Supporting a Healthy Microbiome for the Primary Prevention of Eczema

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Abstract

Eczema is increasing worldwide with associated increases in health costs and decreases in quality of life. There are many factors that are speculated to interact in the development of eczema including genetics and environmental exposures. Prevention of the development of eczema may prevent the further development of food allergies and asthma. This concept has prompted a variety of research into the area of primary prevention of eczema in infants. This exploration includes a growing body of research examining infants supplemented with probiotics, prebiotics, or both (synbiotics) often compared with their breastfed counterparts. The goal of this paper is to examine the evidence for manipulating the microbiome in the prevention of eczema. Several strains of probiotics, compositions of prebiotics, and varied combinations of both are commercially available. Evidence supports altering the microbiome in infants at high risk of atopy who are not able to breastfeed with *Lactobacillus* strains when given both prenatally followed by prolonged use (greater than 6 months) postnatally for the primary prevention of eczema. Prebiotics have also been shown beneficial for primary prevention of eczema in formula-fed infants with prolonged use greater than 6 months. These findings are in keeping with the World Allergy Organization (WAO) recommendations that support interventions to manipulate the microbiome with both probiotics and prebiotics.

Keywords Primary prevention of eczema · Eczema · Atopic dermatitis · Microbiome · Prebiotics · Probiotics · Postbiotics · Synbiotics

Abbreviations

GI	Gastrointestinal
OS	Oligosaccharides
GOS	Galacto-oligosaccharides
FOS	Fructo-oligosaccharides
TLRs	Toll-like receptors
DBRPC	Double-blind, randomized, placebo controlled
SCFA	Short-chain fatty acids

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Introduction

Burden of Disease

Eczema is increasing worldwide with associated increases in health costs and decreases in quality of life. In a population analysis, the prevalence of eczema was found to be approximately 20–30% of infants in the USA with a somewhat higher risk of developing eczema found in those infants with at least 2 family members with some form of allergic disease [1]. Previously, Leung and Bieber reported a rate of 10–20% in 2003 [2]. Eczema is the first step in the atopic march. Lowe et al. discussed the theory that the trigger for the progression of the atopic march may be impaired skin-barrier function in eczema and that prevention of the development of eczema may prevent the further development of food allergies and asthma [3]. The risk of developing eczema by age 2 years of life in high risk infants may be as high as 30–50% [4], making the infant period is a critical time frame if primary prevention of eczema is to be undertaken. Most

research articles define "high risk" of development of eczema defined as having at least one atopic first relative. There are many factors that are speculated to interact in the development of eczema including genetics and environmental exposures. More recently, there is evidence that the microbiome may offer options for the treatment and prevention of eczema.

Definitions

A commonly held definition of the human microbiome is "a community of microorganisms living in or on the human body" [5]. The term microbiome is often used to refer to the bacteria living in the gastrointestinal (GI) tract; however, the term may be extended to composition of organisms (bacteria, fungi, or viruses) residing on any epithelial or mucosal surface, such as the skin or sinuses. It is also important to note that the microbiome is a term defining the acknowledged existence of microbes; it is neither inherently beneficial nor harmful. In contrast, probiotics are microorganisms that "confer a health benefit on the host" according to the World Health Organization. Two examples of commonly encountered probiotics include various strains of *Lactobacillus* and *Bifidobacterium*. Prebiotics are further contrasted as non-digestible, non-living carbohydrates that the microflora of the gut uses as nutrition. They are components of food that are not digestible by the human gut, but are metabolized and used by the microorganisms colonizing the GI tract. Prebiotics are nourishment for the commensal flora in the gut and can foster an environment leading to a flourishing, well-diversified microbiome. Most commonly encountered prebiotics are non-digestible carbohydrates. Examples include oligosaccharides (OS), galacto-oligosaccharides (GOS), fructo-oligosaccharides (FOS), lactulose, and inulin. These prebiotics can be found in high amounts in human breast milk [6–8] and in foods rich in fermentable fiber such as chicory root, onions, and jicama. The term synbiotic simply refers to the combination of both prebiotics and probiotics and is generally used to describe a form of supplement. Finally, the term postbiotic refers to the short-chain fatty acids (SCFA) produced when probiotics metabolize prebiotics. In an article published in Annals of Allergy and Immunology, Ciaccio summarized the symbiotic relationship between prebiotics, probiotics, and postbiotics explaining that prebiotics are provided via the diet to the probiotics of our gut microbiome. These probiotics then metabolize the otherwise non-digestible fibers and give back SCFAs (postbiotics), which are in turn used by our gut epithelial cells for energy in addition to other anti-inflammatory properties [9]. However, the use of postbiotics is limited as they currently are not produced in a way that can be absorbed orally.

Proposed Mechanisms of Action

The microbiome is an area of intense research, which has shown that the microbiome can and does have many immunomodulatory effects on its host. Probiotic use in supplement form has been recognized since Elie Metchnikoff began recommending the use of fermented milk in 1907 and has more clinical research than prebiotics or synbiotics. Proposed mechanisms for probiotics include changes in the innate immune system such as induction of regulatory T cell development [10] and alteration in toll-like receptor (TLR) expression [11]. It is also clear that different probiotic strains may have varying effects. In a study using the buccal smears from 331 children, Marlow et al. evaluated the role of *Lactobacillus* or *Bifidobacterium* supplements on TLR expression. It was determined that *Lactobacillus* was associated with 26 polymorphic TLR changes that reduced the risk of developing eczema (p values < 0.02), contrasted with only two polymorphisms in those supplemented with *Bifidobacterium* [12].

It is known that the prebiotics in human milk have many mechanisms of action that may modulate the immune system and potentially protect against atopy. Increased populations of *Bifidobacteria* in the stool of breastfed infants have been recognized since 1926 when Schonfeld termed a then unknown growth-promoting factor present in breastmilk [7]. In the 1950s, the growth factor termed "Bifidus factor" was determined to be a non-digestible oligosaccharide (prebiotic), but still without known purpose [13–16]. Now, greater than 150 forms of oligosaccharide structures alone are known to exist, and the detailed composition of breastmilk is still under evaluation [8]. Proposed mechanisms of action of prebiotics are an area of active research. Prebiotics in human milk have been shown in vitro to act as decoy glycan receptors that block various bacteria, viruses, and parasites from binding to epithelial cells [17–20]. These prebiotics have also been shown to directly affect gene expression of epithelial cell surface glycans [21]. The effects of reduced cell surface binding and improved glycan expression would theoretically aid in the epithelial barrier function, which is known to be important in prevention of atopy. Beyond these indirect mechanisms, in vitro studies have shown that prebiotics directly modulate immune responses to reduce IL-4 production, a known allergy mediator, in the lymphocytes of peanut allergic adults [22]. In mice supplemented with prebiotics, there was found to be an improved Th1 response and reduced Th2 (allergic) response to vaccination [23]. Furthermore, the prebiotics in human milk have been shown in vitro to reduce leukocyte rolling on TNF-alpha-activated human cells [24] as well as platelet-neutrophil complex formation and neutrophil activation [25] potentially translating to lessened inflammatory responses.

There is broader evidence for the effects of the microbiome on allergic diseases. Changes in the microbiome composition have been found associated with a variety of allergic diseases. One such finding demonstrated that children with eczema have shifts in their cutaneous microbiome during eczema flares [26]. Additionally, there have been several studies

which demonstrate that patients with eczema have reduced diversity of their gut microbiome compared with their healthy counterparts [27–30]. It has been postulated that the microbiome may either impact eczema or affect the development of eczema [31, 32], which is the focus of this paper.

Probiotics and Their Role in the Primary Prevention of Eczema

There have been a number of researchers reporting positive effects of probiotics on the prevention of eczema in infants. The first study demonstrating a protective effect of probiotics on the prevention of eczema was a double-blind, randomized, placebo controlled (DBRPC) trial published in Lancet in 2001 based on 94 high-risk infants in Finland [33]. This study involved maternal supplementation with *Lactobacillus rhamnosus* GG for 4 to 6 weeks before delivery and subsequent infant supplementation through the first 6 months of life. There was a significant risk reduction in the development of eczema at 2 years of age (RR 0.51; CI 0.32–0.84). Follow-up studies provided data that the protective effect persisted in those receiving *Lactobacillus* through age 7 years old [34, 35]. In another DBRPC, 331 mothers of high-risk infants were provided with either *Lactobacillus* (strain HN001) or *Bifidobacterium* (strain HN019) during their third trimester followed by infant administration for the following 2 years and found a protective effect of the *Lactobacillus* strain (RR 0.51; CI 0.30–0.85), but not with the *Bifidobacterium* strain (RR 0.90; CI 0.58–1.41) [36]. This protective effect was shown to extend through 6 years of life in the *Lactobacillus* group [37, 38]. This cohort was further analyzed based on genetic variants associated with increased susceptibility to eczema and not on family history alone. Risk reduction was again found in the *Lactobacillus*, but not *Bifidobacterium*, group [39].

Despite the promising evidence above, there have also been several studies finding no benefit associated with probiotic supplementation. In 2007, Taylor et al. published the effects of *Lactobacillus acidophilus* supplementation for the first 6 months of life without prenatal maternal ingestion vs placebo in high-risk infants. They found no risk reduction in the development or severity of eczema in the first year of life. Interestingly, there was an increased risk of positive skin prick testing to common allergens by 1 year in the treatment group (*n* = 178; *p* = 0.03) [40]. Kopp and colleagues mirrored the initial study by Kaliomaki et al. with *Lactobacillus* GG and failed to display a risk reduction and in fact reported an increased rate of recurrent wheezing (≥ 5 episodes over the first 2 years of life) in the supplemented infants compared with placebo (26% vs 9.1%, *p* = 0.03) [41]. Later studies have found lack of effect with prenatal and 6 months of postnatal infant supplementation comparing *Bifidobacterium* and

Lactobacillus strains without noted side effects or adverse effects [42–44]. It is important to note that these studies which found no benefit capped their postnatal infant supplementation at 6 months.

The studies above evaluated direct infant supplementation with probiotics. It has been shown that live lactobacilli can be found in the breastmilk of probiotic supplemented mothers, potentially conferring benefit to their nursing infants [45]. Rautava et al. performed a DBRPC study to evaluate the effects of exclusive maternal probiotic supplementation in the 2 months prior to delivery and 2 months postdelivery in nursing mothers. The infants of 241 mothers with atopy confirmed by skin prick testing to food or aeroallergen were given either placebo, *Lactobacillus rhamnosus* with *Bifidobacterium longum* or *Lactobacillus paracasei* with *Bifidobacterium longum*. The infants in both treatment groups whose mothers were supplementing displayed a decreased risk of developing eczema (OR 0.16 and 0.17, CI 0.08–0.35, *p* < 0.001) with no adverse effects noted [46]. Other reports have also evaluated exclusive maternal probiotic supplementation and found similar beneficial treatment effects [47, 48]. In contrast, Wickens and colleagues reported on the effects of exclusive maternal supplementation from the second trimester through 6 months postnatally if breastfeeding and found no benefit in prevention of eczema or sensitization by 12 months of life [49].

In attempts to evaluate the conflicting data, several meta-analysis studies have been performed finding a variety of evidence. A Cochrane review meta-analysis of five studies on 1477 infants found that all studies including high-risk infants using a *Lactobacillus rhamnosus* strain had a statistically significant risk reduction in the development of eczema (RR 0.82, CI 0.70–0.95) [50]. Lee et al. produced a meta-analysis looking at probiotics for both prevention and treatment of eczema using more stringent inclusion criteria and random effects models. Six prevention trials were included, and supporting evidence was found for the use of probiotics in prevention of eczema to 2 years of life (*n* = 1581; RR 0.69, CI 0.57–0.83). The risk reduction associated with the use of probiotics was magnified when only studies that involved maternal prenatal supplementation were included (RR 0.61, CI 0.49–0.76). This suggests that prenatal maternal supplementation may play an important role in prevention of eczema [51]. A meta-analysis by Panduru and colleagues concluded similar results when postnatal infant supplementation with *Lactobacillus* was coupled to prenatal supplementation in both high-risk infants (OR = 0.66, CI = 0.57–0.77) and in the general population (OR = 0.53, CI = 0.34–0.83) [52]. Cuello-Garcia et al. performed a large meta-analysis of 23 randomized controlled trials (*n* = 3447) and found overall risk reduction in development of eczema (RR 0.81, CI = 0.70–0.94). This study did identify inconsistent inter-study results and risk of bias in several of the studies [53].

Conclusions

Based on a wide spectrum of evolving research, it is known that the microflora of the GI tract modulates the innate and adaptive immune responses both locally and systemically. Commensal organisms effect TLR expression, stimulate repair of intestinal wall, increase protective mucins and defensins, help develop regulatory T cells, and activate ongoing immunoglobulin A production [54]. The safety of probiotics in infants appears reassuring. Kopp et al.'s study was the only study performed to have any potential negative findings greater than placebo with increased frequency of wheezing in infants sited. Furthermore, several probiotic strains are included in over-the-counter infant formula preparations without known negative consequences to date.

Based on the strength of existing evidence of safety and efficacy, in a high-risk infant who is unable to breastfeed, a probiotic supplement is an appropriate recommendation for both mother prenatally and directly to infant postnatally. Lactobacillus strains with prolonged postnatal use continued throughout the first 2 years of life have the most convincing data backing their use for primary prevention of eczema. In 2015, the World Allergy Organization published their recommendation to use probiotics in pregnant mothers and their infants who are at high risk of eczema development by having a first-degree relative with atopic disease [55].

Prebiotics and Their Role in the Primary Prevention of Eczema

There is growing evidence that supplemented prebiotics can have an effect on the microbiome content [56–60]. In an early clinical study on prebiotics, formula-fed infants supplemented with prebiotic oligosaccharides mirroring human milk composition were compared with standard formula-fed infants without prebiotics. Breastfed infants were used as a control group. Fecal content was compared including microbial composition, stool characteristics, infant growth, and side effects. Similar *Bifidobacteria* counts were found in those provided with prebiotics compared with those given human milk. A significant increase in stool frequency was also noted in those provided supplementation ($p = 0.0079$) and those given human milk. There were no side effects in either arm of the study [56].

Wopereis et al. further characterized the effects of prebiotics in formula-fed infants. A total of 138 high-risk infants were either given partially hydrolyzed formula supplemented with prebiotics or standard milk-based formula without prebiotics during the first 26 weeks of life. Metabolite levels of microbes, stool pH, and microbiome composition were analyzed. The colonic compositions were compared with each other and with a reference group of exclusively breastfed infants. The infants given prebiotics had colonic contents closer in composition to that of exclusively breastfed infants compared with those receiving standard milk-based formula alone. The authors speculated that lower gut pH and dominance of *Bifidobacterium* provided a level of protection not only against potential pathogens but also against atopy development by providing higher levels of immunoregulatory SCFAs [60].

Due to the high prebiotic content of breastmilk, only formula-fed infants have been studied to evaluate the use of prebiotics. In 2010, Gruber et al. reported a DBRPC comparing standard formula-fed infants at low risk of allergic disease. They were given prebiotic supplement or placebo with breastfed infants as controls. There was a significant risk reduction in the prebiotic group with rates of atopy within the first year of life similar to the breastfed infants and less than the placebo formula ($n = 460$, RR 0.57, CI 0.32–0.97, $p = 0.04$) and no difference in rates of sensitization to milk or eggs [61]. This study was unique in that it specifically evaluated low-risk infants, making the data potentially more applicable to the general population. In 2013, a Cochrane review examined the effects of supplementing formula-fed infants with prebiotics and the development of atopy from 4 months to 2 years of age. A total of four studies which included 1218 infants were evaluated. Overall, the prebiotic supplemented infants had a significant reduction in the risk of developing eczema ($n = 1220$, RR 0.68, CI 0.48–0.97, $p = 0.03$) with a number needed to benefit of 25. In a closer examination of the data, the two studies favoring prebiotics provided prolonged supplementation for 6 to 12 months, while the studies that did not show risk reduction limited use of prebiotics to less than 3 months [62]. In 2017, a meta-analysis examining prebiotic use in infants for prevention of atopy was performed with most of the included studies using GOS/FOS combinations. Specific to the development of eczema, six studies ($n = 2030$) were included with follow-up ranging from 3 months to 2 years of age. A risk reduction in those receiving prebiotic supplements was found (RR 0.68, CI 0.40 to 1.15). Importantly, none of the 22 studies found any negative associations with the use of prebiotics on nutritional evaluations, growth parameters, or adverse effects [63].

Conclusions

It is generally accepted that breastfed infants are at lower risk for atopy. It is known that prebiotics in the form of human milk oligosaccharides are the third largest solid component, comprising 20% of total carbohydrates and exceeding the concentration of total milk protein. It is further known that these prebiotics support the growth of beneficial bacteria among the many previously discussed potential benefits and mechanisms of action [6–8, 17]. Formula-fed infants consuming prebiotics have colonic compositions similar to breastfed

infants [56, 57, 60]. Prebiotics have not been linked to any adverse outcomes including any adverse effects on growth rate or final weight of infants.

The studies performed on prebiotic supplements in infants for primary prevention of eczema are promising. The evidence backing the consumption of prebiotics for the primary prevention of eczema appears to show a beneficial effect that may be more consistent than probiotics. The most benefit has been seen with prolonged use of prebiotics during the first 6 to 12 months of life in formula-fed infants. More study is needed to clarify the length of time for supplementation, the various forms of prebiotic supplements, and the formula co-ingested with prebiotics. In contrast to the studies using probiotics which showed benefit when maternally ingested in the prenatal period, maternal consumption does not appear necessary to derive the benefits of prebiotics.

Formula-fed infants both at high or low risk of atopy can safely consume prebiotics in the first 6 to 12 months of life which may reduce their risk of developing eczema. In keeping with these assessments, the World Allergy Organization made the recommendation that prebiotics be administered to all infants who are not breastfed [64].

Synbiotics and Their Role in the Primary Prevention of Eczema

Synbiotics are supplements that include both prebiotics and probiotics simultaneously. A few studies have evaluated the effects on eczema development with the combination of prebiotics and probiotics provided to infants with early promising results. In DBRPC trial, Kukkonen and colleagues compared 925 breast- and bottle-fed infants for the effects of synbiotics on eczema development. Prenatally, mothers ingested four probiotic strains 2 to 4 weeks prior to delivery. Their infants were given these same strains in addition to prebiotics (GOS) for the first 6 months of life and evaluated clinically at 3, 6, and 24 months and as needed. Fecal samples of stool at birth, 3, six, and 24 months of life with skin prick testing at 6 months and IgE specific serology at 24 months were also evaluated. There was no change in cumulative incidence of atopy, but there was a significant risk reduction in the development of eczema (OR 0.74, CI 0.55–0.98), which was heightened in a subset of eczema patients who had positive specific IgE (OR 0.66, CI 0.46–0.95) [65]. In a multicenter evaluation by Rozé et al., formula-fed infants were compared in a DBRPC trial ($n = 97$) and given either a formula with probiotics (*Lactobacillus* and *Bifidobacterium*), prebiotics (GOS/ scFOS), and α-lactalbumin (whey protein) or placebo. At 1 and 6 months of life, the infants were clinically evaluated on multiple outcomes including growth parameters, dermatologic assessment, fecal content, sleep time, general well-being, and bowel habits. After completion of the trial with supplemented formula use for 6 months, there was a decreased risk of developing eczema in the treatment arm (OR 0.11, CI 0.01–0.94). There was also an increased rate of colonization of the supplemented probiotics in the treatment arm and decreased amount of secretory IgA and increased staphylococcal colonization in the stool of the placebo arm [66].

In a meta-analysis by Chang et al. published in 2016 *JAMA Pediatrics* on the use of synbiotics for prevention and treatment of eczema, the two studies above were analyzed in addition to six treatment studies ($n = 369$). Although there was a significant effect of synbiotics on the treatment of eczema, they did not find statistically significant benefits of synbiotics on the prevention of eczema (RR = 0.44, CI, 0.11–1.83; $p = 0.26$) [67].

Summary

The role of the microbiome in prevention and treatment of diseases caused by immune dysregulation such as atopy and autoimmune conditions is an active area of research. The quantity of data and studies on the microbiome and atopy is expanding rapidly; nevertheless, there is a continued need for additional high quality data to provide specific evidence regarding the best agents and the proper patient risk profile. Current evidence supports supplementing infants with probiotics, prebiotics, or both (synbiotics) to prevent the primary development of eczema. Several strains of probiotics, compositions of prebiotics, and varied combinations of both are commercially available.

At its inception, the goal of formula was created by the chemist von Liebig in 1865 to replace human breast milk [68, 69]. There is a substantial and growing body of evidence that the microbiome of the human GI tract has significant effects on the immune system. For nearly a hundred years after its inception, the influence of breastmilk prebiotics on the microbiome was not known. Prebiotics are the third most abundant component in human breast milk and provide nourishment for the infant's microbiome [6–8, 17]. With this knowledge of prebiotic composition of breastmilk along with their effects on the immune system and potential to prevent the development of eczema, the next logical step in refining the production of formula to match its human milk counterpart would be the addition of prebiotics.

Evidence supports altering the microbiome in infants at high risk of atopy who are not able to breastfeed with *Lactobacillus* strains when given both prenatally followed by prolonged use (greater than 6 months) postnatally for the primary prevention of eczema. Prebiotics have also been shown beneficial for primary prevention of eczema in formula-fed infants with prolonged use greater than 6 months. These findings are in keeping with the WAO recommendations that support interventions to manipulate the microbiome with both probiotics and prebiotics.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Ethical Approval NA (this is a review of literature and no patients or patient information was used in the writing of this article).

Informed Consent NA (this is a review of literature and no patients or patient information was used in the writing of this article).

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Introduction

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