accounting to around 50% of all paediatric GI clinic visits [52]. In Rome IV criteria, FAP and irritable bowel syndrome (IBS) have been categorized under the umbrella term, functional gastrointestinal disorders (FGID), defined by recurrent abdominal pain for at least 3 months interfering with the quality of life of the child when all the known organic causes have been ruled out [25]. Childhood FAPD is prevalent in around 15% of children [53], resulting in missing school and frequent doctors' visits with significant decline in mental, physical, and emotional health of the children and their families in 80.5% cases [54]. Unfortunately, there in no known treatment modality for FAD; therefore, exploring new treatment modalities is urgently indicated for FAP.

Several trials have investigated the role of Lactobacillus reuteri DSM 17938 in children with FAPD and IBS, but the results were conflicting. L. reuteri DSM 17938 at 10^8 CFU given twice daily for four weeks showed improvement in pain symptoms among children, compared to placebo in a trial on 50 children [55]. On the contrary, a study (n=54) found that frequency and intensity of abdominal pain decrease in both L. reuteri DSM 17938 and placebo [56]. *L. rhamnosus* GG ATCC53103 was another studied strain with significant reduction of pain symptoms in placebo-controlled studies [57,58]. Lastly, a commercially available probiotic mixture of lactobacillus and bifidobacteria strains (L. plantarum, L. delbrueckii subsp. bulgaricus, L. casei, L. acidophilus, B. breve, B. longum, B. infantis and S. salivaris subsp. Thermophilus) was given in children with IBS (N=59) for 6 weeks. It could show significant relief of abdominal pain, bloating and discomfort compared to placebo group, though no significant difference in stool pattern could be observed [59].

Though there are evidences supporting the positive role of probiotics among children with FAP and IBS, majority of the trials have limitations in terms of participant allocations, randomization, and lastly, the sample sizes were too small to propose a scientific recommendation.

Probiotics in necrotizing enterocolitis (NEC)

Necrotizing enterocolitis is a dreadful complication predominantly seen in low-birth weight and premature babies. It presents with abdominal distension, feed intolerance, bloody stool and can lead to fulminant sepsis, intestinal perforation and death, with associated mortality of 25%. Immature gut barrier, prematurity, and dysbiosis have been postulated as the major pathogenesis of

NEC. The role of gut microbiota in the pathogenesis of NEC is controversial to date [14-16]. In treating NEC, probiotics have no proven role, but they can be beneficial to prevent NEC in preterm infants in addition to the introduction of mothers' milk. Till 2010, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Committee on Nutrition did not recommend use of any probiotics in infants less than 1800 g [18]. Thereafter, numerous meta-analyses have been published that investigated the role of probiotics in the prevention of NEC. But, the experimental arm contained a wide variety of different probiotic strains; hence, any definite conclusion couldn't be inferred in most of the analyses.

To overcome such limitations, ESPGHAN Working group performed a network meta-analysis based on a strain-specific review including 51 RCTs involving more than 11000 preterm infants [60]. The study showed, only 3 trials using probiotic mixtures could reduce infant mortality significantly. The administered probiotic mixtures were: B. bifidum strain NCDO 1453 and L. acidophilus NCDO 1748; B. bifidum and L. acidophilus and B. infantis, L. acidophilus, L. casei, L. plantarum, L. rhamnosus and Streptococcus thermophilus. Besides, 7 probiotic combinations showed evidences of prevention of NEC. They were B. lactis BB12 or B94; L. reuteri ATCC 55730 or DSM 17938; L. rhamnosus GG ATCC53103; combination of B. infantis ATCC 15697 and L. acidophilus ATCC 4356; B. infantis BB02, B. lactis BB12 and Streptococcus thermophilus TH-4; and combination of B. longum 35624 and L. rhamnosus GG. The combination of B. bifidum, B. infantis, B. longum and L. acidophilus and the combination of B. longum R00175, L. helveticus R0052, L. rhamnosus R0011 and S. boulardii CNCM I-1079 could prevent late-onset neonatal sepsis in preterm infants. Based on these findings, the ESPGHAN WG proposed a conditional recommendation to use either L. rhamnosus GG ATCC53103; or the combination of B. infantis Bb-02, B. lactis Bb-12, and Streptococcus thermophilus TH-4 in the reduction of the incidence of NEC among preterm neonates, provided the safety concerns are met [61].

A latest network meta-analysis of trials concluded that multi-strain probiotic preparations of *Lactobacillus* subsp. and *Bifidobacterium* subsp. showed better outcomes in preterm, low birth weight (LBW) infants. Probiotic mixtures containing Bacillus subsp., Enterococcus subsp., Bifidobacterium subsp., and Streptococcus thermophilus were associated with less incidence of NEC [62]. The American Gastroenterological Association (AGA) recommended the administration of Lactobacillus spp and Bifidobacterium spp.; or B. animalis lactis; or L. reuteri; or L. rhamnosus GG ATCC53103 in preterm (<37 weeks gestational age), and LBW infants (moderate to high quality evidence) [19]. AGA also expressed their concern regarding the safety issues of probiotics in preterms. Therefore, the dose of administration differs in different centres despite having clear recommendations. Only a few trials have reported adverse events like post-administration *Lactobacillus* or *Bifidobacterium* sepsis among infants [63,64]. Pre-existing short bowel syndrome or immunodeficiency might have a contributing role in developing such adverse reactions. Considering a variable risk-benefit ratio, the American Academy of Pediatrics (AAP) didn't support routine use of probiotics among pre-term infants, especially if birth weight is less than 1000 grams [65].

Probiotics in Pouchitis

Pouchitis is a post-operative complication of total proctocolectomy and ileal pouch-anal anastomosis, a modality of treatment of Ulcerative colitis. Studies showed abundance of Fusobacteriaceae family and reduction of Faecalibacterium is associated with the development and recurrence of pouchitis in children [66]. The role of gut dysbiosis in the pathogenesis has led to interest in the use of probiotics in managing pouchitis.

A meta-analysis of 8 RCTs showed positive role of probiotics in management of pouchitis [67]. An 8-strain probiotic mixture of four strains of lactobacilli, three strains of bifidobacteria, and one strain of streptococcus is found to be beneficial in both prevention and maintenance of remission of pouchitis [68]. All the studies have very low quality of evidences due to small sample size, defects in randomization, allocation error. Therefore, AGA has recommended use of 8-strain probiotic combination in prevention and management of pouchitis [19].

Probiotics in CMPA and Allergic Diseases

Cow milk protein allergy is one of the most frequent food allergies among the children. The incidence of CMPA during the first year of life is estimated to be around 5% [69]. It is a major health concern for the children as it is linked to various other allergic manifestations of later life like, atopic dermatitis or eczema. Based on the pathogenesis and immune-pathogenesis mechanisms, CMPA can be classified as IgE-mediated and non-IgE-mediated. IgE-mediated CMPA can present as a life-threatening anaphylactic shock, immediately after ingestion of the offending food. Whereas the latter presents as a delayed reaction to an allergic food protein, causing proctocolitis and enteropathy [70].

Recent studies have reported that the exaggerated immune response to food protein is modulated by the gut microbiota. Disruption in the gut microbiota during early life increases the risk of food allergy; therefore, gut dysbiosis has been hypothesized as a triggering factor of various childhood allergic diseases, including CMPA [71]. Fecal microbiota profiling revealed an abundance of Bacteroids among children with CMPA, with reduced Bifidobacterium, Ruminococcus, Faecalibacterium, and Parabacteroides [72]. Considering the role of gut dysbiosis in pathogenesis, Probiotics have been proposed as a promising strategy to prevent and treat CMPA. In 2015, the World Allergy Organization (WAO) advocated a prophylactic benefit of the use of probiotics among pregnant and lactating women whose infants are at high risk of developing allergy [69]. A systemic review of 29 trials concluded that probiotic supplements have significant benefits in the reduction of eczema, but such results weren't consistent in other allergic conditions [73]. Another review by the European Academy of Allergy and Clinical Immunology (EAACI)

didn't support the use of probiotics in preventing food allergy [74]. Both studies were non-specific regarding the probiotic strain, dosage, and duration probiotic use. *L. rhamnosus* GG is probably the most studied strain with evidence of a positive role in treating atopic dermatitis, according to a meta-analysis of 28 studies [75]. However, another meta-analysis investigating the role of *L. rhamnosus* GG ATCC53103 couldn't find any evidence of reduced risk of developing atopic eczema [76]. Lastly, a Cochrane review found no difference in improving the symptoms of atopic eczema when Lactobacillus or Bifidobacteria species, alone or in combination, were administered for 4 weeks to 6 months [77].

In a nutshell, no high quality scientific evidence of therapeutic or prophylactic role of any probiotics is available in the literature. However, a certain strain of *L. rhamnosus* GG has shown some promising results, but more trials are required for a strong recommendation.

Probiotics in Infant Formula

The fetus stays in a sterile environment in the mother's womb; the first contact to external microbes occurs during the delivery. studies have shown that he infants born by virginal delivery have more diverse gut microbes compared to those with caesarean section. Therefore, the first contact of newborns has an important role in determining the overall health status and immunity of the baby, and it can be crucial in preventing various immune-mediated diseases in later life [78]. Next, the gut gets exposed to various microbes during breastfeeding. Early feeding and the type of feeding is, therefore, an important factor that modulates the ecosystem of gut microbes. Mother's milk (MoM) contains a number of live bacteria, including bifidobacterium, lactobacillus, etc. that help in a child's growth and healthy development [79]. Additionally, MoM facilitates "prebiotic effect" as it consists of more than 150 oligosaccharides that undergo fermentation in the baby's colon and trigger the growth of different symbiotic bacteria in the faeces. The study has shown that the microbiota of formula-fed infants resembles that of adults, containing genes related to bile acid synthesis and methanogenesis [80].

Such differences in gut microbiota between exclusively breastfed and formula-fed infants had lead to the concept of supplementation of infant and follow-up formulas with probiotics. The committee of Nutrition of ESPGHAN investigated the efficacy of probiotic-supplemented infant formulas and their safety concerns in a systemic review. It couldn't find any strong evidence to recommend routine use of such a formula for infant growth [81]. Later in 2017, another review, based on contemporary trials, advocated the possibilities of reduction of frequency and severity of gastrointestinal and respiratory infections among children fed with supplemented formulas [82]. However, the evidence was of very low quality, and there were multiple loopholes in the methodology of those trials. Another recent systemic review and meta-analysis couldn't reveal any significant differences in the abundance of Bifidobacterium (Mean difference: 0.13; 95% CI, –0.09 to 0.35; I^2=20%; P=.23) and Lactobacillus spp. (MD: 0.27; 95% CI, –0.05 to 0.59; I^2=41%; P=.10) in the guts of probiotic formula-fed and standard formula-fed infants [83]. Lastly, a latest network meta-analysis could identify only a marginal reduction of in the numbers of diarrhoeal episodes with a relative risk (RR) of 0.85, (95% CI, 0.75-1.02, p>0.05) when infant formulas were supplemented with 7 different combination of probiotics like B. longum BL999, B. lactis, B. infantis, B. breve and L. fermentum. Similarly, different combinations of these probiotics had an insignificant reduction in the duration of diarrhoea [84]. Therefore, despite having some isolated studies advocating the positive impact on infections and overall health, it lacks strong evidences to support routine use of probiotic-supplemented infant formula.

Various probiotics that have been used in commercial formulas or experimentally are found to carry the antimicrobial resistant genes (ARGs), causing a considerable public health risk. Studies have shown that the probiotics transmit ARGs to commensals in the gut microbiota. It forms a reservoir of ARGs in the gut and thus risks exposure of such ARGs in opportunistic pathogens. Till now, the probiotic-transmitted ARGS are known to be responsible for resistance against tetracycline, macrolides, aminoglycosides, and glycopeptides [4]. Therefore, it is important to regulate the commercial availability and distribution of probiotics, especially the mixture forms, based on proper scientific evidence.

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