

Review Article

The world of synbiotics: a review of literature and clinical evidence in diarrhoea from the lens of a paediatrician

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ABSTRACT

The use of synbiotics in the management of acute diarrhoea in children is becoming a common practice in India. However, since this is an upcoming modality of treatment, it is essential to review the scientific rationale and evidence on clinical efficacy and safety in the context of paediatric diarrhoea. In addition, most synbiotics contain a combination of multiple probiotics along with a prebiotic. Thus arises, a parallel need to understand whether a combination of probiotics performs better than single probiotics, hence justifying the rationale for such combinations. A review of available evidence suggests that synbiotics are indeed safe and superior in efficacy to single probiotics (like *Bacillus clausii*, *Lactobacillus rhamnosus* GG etc) and that there is a good body of evidence to support the efficacy and tolerability of synbiotics in the management of paediatric acute gastroenteritis. There is also evidence to suggest that combination probiotics have superior benefits compared to single probiotics, thus justifying their use as part of synbiotics. The overall benefits of synbiotics reported in various clinical trials on paediatric diarrhoea include, a rapid normalization of the gastrointestinal flora, a reduction in the duration of diarrhoea, quicker improvement in stool consistency, lesser administration of additional medications like antibiotics, antiemetics and antipyretics, higher physician reported treatment satisfaction scores and enhanced overall efficacy against gastrointestinal pathogens, including diarrhoea of rota virus origin. Hence, synbiotics put up a strong case to look beyond probiotics and single probiotic formulations in paediatric diarrhoea.

Keywords: Combination probiotics, Diarrhoea, Multi-strain probiotics, Prebiotics, Probiotics, Synbiotics

INTRODUCTION

The concept of synbiotics is exciting and the clinical application of synbiotics in the management of acute diarrhoea in children is becoming a common practice in our country. However, it is not without some amount of skepticism on the scientific rationale and presumed lack of documented evidence on clinical efficacy and safety in the target population and indications. In addition, most synbiotics carry a combination of multiple probiotics along with a prebiotic. There is also a need to understand if a combination of probiotics performs better than single probiotics, hence justifying the underlying rationale for combination and also understanding the mechanisms for

achieving the same. Hence, this review aims to address the following questions on synbiotics and combination probiotics and thereby clarify and establish the role of synbiotics in the context of management of diarrhoea, with special focus on paediatric age group.

- What are synbiotics and their clinical applications?
- What is the rationale and benefit of synbiotics?
- What is the rationale and benefit of combining multiple probiotic organisms over single probiotic products?
- What is the available clinical evidence on the efficacy and tolerability of synbiotics in children with acute diarrhoea?

Are there any clinical studies demonstrating the superiority of synbiotics over probiotics and other agents used in the management of acute diarrhoea in children?

Synbiotics and their clinical applications

Synbiotics are a combination of probiotics and prebiotics and are formulated in order to overcome some possible difficulties in the survival of probiotics in the gastrointestinal tract. Therefore, an appropriate combination of both components in a single product is expected to ensure a superior effect, compared to the activity of the probiotic or prebiotic alone.¹ Synbiotics have been studied for use in several indications like obesity, insulin resistance, type 2 diabetes mellitus, non-alcoholic fatty liver disease, irritable bowel syndrome, inflammatory bowel diseases, diarrhoea, dysentery, constipation, atopic dermatitis and other conditions like lactose intolerance.¹

RATIONALE AND BENEFITS OF SYNBIOTICS

Rationale of synbiotics¹

Prebiotics are used mostly as a selective medium for the growth of a probiotic strain, fermentation, and intestinal passage. A probiotic is essentially active in the small and large intestine, and the effect of a prebiotic is observed mainly in the large intestine. It has been reported that, due to the use of prebiotics, probiotic microorganisms acquire higher tolerance to environmental conditions, including: oxygenation, pH, and temperature in the intestine of a particular organism. Hence, the combination of the two is expected to have a synergistic effect.

Two modes of synbiotics action are known:

- Action through the improved viability of probiotic microorganisms;
- Action through the provision of specific health effects.

The stimulation of probiotics with prebiotics results in the modulation of the metabolic activity in the intestine with the maintenance of the intestinal biostructure, development of beneficial microbiota, and inhibition of potential pathogens present in the gastrointestinal tract. Synbiotics may confer additional benefits over a probiotic by increasing bifidobacteria levels in the intestine.² Synbiotics result in reduced concentrations of undesirable metabolites, as well as the inactivation of nitrosamines. Their use leads to a significant increase of levels of short-chain fatty acids, ketones, carbon disulphides, and methyl acetates, which potentially results in a positive effect on the host's health.

Benefits of Synbiotics in diarrhoea^{2,3}

- Rapid normalization of the gastrointestinal flora.²

- Reduction in the duration of diarrhoea.
- Quicker improvement in stool consistency.²
- Lesser administration of additional medications like antibiotics, antiemetics and antipyretics.²
- Higher physician reported treatment satisfaction scores.²
- Enhanced overall efficacy against GI pathogens.³
- Clinical efficacy in diarrhoea of rota virus origin also.⁴⁻⁶

Combination of probiotics are superior to single probiotics: rationale and clinical evidence

Rationale of combination probiotics superiority

Combination of multiple probiotic organisms are superior to single probiotics in various clinical conditions including diarrhoea. Vandenas et al reported a review of 16 studies, where the effects of combination probiotics were compared with that of their component probiotic strains separately. In 75% (12) of these studies, the combination of probiotics was found to be more effective than the single probiotics. However, in a few studies, the single probiotics was equally or slightly more effective than the combination.² Thus, overall there is merit in preferring combination probiotics over single probiotics. The probable reasons for the combination probiotics to perform better than single probiotics are multi fold. Listed below are some benefits derived due to synergism between the different probiotics present in a combination probiotic.

Improved probiotic adherence

There is evidence to suggest that intestinal adherence of one probiotic can be enhanced by the presence of other probiotics. Better adherence of probiotics to the intestinal epithelium can lead to more IgA secretion and also greatly enhances successful colonization of combination probiotics.

This feature additionally helps promising probiotic species such as representatives of the Propionibacterium genus, which by themselves would be considered as non-probiotic, because of their low adhesiveness. Juntunen et al demonstrated that B.Bb12 probiotic strain has better adherence in the presence L.rhamnosus GG.² Similarly, Ouwehand et al reported that the presence of L. rhamnosus GG or L. delbrueckii subsp. Bulgaricus more than doubled the adhesion of Bifidobacterium animalis BB-12, while the adhesion of Propionibacterium freudenreichii P6 was more than tripled by the presence of L. rhamnosus GG and almost doubled by the presence of B. animalis BB-12.³

Decreased pathogen adherence

Adhesion to intestinal mucosal surface is an important step in pathogenic infection. Collado et al, using an in

in vitro intestinal epithelial model demonstrated that combination probiotics have almost 40% higher effectiveness compared to single probiotics, in inhibiting pathogen adhesion to the intestinal mucus lining and hence influence their colonization.

The study results additionally reported that the combination of probiotics (especially a combination of *L. rhamnosus* GG, LC 705, *B. breve* 99 and *Propionibacterium* JS) demonstrated properties like displacement and competing behaviours against model pathogens.⁷

Increased antimicrobial coverage

Chapman et al, in an in vitro study comparing 15 single and 5 probiotic combinations showed that combination probiotics had a greater inhibition of pathogens compared to single probiotics in 50% of the cases when tested at approximately equal concentrations of biomass.

This is in contrast to reports that probiotic species may inhibit each other when incubated together.

The single and combination probiotics were studied to check their inhibition of pathogens like *Clostridium difficile*, *Escherichia coli* and *S. typhimurium*, using the agar spot test.

Thus, using combination probiotics might be more effective at reducing gastrointestinal infections, and that creating a combination using species with different effects against different pathogens, may have a broader spectrum of action than that provided by a single probiotic.⁸

Inhibition of intestinal cell inflammation

Intestinal epithelial cells (IEC) act as a physical barrier and the first line of defence against pathogens and pathogen-associated molecular patterns (PAMPs) at the gut mucosal level and are an active participant in the host-microbiota cross-talk.

MacPherson et al demonstrated in a vitro IEC cell model using genome wide transcription analysis, a synergistic effect of the probiotic combinations relative to the single probiotics in resolving inflammation in IEC and maintaining cellular homeostasis, thus reinforcing the rationale for using combination probiotic formulations.⁹

Higher dose

While there is evidence to demonstrate the positive interaction between different probiotics in a mixture, the improvement in the overall effectiveness of combination probiotics as compared to individual probiotics could be also due to the overall higher dose of probiotics in the combination.²

Positive effect on promoting eubiosis

Zoppi et al, through a study in 51 children treated with an antibiotic, compared single probiotics with combination probiotics and reported that combination probiotics had the highest impact on the change in the gastrointestinal microflora composition.

Further, probiotics containing multiple species of Lactobacilli and Bifidobacteria were reported to be more effective in preventing dysbiosis as well as countering the stool frequency increase induced by the antibiotic treatment compared to other probiotic preparations.³

Decrease in stool pH

An acidic environment inhibits the growth of pathogenic bacteria and reduces bacterial putrefactive activity. Zoppi et al, through a study in children treated with an antibiotic, compared single probiotics with combination probiotics and reported that only combination probiotics produced a statistically significant reduction in the stool pH (considered as a positive effect) as compared to single probiotics.³

Clinical Evidence on combination probiotics Vs single probiotics

Canani et al, compared the efficacy of 4 single probiotics and 1 combination probiotic in a study enrolling 571 children aged 3-36 months suffering from diarrhoea.

The four single probiotics studied were *Lactobacillus rhamnosus* strain GG(LGG), *Saccharomyces boulardii*, *Bacillus clausii* and *Enterococcus faecium* SF68. The combination probiotic product contained a mix of 4 probiotics i.e. *L. delbrueckii* var *bulgaricus*, *Streptococcus thermophilus*, *L. acidophilus*, and *Bifidobacterium bifidum*.

The median duration of diarrhoea was shortest in the combination probiotic group (70.0 hours; $P < 0.001$) followed by children who received LGG (78.5 hours; $P < 0.001$) and not statistically significant in all the other groups.

One day after the first probiotic administration, the daily number of stools was significantly lower ($P < 0.001$) in children who received LGG and in those who received the combination probiotic than in the other groups. The remaining preparations did not affect primary outcomes.¹⁰

Other studies that administered multiple species products found a rather more pronounced effect, i.e. a 30-hour reduction (Cucchiara et al., 2002; Szymanski et al., 2006) and 30-36-hour reduction in diarrheal duration (Pham et al., 2008; Htwe et al, Billoo et al, Kurugol and Koturoglu).

These results also support the effect of probiotics on vomiting, showing decreased time of vomiting in the intervention groups as compared with controls (0 vs 40h). However, only in the multiple species' product-treated group did the shorter time of vomiting reach significance.¹⁰

Clinical evidence on the safety and efficacy of synbiotics in paediatric diarrhoea management

There are several clinical studies demonstrating the efficacy and tolerability of synbiotics in the management of acute diarrhoea in children. While some of these are non-comparative single arm clinical studies others are well designed placebo-controlled studies or studies with an active comparator. Table 1 (a, b, c, d) lists brief details of all the clinical studies where a synbiotic was studied in paediatric diarrhoea.

The results of these studies clearly demonstrate the efficacy and tolerability of synbiotics in the management of acute diarrhoea in children. Overall, there is evidence to suggest that synbiotics reduce the duration of diarrhoea, reduce stool frequency, improve stool consistency and reduce the requirement of additional medications. Evidence also favours the efficacy and use of synbiotics in diarrhoea irrespective of the underlying cause, antibiotic associated diarrhoea, rota-virus diarrhoea etc.

Review of clinical evidence comparing synbiotics with probiotics and other commonly used agents in diarrhoea

While details listed in the previous section and Table 1 establish the efficacy and tolerability of synbiotics in the management of paediatric diarrhoea, it would be interesting to see how synbiotics fare in terms of efficacy and overall benefits, when compared to some of the very commonly employed or guideline recommended treatment modalities and probiotics. ORS and Zinc are recommended by IAP11 as well ESPGHAN guidelines in the management of paediatric diarrhoea.¹² In addition, certain probiotics like *B. clausii*, *S. boulardii*, *L. rhamnosus* are commonly used as single probiotics in the management of paediatric diarrhoea. ESPGHAN guidelines have a strong recommendation for the use of *S. boulardii* and *L. rhamnosus GG* in the management of paediatric diarrhoea, as an adjunct to rehydration therapy.¹² The subsequent section reviews the clinical studies on the efficacy of synbiotics compared to each of these agents, i.e. *B. clausii*, *S. boulardii*, *L. rhamnosus* and Zinc.

Clinical trial evidence: Synbiotic Vs Probiotic Bacillus clausii¹³

The comparative efficacy of a synbiotic and the single organism probiotic product containing *Bacillus clausii*

spores was studied by Bastola et al, in an RCT enrolling 100 children aged 6 months to 6 years, suffering from acute diarrhoea. The children were randomized to receive either a synbiotic combination product containing a prebiotic (details not reported) and four probiotic organisms (*Streptococcus faecalis* T-110-30 million, *Clostridium butyricum* TO-A - 2 million, *Bacillus mesentericus* TO-A-1 million, *Lactobacillus sporogenes* - 50 million) twice daily for a week or the single organism probiotic - *Bacillus clausii* (2 billion spores / 5mL) twice daily for a week. Standard therapy (ORT and Zinc) were administered to both groups. The study results highlighted a statistically significant superiority in the efficacy of the synbiotic over the *Bacillus clausii* probiotic, both in terms of frequency and mean duration of diarrhoea.

While the frequency of diarrhoea in the synbiotic group reduced from 9.03 on day 1 to 0.81 on day 3, [91% decrease] the frequency of diarrhoea in the *Bacillus clausii* group reduced from 10.1 on day 1 to 6.24 [38% decrease] on day 3 ($P < 0.02$). Similarly, the mean duration of diarrhoea in the synbiotic group was 36.2 hours [~50% less than *B. clausii* group), as compared to 72.6 hours in the *Bacillus clausii* group ($P < 0.001$).

None of the children had dehydration on day 3 of the study. The study results suggest that the synbiotic is significantly superior to the probiotic *Bacillus clausii* in the management of pediatric acute diarrhoea.

Clinical trial evidence: Synbiotic Vs Probiotic Lactobacillus rhamnosus GG^{12,14,15}

Lactobacillus paracasei B 21060 is a novel strain of lactobacillus isolated from the faeces of breastfed babies. In Table 1, a placebo-controlled trial demonstrating the superior efficacy of a synbiotic (containing the probiotic *Lactobacillus paracasei* B 21060, 2.5 X 10⁹ CFU and the prebiotics arabinogalactan 500 mg, and xilooligosaccharides 700 mg) in the management of acute diarrhoea in children has already been discussed.

Lactobacillus rhamnosus GG is a probiotic strain that is considered to be effective in the management of acute diarrhoea in children and it also has strong recommendation for use in such cases by ESPGHAN 2014 guidelines also. In this backdrop, the results of yet another interesting clinical study, further strengthen the case of superiority of synbiotics over probiotics, only this time the compared probiotic is LGG, which further makes the review of this study results more important.

Grossi et al compared the therapeutic efficacy and tolerability of the synbiotic product (*Lactobacillus paracasei* B21060, 2.5 X 10⁹ CFU, arabinogalactan 500 mg, and xilooligosaccharides 700 mg) with *Lactobacillus rhamnosus GG* in 174 patients with acute diarrhoea.

Table 1a: Clinical trials evaluating the efficacy and tolerability of synbiotics in diarrhoea patients.

Investigators	Study design	Treatment arms	Sample size	Age group	Treatment duration	Results
EC. Dinleyici et al ¹⁸	RCT-2 arm Single blind	Synbiotic Vs Control Synbiotic: 2.5×10 ⁹ CFU live bacteria including L.acidophilus, L.rhamnosus, B.bifidum, B.longum, E.faecium, and fructooligosaccharide 625 mg	n=209	3 month - 10 years	5 days	The duration of diarrhoea was significantly shorter (~36 h) in children receiving the synbiotic group than the controls (77.9±30.5 vs. 114.6± 37.4 h, p<0.0001). The duration of hospitalization was shorter in children receiving the synbiotic group (4.94±1.7 vs. 5.77±1.97 days, p=0.002). The percentage of diarrhoea-free children is significantly higher in synbiotic group at 48th and 72nd hours of synbiotic group.
A. Passariello et al ¹⁵	RCT-2 arm Double blind	Synbiotic Vs Placebo Synbiotic: 2.5×10 ⁹ CFU L. paracasei B21060, Arabinogalactan 500 mg, Xilooligosaccharides, 700 mg	n=107	3-36 months	5 days	Resolution rate of diarrhoea at 72 h was significantly higher in synbiotic group (67%) compared to placebo group (40%, P = 0.005). Children in synbiotic group showed a significant reduction in the duration of diarrhoea (90.5 h, 78.1–102.9 vs. 109.8 h, 96.0–123.5, P = 0.040), daily stool outputs (3.3, 2.8- 3.8 vs. 2.4, 1.9-2.8, P = 0.005) and stool consistency (1.3, 0.9–1.6 vs. 0.6, 0.4–0.9, P = 0.002) compared to placebo group. Rate of parents that missed at least one working day (41.8% vs. 15.4%, P = 0.003). Rate of children that needed adjunctive medications (25.5% vs. 5.8%, P = 0.005) or hospitalisation (10.9% vs. 0%, P = 0.014) after the first 72 hour of treatment, were reduced in synbiotic group.

In this RCT, both the products were administered according to their standard recommended dosage for a duration of 10 days. The mean duration of diarrhoea reported in the synbiotic group was 4.24 ± 2.73 days versus 5.09 ± 3.72 days in the LGG group, P=0.09. However, comparison of the clinical success rates in terms of absence of abdominal pain and absence of diarrhoea (defined as <2 bowel movements of watery or loose stool consistency) recorded at different time-points, were statistically superior in the synbiotic group (Kaplan-

Meyer P=0.05 for both the symptoms). Also, the physician rating for overall efficacy was ‘good’ or ‘very good’ in 91.8% of the patients in the synbiotic group, compared to 83.7% in the LGG group, P=0.003. The study thus concluded that the synbiotic is more effective than LGG and has a good tolerability profile in the management of diarrhoea. In the context of this review, it must be noted that the study population enrolled was adults. However, the efficacy and tolerability of the same synbiotic has already been demonstrated in children age group in another study by Pasariello et al.

Table 1b: Clinical trials evaluating the efficacy and tolerability of synbiotics in diarrhoea patients.

Investigators	Study design	Treatment arms	Sample size	Age group	Treatment duration	Results
Rizwan R. et al ¹⁹	RCT-2 arm Double blind	Synbiotic Vs Placebo Synbiotic: 1×10 ⁹ CFU L. casei, L. rhamnosus L. acidophilus L. bulgaricus B. breve B. infantis S. thermophiles	n= 102	3-60 months	5 days	In the synbiotic group, a more rapid improvement in the stool texture and average stool remission time was seen significantly better as compared to control group. Similar results were also seen in stool remission, where there was a significant decrease in synbiotic group. The average duration of stool remission time in the synbiotic group was 41.53 hours. This was significantly different when compared to control group average time of 74.94 hours.
MD Ratna et al ⁴	RCT-2 arm Double blind (Confirmed Rota Virus diarrhea)	Synbiotic Vs Placebo Synbiotic: 1.x10 ⁹ CFU Lactobacillus sp. Streptococcus sp. Bifidobacterium sp. Fructooligosacharide (FOS). 990.00 mg	n=70	6-59 months	5 days	The median duration of diarrhea in the synbiotic group was 50.0 (SE 1.1); 95%CI 47.9 to 52.1 hours, while that of the placebo group was 63.0 (SE 5.9); 95%CI 51.4 to 74.6hours. (Kaplan Meier survival analysis, P <0.0001)
EG Menor et al ²⁰	RCT-2 arm Open label Suspected viral diarrhoea	Synbiotic Vs Control Synbiotic: 1×10 ⁹ CFU L casei PXN 37 L. rhamnosus PXN 54 S. thermophilus PXN 66 B. breve PXN 25 L. acidophilus PXN 35 B. infantis PXN 27 B. bulgaricus PXN39 Fructooligosaccharide	n=85	6 months -12 years	7 days	The proportion of patients without diarrhea over the study period was greater in the synbiotic group than in the control group at all study time points, showing a statistically significant difference on the fifth day (95% vs 79%, p < 0.001). The duration of diarrhoea (median and interquartile range) was reduced by 1 day in the synbiotic-treated patients (3 [2-5] vs 4 [3-5], p = 0.377). The tolerability of the treatment regimen, as evaluated by the parents, was significantly better in those receiving the synbiotic than in the control group. Overall, 96% of the parents of children receiving the synbiotic reported being satisfied to very satisfied with the treatment regimen.

Clinical trial evidence: Synbiotic Vs Zinc¹⁶

In a one of its kind study conducted by Yazar et al, the clinical efficacy of synbiotics was compared with zinc in

the management of acute diarrhoea in 165 children, 6 months to 120 months old. In this RCT, the children were randomized into three arms, the synbiotic group (1 sachet synbiotic / day + ORS + I.V therapy, if required), the zinc

group (zinc suspension 15mg / day + ORS + I.V therapy, if required) and the control group (only ORS + I.V therapy, if required). The synbiotic used in the study contained the probiotics *L. casei*, *L. rhamnosus*, *L. plantarum*, *B. lactis* (4.5×10⁹ CFU in total), prebiotics such as fructose and galacto oligosaccharides and polydextrose (1996.57 mg). The effect of both synbiotics and zinc started to be observed after 48 hours. With respect to the duration of diarrhoea, no statistically significant difference was observed between the synbiotic and zinc groups (91.0±28.9 hours vs. 86.4±30.8 hours, p>0.05, respectively).

While at 72hours, there were less children with diarrhoea in the zinc group compared to the synbiotic group (~45%

Vs ~62% respectively, P <0.05), at the end of evaluation (120 hours) there were less children with diarrhoea in the synbiotic group compared to the zinc group (~7% Vs ~11% respectively, P>0.05). Overall, the duration of diarrhoea was significantly reduced in both the synbiotic and the zinc groups compared to the control group (91.0±28.9 hours vs. 114.3±30.9 hours, p<0.001; 86.4±30.8 hours vs. 114.3±30.9 hours, p<0.001, respectively).

The investigators thus concluded that, both zinc or synbiotic supplementation reduced the duration of diarrhoea, with better clinical outcomes at 72 and 96 hours, and both can be used in children with acute diarrhoea.

Table 1c: Clinical trials evaluating the efficacy and tolerability of synbiotics in diarrhoea patients.

Investigators	Study design	Treatment arms	Sample size	Age group	Treatment duration	Results
Expedito T. Yala ²¹	RCT-2 arm Single blind	Synbiotic vs Control Synbiotic: 1×10 ⁹ CFU <i>L. casei</i> PXN 37 <i>L. rhamnosus</i> PXN 54 <i>S. thermophilus</i> PXN 66 <i>B. breve</i> PXN 25 <i>L. acidophilus</i> PXN 35 <i>B. infantis</i> PXN 27 <i>B. bulgaricus</i> PXN39 Fructooligosaccharide	n=51	2 months- 2 years	5 days	The synbiotic group had a significant decline in purging rate—as early as the second day—which is almost half the purging rate in the control group. Although both groups showed improvement in stool consistency, the synbiotic group showed significant improvement on the second hospital day. The experimental group had a significantly shorter course of hospitalization of at least one day.
De Hert et al ²	RCT-2 arm Double blind	Synbiotic Vs Placebo Synbiotic: 19.5 X 10 ⁹ CFU <i>S. thermophilus</i> 60 mg <i>L. rhamnosus</i> 28 mg <i>L. acidophilus</i> 28 mg <i>B. infantis</i> 20 mg <i>B. lactis</i> 20 mg Fructo-oligosaccharides 20 mg	n=111	3 months- 186 months	7 days	The median duration of diarrhoea was 3 days (IQ 25–75: 2–4 days) in the synbiotic group, compared with 4 days (IQ 25–75: 4–5 days) in the placebo group (P < 0.005). The number of children with normal stool consistency (defined as stool Bristol score ≤4) was higher in the synbiotic group on days 2 and 3 [21 vs. 2% (P < 0.001) and 50 vs. 24% (P < 0.001) respectively]. Less additional medication (antipyretics, antiemetics, antibiotics) were administered in the synbiotic group. Physicians were globally more satisfied with the synbiotic food supplement treatment than with placebo (P = 0.005).

Table 1d: Clinical trials evaluating the efficacy and tolerability of synbiotics in diarrhoea patients.

Investigators	Study design	Treatment arms	Sample size	Age group	Treatment duration	Results
D.Narayanappa ⁵	RCT-2 arm Double blind	Synbiotic Vs Placebo Synbiotic: Not reported*	n=80	2 months- 3 years	14 days	The median duration of diarrhoea was 4.35 days in the synbiotic group, compared with 5.45 days in the placebo group (P=0.001). The mean duration of IVF administration, (which can reflect the duration of dehydration) was 4 days for the Synbiotic group and 9 days for the placebo group (P=0.03). In the Synbiotic group, only 2 patients showed rotaviral shedding in the faeces [positive for rotaviral antigen] at the time of discharge whereas, in the placebo group, 9 patients showed rotaviral shedding in the faeces [positive for rotaviral antigen] at the time of discharge group (p=0.04).
Gundogdu Z ²²	Abstract					
Ali İşlek, Ersin Sayar et al ⁶	RCT-2 arm Double blind (Rota Viral Diarrhoea)	Synbiotic Vs Placebo Synbiotic: B. lactis B94 – 5 X10 ¹⁰ CFU Inulin – 900mg	n= 156	2-60 months	5 days	The duration of diarrhoea was significantly reduced in the synbiotic group in comparison with the placebo group (3.9±1.2 days vs. 5.2±1.3 days, respectively; p<0.001). The number of diarrheal stools on the third day was significantly lower in the synbiotic group than in the placebo group (5.5±2.9 vs. 8.3±3.01, respectively; p<0.001). Diarrhoea in the synbiotic-group patients with rotavirus infection was of a significantly shorter duration (3.2±1.3 days vs. 5.2±1.3 days, respectively; p=0.001). Duration of diarrhoea in patients who started the synbiotic treatment within the first 24h was shorter than that in the patients who started the treatment later (3.9±1.1 days vs. 4.8±1.8 days, respectively; p=0.002).

Clinical trial evidence: Synbiotic vs Probiotic *Sacharomyces boulardii*

At the time of this review, there were no clinical studies comparing the efficacy of a synbiotic with *S. boulardii*.

Safety of Synbiotics in children

Nieuwboer et al reported the results of a study aimed to systematically evaluate safety of probiotics and synbiotics in children ageing 0-18 years. In the eligible 74 studies, a total of 15,885 participants were randomly

allocated to the treatment and control arms. In the treatment arm, 8,472 participants were subjected to a probiotic and/or synbiotic treatment, with a drop-out of 7.96%, resulting in a per-protocol population of 7,798 participants. The results indicated that probiotic and/or synbiotic administration in children is safe with regard to the specific evaluated strains, dosages and duration.

The population of children include healthy, immune compromised and obese subjects, as well as subjects with intestinal disorders, infections and inflammatory disorders.

This study revealed no major safety concerns, as the adverse events were either unrelated, or not suspected to be related, to the probiotic or synbiotic product.

Overall, AEs occurred more frequent in the control arm compared to children receiving probiotics and/or synbiotics. In general, the study products were well tolerated.¹⁷

CONCLUSION

Synbiotics are a combination of probiotics and prebiotics. It has been reported that, due to the use of prebiotics, probiotic microorganisms acquire higher tolerance to environmental conditions, including: oxygenation, pH, and temperature in the intestine of a particular organism. Hence, the combination of the two is expected to have a synergistic effect. A review of available evidence suggests that synbiotics are indeed safe and superior in efficacy to single probiotics (like *Bacillus clausii*, *Lactobacillus rhamnosus* GG etc).

There is a good body of evidence to support the efficacy and tolerability of synbiotics in the management of paediatric acute gastroenteritis. There is also evidence to suggest that combination probiotics have superior benefits compared to single probiotics, thus justifying their use as part of synbiotics. The overall benefits of synbiotics reported in various clinical trials on paediatric diarrhoea include, a rapid normalization of the gastrointestinal flora, a reduction in the duration of diarrhoea, quicker improvement in stool consistency, lesser administration of additional medications like antibiotics, antiemetics and antipyretics, higher physician reported treatment satisfaction scores and enhanced overall efficacy against gastrointestinal pathogens, including diarrhoea of rota virus origin. Hence, there is a need to re-evaluate the recommendations for management of paediatric diarrhoea by various bodies like IAP, ESPGHAN, WHO etc., as synbiotics put up a strong case to look beyond probiotics and single probiotic formulations in the management paediatric diarrhoea.

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