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The Effect of Synbiotic-Enhanced Formula on Rates of Infection in Infants

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Abstract

Background: The function of prebiotics and probiotics, both individually and synergistically (synbiotics) has been a growing area of interest in health and medicine in recent years. For much longer, the search to best replicate human breast milk as infant formula continues to challenge scientists and researchers. Naturally, the question as to whether or not probiotics and prebiotics play a role in improving the replication of breast milk has come into the research spotlight. In particular, studies have begun to look at how synbiotics may play a role in the infant immune system and rates of infections.

Methods: An exhaustive search of available medical literature was conducted using Web of Science, PubMed-MEDLINE, CINAHL and ProQuest. Key words included: infant, synbiotic, prebiotics and probiotics and respiratory tract infection. Studies were evaluated for quality using the GRADE criteria.

Results: Of the 27 studies found during preliminary screening, 2 articles met all inclusion criteria to be included in this review. One study found no significant difference in rates of infection between synbiotic and control groups. Another study found a lower rates or respiratory and GI infections in the synbiotic group compared to the prebiotic-only control group.

Conclusion: Research at this time cannot definitively state that synbiotic-enhanced formula is superior in protecting full term infants from respiratory or GI infection. However, evidence does suggest that certain strains of probiotics and types of prebiotics could help in reducing rates of these infections if further research can confirm initial findings.

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The Effect of Synbiotic-Enhanced Formula on Rates of Infection in Infants

Katherine Geller

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Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

[redacted]
Abstract

Background: The function of prebiotics and probiotics, both individually and synergistically (synbiotics) has been a growing area of interest in health and medicine in recent years. For much longer, the search to best replicate human breast milk as infant formula continues to challenge scientists and researchers. Naturally, the question as to whether or not probiotics and prebiotics play a role in improving the replication of breast milk has come into the research spotlight. In particular, studies have begun to look at how synbiotics may play a role in the infant immune system and rates of infections.

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Keywords: Synbiotic, probiotics, prebiotics, infant formula, respiratory tract infection
Acknowledgements

To my professors, preceptors and mentors: Thank you for believing in me, supporting and encouraging me and helping me to achieve my goals.

To my family and friends: Thank you for getting me here. I would never have made it this far without each and every one of you.

“Let food be thy medicine and medicine be thy food”

-Hippocrates
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List of Abbreviations

AAP American Academy of Pediatrics
AEs Adverse events
BMOS Bovine milk-derived oligosaccharide
B. lactis Bifidobacterium animalis ssp lactis
ESPGHAN European Society of Pediatric Gastroenterology Hepatology and Nutrition
GI Gastrointestinal
GOS Galactooligosaccharide
HMOS Human milk oligosaccharides
IOM Institute of Medicine
L. fermentum Lactobacillus fermentum CECT5716
SCFA Short chain fatty acid
USFDA United States Food and Drug Administration
The Effect of Synbiotic-Enhanced Formula on Rates of Infection in Infants

BACKGROUND

Breastmilk is widely regarded as the gold standard source of nutrition for most healthy, full-term infants. Authorities on infant nutrition support evidence that breastfeeding for the first 6 months of life can reduce rates of acute infections and chronic disease.\textsuperscript{1-3} Despite its benefits there are occasions where breastfeeding is not possible or even contraindicated. In these instances, commercial infant formula is often the next best choice. Safety and nutritional standards are set and regulated by the United States Food and Drug Administration (USFDA). These standards ensure that all available commercial formulas are adequate to promote infant growth and development.\textsuperscript{4}

Research is ongoing regarding what additional ingredients could be utilized to produce a formula that supports outcomes in acute and chronic disease more similar to those of breast fed infants. One area of investigation for this has been the use of probiotics and prebiotics and how the addition of these may contribute to the prevention of disease in infants.

Prebiotics are non-digestible carbohydrates most commonly recognized by the names oligosaccharide, inulin, galactooligosaccharide and fructooligosaccharide. It is well established
that prebiotics, while not digestible by humans, are a primary fuel source for bacteria of the microbiome. The microbiome is the compilation of bacteria that reside in the human gastrointestinal (GI) tract. At birth, the infant GI tract is considered immature due to lack of an established microbiome. Many factors, including, but not limited to, the process of birth, introduction to the environment outside the uterus and enteral feeding are proposed to all play roles in the development in the infant’s microbiome. Prebiotics known to occur in breast milk, human milk oligosaccharides (HMOs), and are proposed to play a role in establishing the infant intestinal microbiome.

Probiotics are commonly referred to as “good bacteria”, i.e. microorganisms that provide beneficial effects to their host. These are the bacteria that make up the intestinal microbiome. Probiotic bacteria digest prebiotic fibers producing metabolic byproducts, such as short-chain fatty acids (SCFAs), that can influence host function through various mechanisms. Research has found that in breastfed infants there is a dominance in the proliferation of the bifidobacteria species of bacteria. While the clinical implication of this remains unclear, it is suggested that presence of the dominance of this species may play a role in reduced infant morbidity. Further research is needed to establish how the dominance of bifidobacteria species could play a role
in reduced infant morbidity and how other strains of bacteria could be implicated in this process as well.

Recently, the term ‘synbiotic’ has been used to describe the combination of probiotics and prebiotics used together.\textsuperscript{5} Knowing that probiotic bacteria utilize prebiotics to proliferate and produce metabolically active byproducts, it is reasonable to suggest that their use together could provide enhanced benefit than when used individually.

A 2012 systematic review of the research\textsuperscript{10} concluded that insufficient evidence in regard to improved outcomes in infant growth or clinical benefit related to infant morbidity to support routine supplementation of probiotics, prebiotics or synbiotics in infant formula. Investigators did state that prebiotic-enhanced formulas alone do not result in any adverse events and may provide some clinical benefit related to weight gain and stool frequency; however, similar conclusions could not be drawn regarding synbiotic-enhanced or probiotic-enhanced formulas. Recent clinical trials\textsuperscript{11,12} found that synbiotic-enhanced formulas appear safe and promote adequate growth in infants. An additional study\textsuperscript{13} evaluating the effects of synbiotic-enhanced formula on the diversity and composition of the infant GI tract concluded that the prebiotic, bovine milk-derived oligosaccharide (BMOS), rather than the probiotic, contributed more to
the changes in the infant microbiome, specifically towards the proliferation of bifidobacteria.

Given the current body of research on the effects of probiotics, prebiotics and synbiotics, it is reasonable to suspect their addition to infant formula may provide benefits similar to those of breastmilk. For the purpose of this review we look specifically at the effects of synbiotic-enhanced formula on acute respiratory and gastrointestinal infections, in an effort to establish a correlation between synbiotic-enhanced formula use and specific health outcomes in otherwise healthy, full term infants.

**METHODS**

An exhaustive literature search was completed using Web of Science, PubMed-MEDLINE, CINAHL and ProQuest. Additionally, references of articles found in the preliminary search were reviewed for inclusion. The search was conducted using the terms “infant” AND “synbiotic” OR “prebiotics and probiotics” AND “respiratory tract infection”. The search was limited to peer-reviewed studies in humans, appearing in scholarly journals from 2012-present (2018 at the time of review). Studies chosen for inclusion had to be randomized control trials, cohort studies or case-controlled studies. Studies had to be in English language. Inclusion criteria for this review included full-term infants transitioning or starting on infant formula within the first twelve
months of life. Studies were excluded if they contained premature infants, “high-risk” infants (i.e.: allergic infants or infants with congenital abnormalities or infections), neonates-only, actively breast-fed infants or studies comparing the intervention groups to only breast fed, donor milk fed or probiotic-enhanced formulas alone (i.e.: lack of sufficient control group). Prebiotic-enhanced control groups were included based on research\textsuperscript{10,13} suggesting prebiotics alone may promote clinically improved outcomes compared to standard formula.

The GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach was utilized in assessing the articles meeting inclusion criteria for this review\textsuperscript{14}.

**RESULTS**

The initial search resulted in 27 studies to be reviewed (5 CINAHL, 7 PubMed-MEDLINE, 5 Web of Science, and 10 ProQuest). Including a review of the references, 2 articles met inclusion criteria.\textsuperscript{15,16} See Table 1. Several articles involving synbiotic-enhanced formula existed for the purpose of safety and infant growth outcomes; these articles were excluded from this review due to lack of outcome measures regarding rates of infection.

**Radke et al**
This study\textsuperscript{15} was a randomized, double blind, control trial that evaluated the effects of prebiotic plus probiotic-enhanced formula, compared to standard formula, on rates of infections in infants. A reference group of breast-fed infants was also included for comparison. The trial was conducted across multiple sites in Germany, France and the Netherlands. Healthy, full-term infants (0-14 days old) were included in the study. Mothers who chose to continue breastfeeding their child were enrolled in the reference group, while others were allocated to the test or control groups. Initially 476 infants were enrolled in the trial, not including 63 infants in the breastfeeding reference group. Of these, 150 infants in the test group, 157 in the control group and 47 of the breastfed group completed the trial in entirety. Baseline characteristics of both the test and control groups were fairly equal. The test formula included bovine milk-derived oligosaccharides (BMOS) and \textit{Bifidobacterium lactis} (B. lactis). The control formula had neither added. Both formulas were identical in macro and micronutrients.\textsuperscript{15}

The study intervention time was the first 6 months of life with either intervention or control formula followed by ongoing follow-up for up to 12 months of age on standard formula. Baseline data was recorded prior to study initiation. Infants were assessed at 1, 2, 3, 6, 9, and 12 months of age. Parents were provided diaries for recording
formula intake and tolerance. At each assessment infants were weighed, examined, assessed for adverse events (AEs), and reviews of their formula diaries and medical records were taken. Saliva and fecal samples were taken from some infants at 3 and 6 months for additional evaluations. The primary outcome measures of this study were incidence of diarrhea and all infections with fever during the first 6 months and 1 year of life. The study did not directly describe what was included in ‘all infections’; however, the authors did separately define characteristics of upper and lower respiratory tract infections based on classic symptoms of these types of infections. Fever was assessed based on occurrence of temperature >38 C and reaching 38.5 C at least once in 24 hours. Diarrhea was defined as three or more loose or watery stools in 24 hours or parent-perceived episodes of diarrhea in conjunction with additional symptoms, which were not directly defined.¹⁵

The study found no statistically significant difference in incidence of diarrhea between test and control groups at 6 months (odds ratio 0.56, 95% CI: 0.26 to 1.15; p-value 0.096) or at 12 months (odds ratio 0.66, 95% CI: 0.38 to 1.14; p-value 0.119). Incidence of infection was reported as comparable among groups with 21.2% and 21.1% incidence of infection with fever at 6 months and 45.2% and 44.4% at 12 months in the test group and control groups, respectively.
(p-value 1 and 1). This was also compared to the breastfed group, which saw 16.9% incidence of infection with fever at 6 months and 45.7% incidence at 12 months. The study reported overall the most common adverse event (infectious and non-infectious) occurrences were infection-related, of which occurred in 21 of the test group infants, 16 in the control group infants and 3 in the breastfed infants.\textsuperscript{15}

**Maldonado et al**

In this\textsuperscript{16} randomized, double-blind, control trial, researchers studied the effects of synbiotic-enhanced formula (test) compared to prebiotic-only enhanced formula (control). The study was conducted across 3 Spanish hospitals and initially enrolled 215 total infants, but completed the study with 91 control and 97 experimental group infants. Healthy, full-term infants participated in this study. Of these infants, 69-71% had been breast-fed prior to enrollment for an average of 2.8-3.0 months. Otherwise, baseline characteristics were fairly equal between test and control groups. All infants were transitioned to formula feeding at trial initiation. The test formula contained galactooligosaccharides (GOS) plus *Lactobacillus fermentum CECT5716 (L. fermentum)* while control formula contained GOS only. The formulas were otherwise the same regarding nutritional composition.\textsuperscript{16}
The primary outcome measure of this study was incidence of infection. The intervention was performed for 6 months in duration and infants were monitored at baseline, 3, 6, and 12 months after initiation. Fecal samples were collected from some infants at various points throughout the study. Parents were provided questionnaires and a diary, which included documentation of infant’s symptoms, doctor visits including any diagnoses and antibiotics, crying, sleeping and diapering. Study pediatricians also administered questionnaires at each interval check up. The diagnosis of infection for this study was made by the study pediatricians based on specific symptoms and standard diagnostics.\(^\text{16}\)

During the study, 72.5% of all infants experienced respiratory infections and 15.7% of experienced GI infections. Statistical analysis showed a 26% reduction in the incidence of respiratory infections in the experimental group compared to the control (IR ratio 0.74, 95% CI 0.580-0.957; p-value 0.022). Additionally, analysis showed a 46% reduction in the incidence of GI infections in the experimental group compared to the control (IR 0.54, 95% CI 0.307-0.950; p-value 0.032).\(^\text{16}\)

**DISCUSSION**

While infections are a natural occurrence during of the human lifespan, it is crucial to develop formulas that support health outcomes
in formula-fed infants comparable to those whom are breastfed. Research, like that in this article, may help guide formula development to better reduce morbidity in formula fed infants. At this time, the American Academy of Pediatrics (AAP) supports the use of prebiotic-enhanced formulas in infants age 5 months or older. They suggest more robust research be conducted to establish better guidelines for their use in prevention of disease.\textsuperscript{17} The European Society of Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) does not recommend the routine use of probiotics, prebiotics or synbiotics in infant formula.\textsuperscript{18} The ESPGHAN does acknowledge that probiotic and prebiotic-enhanced formulas do not appear to show any significant concern in regard to safety or growth in otherwise healthy infants and there may be some evidence of clinical benefit with either prebiotics or probiotics, however, the data is insufficient. The same could not be stated regarding synbiotic-enhanced formulas at the time of their review.\textsuperscript{18}

The studies\textsuperscript{15,16} presented here attempt to establish whether or not synbiotic-enhanced formulas could promote positive clinical outcomes for otherwise healthy infants. Both studies were multi-center, randomized control trials. Both studies evaluated synbiotic-enhanced formulas in their test groups and assessed for outcome measures related to acute infections. The trials designs were different
based on timing of intervention. While Radke et al\textsuperscript{15} initiated their intervention within the first 2 weeks of life, Maldonado et al\textsuperscript{16} had a larger range at which the intervention was initiated. On average infants in the trial were started at 6.5 months of age. The longer duration of breastfeeding or standard formula feeding could cause unknown effects on the infant gut microbiota, which may have confounded the results.

One of the biggest differences in comparing the two studies\textsuperscript{15,16} was the clear difference in strains of probiotics and types of prebiotics used in the intervention groups. It would be inappropriate to directly compare the effects of one probiotic, prebiotic or combination to another as their properties and characteristic effects are likely different. More robust research into each intervention group’s formulation would strengthen the evidence for the particular synbiotic formulation.

Unfortunately, both studies had serious limitations that reduced their validity (Table 1). One issue discussed by Radke et al\textsuperscript{15} was that while rates of diarrhea were comparable among test and control groups (43 and 31 infants in each group), lack of detection of infectious types of bacteria in fecal assessments, lack of associated symptoms (26 in the test and 23 in the control groups) and low rates of antibiotic prescription (2 total) for diarrheal episodes suggested that
infectious etiology of diarrhea was unlikely. The authors stated that the rate of diarrhea in all infants was lower than previously conducted studies. Thus, the study was noted to be underpowered to detect a difference in rates of diarrhea and determined likely underpowered to detect differences in rates of other infections with fever. In regard to other infections with fever, while respiratory infections were well defined in the study design, they were listed under the assessment of adverse events (AEs), rather than outcome measures. It is unclear how, or if, respiratory infections were calculated into the statistical analysis for all infections compared to AEs analysis.\textsuperscript{15}

Maldonado et al\textsuperscript{16} did not have a true control group, reducing its validity in regard to methodology, as the formula they used in both test and control groups had GOS. Because of this, researchers would not make any statements on the effect of the potential synergistic effect of the probiotic plus the prebiotic. Maldonado et al\textsuperscript{16} provided more detailed information regarding how infections were identified in regard to data collection and statistical analysis of each type of infection that occurred during the study, providing a higher quality of data in their report.

In regard to the fecal assessments it should be noted that both studies\textsuperscript{15,16} collected samples in only a subset of the study population. This inconsistency weakens the data points collected in regard to
secondary outcome measures. While they were not the primary focus of this review, these assessments such as fecal SCFA, bacterial counts and fecal IgA may have implications in clinical outcomes and could help drive future research.

CONCLUSION

There is insufficient evidence to conclude that synbiotic-enhanced formula is superior to standard formula in protecting otherwise healthy, full-term infants from acute respiratory or GI infection. However, research here suggests that one strain of probiotic bacteria, L fermentum, in conjunction with GOS may help reduce rates of GI and respiratory infection. Additional trials are needed to confirm efficacy of L fermentum and GOS on rates of infections as well as their use at different doses and in alternative settings and populations. Clinical trials on different strains of probiotics with prebiotics should be conducted prior to recommendations on specific health outcomes of any one combination. The research summarized in this review remains consistent with prior reviews and guidelines that the use of prebiotics and probiotics appears well tolerated and may provide some clinical benefit in healthy infants.
References


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\(^{a}\) Results for respiratory infections, not related to adverse drug reaction, was not specifically reported outside of “all infections”  
\(^{b}\) Study was underpowered to detect difference in rates of diarrhea between groups  
\(^{c}\) The Radke et al study\(^{1}\) was funded by the Nestle and 2 study contributors were Nestle employees  
\(^{d}\) Lack of true control group in Maldonado et al