

The Infant Microbiome and Its Impact on Development of Food Allergy



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KEYWORDS

• Food allergy (FA) • Gut microbiome • Mediterranean diet • *Prevotella copri* (*P copri*)

KEY POINTS

- Infant gut microbiome influences the development of food allergy (FA).
- The gut microbiome begins developing during gestation and is influenced heavily by environmental factors during gestation and early infancy.
- Gut microbiome is impacted by infant feeding method, probiotics, infant diet, and maternal diet during lactation.
- Diet has been linked to the commensal gut microbiota, which can be associated with the risk of inflammation and FA.

INTRODUCTION

Food allergies (FAs) have become a growing public health problem, especially in the United States and other industrialized Western nations. The prevalence of FA has been increasing steadily over the past 2 decades to 3 decades.¹ Moreover, it is more common in pediatric populations, with 8% of children impacted compared with 3% of adults.¹ Of those with diagnosed FAs, approximately 3% experience severe or life-threatening reactions and 2.4% have an FA to multiple foods.^{1,2}

There currently are no cures available for the treatment of FA, with avoidance the primary measure for preventing an acute allergic reaction. A great deal of research has aimed to help better explain which individuals are at risk for the development of

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FA and whether the individual's microbiota may play a role in this risk. Race and ethnicity are major risk factors for the development of FAs and other atopic conditions.^{1,3} Additionally, there is an abundance of modifiable risk factors that have been shown to increase an individual's risk for developing FA, including mode of delivery (vaginal delivery vs cesarean section), infant feeding method (breastfeeding vs formula feeding), use of antibiotics in pregnancy, rural versus urban living, and diet (consumption of dietary fats, antioxidants, and vitamin D).⁴ This abundance of FA-associated risk factors calls into question whether they individually increase a person's risk for development of FA, or, if perhaps, it is a culmination of these factors that modifies an individual's immune system, making that individual more susceptible for FA development. Current research suggests that it likely is a combination of risk factors, and together these modifiable and nonmodifiable risk factors influence the composition of an individual's gut microbiome.⁴

Studies suggest that an individual's gut microbiota begins developing during gestation and is influenced heavily by factors in early infant life. Environmental factors, such as mode of delivery, infant feeding, and various environmental exposures, influence the development of gut microbiota and can lead to disruption of the original gut microbiota composition.⁵ Research suggests that this gut dysbiosis can have an impact on an individual's immune system and lead to the development of FA.⁵ This article discusses how alterations to the gut microbiome may influence the development of FA.

HISTORY

The Crucial Role of the Gut Microbiome in Tolerance or Allergy

In understanding FA, the gut microbiota and the potential role of the gut immune response in oral tolerance first must be understood. The gut microbiome is essential to an individual's immune system function. Trillions of microbes colonize sites within the human body, with a majority of those microbes localized to the gastrointestinal tract.⁵ Studies suggest that these microbes are essential for the health of the gastrointestinal mucosa, which is responsible for producing the majority of antibodies within the human body.⁶ The gut-associated lymphoid tissue (GALT) refers to the inductive sites of the immune system that contain various structures, including lymphoid follicles, mesenteric lymph nodes, and Peyer patches.^{6,7} GALT contains more than half of the peripheral lymphocytes of the body and functions in recognizing foreign food particles.⁷

Oral tolerance refers to the immune system's ability to not respond to orally administered harmless antigens, such as those found in food.⁶ GALT plays a role in oral tolerance by recognizing antigens found within the mucosal surface that covers the intestinal epithelium of the gut.⁷ The intestinal system typically breaks down ingested food antigens via digestive enzymes, and GALT contains structures responsible for properly presenting food antigens to T cells.⁵ The follicle-associated epithelium refers to the collection of the GALT lymphoid follicles and contains microfold (M) cells.⁷ M cells are intestinal epithelial cells that phagocytose antigens from the lumen of the gut and deliver them to dendritic cells (DCs) of the submucosa.^{7,8} Although GALT is considered the inductive region of the intestinal immune system, the effector immune site of the intestine consists of DCs, macrophages, and lymphocytes.⁷ In this complex, stepwise process, stromal cells help with activating these T cells into Foxp3⁺ regulatory T cells (Tregs) and/or interleukin (IL)-10-secreting type 1 regulatory cells,⁵ and deficiency in these processes can lead to inflammation and allergy.⁵

Studies show that the microbiota plays a critical role in the integrity of the mucosal epithelial barrier, thus being a critical factor in the regulation of the immune system and

allergy.^{5,8} In the intestine, mucus is produced by goblet cells and antimicrobial peptides are secreted by Paneth cells to help maintain the integrity of the intestinal epithelium and maintain a barrier between the external environment and internal environment of the body.^{7,8} The amount of mucus and antimicrobial peptides produced correlates to the amount and types of microorganisms present in the gut microbiota, such as *Clostridia*.⁸ Dysbiosis of the gut microbiota triggers the secretion of alarmin molecules, such as IL-33, thymic stromal lymphopoietin, and IL-25 at epithelial barrier surfaces.⁸ These alarmins trigger lymphoid cells to create type 2 helper T (T_H2) cell cytokines, and, consequently, promote B cells to carry out class switching to IgE.⁸ FA typically is associated with the production of IgE antibodies, and, by understanding the role of the gut microbiota in the development of these antibodies, this perhaps can provide important insight in treating allergic disease.^{8,9}

The Evolution of the Hygiene Hypothesis

The hygiene hypothesis first was introduced in 1989 and stated that an increased prevalence of allergies was occurring across populations due to enhanced sanitation practices that decreased exposure to microorganisms.⁵ Some of the enhanced sanitation and public health measures that correlated to this increase in allergy include the pasteurization of food products, vaccination against disease, prescription of antibiotics against bacterial infections, and sanitation of water.¹⁰ Under this hypothesis, the reason for the development of allergy was linked to a shift in allergic responses due to type 1 helper T (T_H1) cells and T_H2 cells. T_H1 cells produce the cytokines, tumor necrosis factor β , IL-1, interferon- γ , and IL-2, and interact with B cells to produce immunoglobulins. Unlike T_H1 cells, however, T_H2 cells produce the cytokines, IL-4, IL-5, IL-9, and IL-13, which cause B cells to produce IgE immunoglobulins that are involved in allergy by triggering the production and activation of mast cells and eosinophils.¹¹ In respect to the hygiene hypothesis, it initially was asserted that when individuals are not exposed to microbes at an early age, this favors T_H2 cell development that causes allergic responses.¹⁰ Consequently, it was hypothesized that when individuals are exposed to microorganisms at an early age, this favors a T_H1 cell response and does not cause a similar predisposition for allergy.¹⁰ Recent studies examining autoimmune diseases, endotoxins, and parasites suggest, however, that this type of helper T-cell interaction not always is the sole explanation for allergy susceptibility.^{10,12} Further studies emphasize the importance of Tregs in allergy risk and more work must be done to understand the role of Tregs in allergy predisposition.¹¹

Although the hygiene hypothesis offers important insights into the susceptibility to allergy, this hypothesis is more simplistic than initially believed. Current studies highlight the importance of understanding both the microbiota found in the external environment and internal environment of those with allergies.⁵ A plethora of studies emphasizes the importance of the gut microbiota as playing a critical role in the development of allergy and exposure to microorganisms—often as early as birth—contributing significantly to the predisposition for developing allergy.¹²

DISCUSSION

Relationship Between the Infant Microbiome and Food Allergy

The gut microbiome is a dynamic environment that constantly is being influenced and modified by external factors. The composition of gut microbiota is impacted by various environmental factors, such as diet, lifestyle, and pathogen exposure. These exposures begin as early as gestation and continue throughout the course of an individual's lifetime, as the gut and immune system are educated on which exposures

require the body to mount an immune response against foreign invaders.⁵ Disruptions occurring throughout this process may result in a malfunctioning or hyperactive immune system, resulting in inappropriate immune responses to innocuous targets, such as harmless food proteins. The immune response against food proteins also has been linked to other comorbid conditions.¹³ Disruptions in this educational process and dysbiosis of an individual's original gut microbiome are associated with the development of FA.⁵

The gut microbiome is established in early gestation and continues to be heavily influenced by external factors throughout infancy and early childhood.¹⁴ Infants are exposed to microbiota via the placenta, meconium, and vaginal canal during gestation and birth, which influence the colonization of their gut microbiome.^{5,15} A significant difference in microbiota composition exists between the neonatal period and infancy. The gut microbiome of a fetus is influenced first by the maternal gut microbiome, diet, and health and consists mainly of *Proteobacteria* species.^{5,15} When infants are born, their microbiome is changed significantly in accordance with the mode of delivery and also changes based on diet during infancy.¹⁵ Another major change occurs between infancy and childhood, when children begin to consume solid food and have an increased diversity of bacteria species, including *Enterococci*, *Enterobacteria*, *Clostridium*, *Streptococcus*, and *Bacteroides* species.¹⁵ At 3 years to 4 years of age, children have a more stable microbiome that is, representative of the adult microbiome; however, the microbiome still can change based on diet, health, and medical treatments.¹⁵ These changes that occur with aging also are indicative of an increase in *Bacteroidaceae* species and decrease in *Enterobacteriaceae* species throughout life—also known as an *Enterobacteriaceae*/*Bacteroidaceae* ratio⁵ (Fig. 1).

Previous studies have shown that early infancy, specifically between 3 months and 6 months of age, is a crucial time where gut microbiota has an impact on the development of FA.^{15,16} Specifically, Azad and colleagues¹⁶ found that a low species richness of gut microbiota in children at 3 months of age is associated with increased likelihood of food sensitization by 1 year of age. The Canadian Healthy Infant Longitudinal Development study found that each quartile increase in species richness at 3 months old reduced the risk of them developing food sensitization at 1 year of age by 55%.¹⁵ Additionally, this study found that each quartile increase in the ratio of *Enterobacteriaceae*/*Bacteroidaceae*, or the greater the abundance of *Bacteroidaceae* species, increased a child's risk of developing food sensitization twofold.¹⁵ Numerous studies have found that individuals with a higher relative abundance of *Bacteroides* and

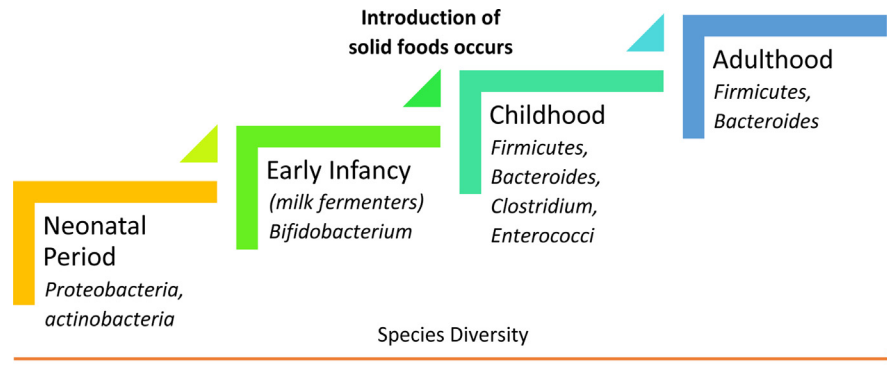


Fig. 1. Predominant gut microbiota throughout the stages of childhood development.

Clostridium clusters have an increased risk of developing atopic dermatitis (AD) and other atopic comorbidities.¹⁷ On the other hand, *Prevotella* species have been found to serve a protective role in the gut against the development of AD, which often is associated with FA in children.¹⁸ Current research suggests that environmental exposures during infancy, including breastfeeding, and both infant and maternal diets may influence gut microbiome development in neonates.

Breastfeeding and Infant Microbiome

Breastfeeding in infancy has many positive effects for both mother and baby, one of which potentially is serving as a protective factor against the development of food sensitization. Breastfeeding currently is recommended for multiple reasons, including but not limited to possible prevention of allergic diseases, including FA.¹⁹ The current scientific basis for this recommendation, however, is based on cohort studies and is not understood completely due to research limitations, because it is unethical to have randomized controlled studies where mothers are asked to refrain from breastfeeding.²⁰ One study found that exclusive breastfeeding demonstrated a protective effect on the development of cow's milk allergy in pediatric patients during early childhood.¹⁹ Goldsmith and colleagues,²¹ however, performed a population-based study of approximately 5000 infants and found that duration of exclusive breastfeeding and use of partially hydrolyzed formula were not associated with development of food sensitization at 1 year of age. Additionally, studies have found that maternal avoidance of the top 8 food allergens during breastfeeding is ineffective in prevention of food sensitization in infants.²²

Although the association between food sensitization and infant feeding still is unclear, there have been confirmed correlations between infant feeding and the development of the infant gut microbiome. One study found that early feeding patterns in infants have a significant effect on the composition of a child's gut microbiome.²³ Breastfeeding has been associated with a higher diversity of gut microbiota in infants compared with infants who are formula-fed.²⁴ Additionally, cohort study findings, including the Wayne County Health, Environment, Allergy, and Asthma Longitudinal Study (see article by Eapen and Kim, in this issue), have found that breastfeeding is a major source of beneficial bacterial species, including *Bifidobacteria*, *Lactobacilli*, and *Enterobacteriaceae*.¹⁹ Conversely, formula-fed infants have been found to have significantly higher concentrations of *Clostridium*, *Streptococcus*, and *Bacteroides*^{25–27} which, when present in high quantities, have been associated with the development of food sensitization.^{15,17} A study by Levin and colleagues²³ found that exclusive breastfeeding was associated with a decreased abundance of taxa from *Clostridia*, *Faecalibacterium*, and *Ruminococcus* genera. These findings are supported further by studies suggesting that once cessation of breastfeeding occurs, the gut microbiota of breastfed infants, which was dominated by *Bifidobacteria*, *Lactobacilli*, and *Enterobacteriaceae* species, is surpassed by *Clostridium* and *Bacteroides* species.^{19,28} A significant change in gut microbiota composition occurs with the cessation of breastfeeding and is seen in most children approximately 9 months to 18 months of age, once they transition from breastfeeding to introduction of solid foods.²⁸ In coordination with infant feeding method, there is evidence suggesting that maternal diet during gestation and lactation has an impact on a child's risk of developing FA.

Infant/Maternal Diet and Infant Microbiome

There are some studies on the association between maternal diet and infant's health and microbiota. The Mediterranean diet is widely recognized as a healthy dietary

pattern that focuses on intake of fruits, vegetables, legumes, nuts, and whole grains, while largely avoiding saturated fats, meats, sweets, and dairy products.²⁹ A maternal Mediterranean diet during gestation has been associated with a lower risk of asthma and atopy development^{30–32} and elements of the Mediterranean diet, such as high maternal intake of fruits, vegetables, fish oil, and vitamin D, may confer protection against atopic disease.^{33–35}

Netting and colleagues³³ conducted a systematic review of 42 studies examining the relationship between maternal diet and atopic disease of the offspring that included more than 40,000 children. Higher adherence to a Mediterranean diet was one of the few consistent associations that could be made between maternal diet during gestation or lactation and protection from subsequent development of allergic disease in the child. In contrast, a maternal diet during gestation consisting of high levels of vegetable oils, margarine, nuts, and fast food frequently, although not universally, were found to increase a child's risk of developing atopic disease.³³ In terms of FA specifically, some studies demonstrated that inclusion of common food allergens in the maternal diet during gestation and lactation may confer protection against development of FA, but others were inconclusive.³³ No studies associated maternal Mediterranean diet with an increased risk of atopy in the child, and, considering its well-demonstrated health benefits,³⁶ it is a safe and advisable dietary pattern during gestation and lactation.³⁷ Another systematic review evaluating 32 studies on maternal diet in relation to atopic disease in offspring largely was inconclusive, demonstrating only a possible protective effect of vitamin D, vitamin E, and zinc against wheeze, and of copper against FA.³⁸ Both reviews cite inconsistent dietary questionnaires and heterogeneity in the outcome measurements of included studies as limitations and suggest cautious interpretation of their results given the considerable potential for confounding.^{33–38}

There also is evidence for an association between infant diet in early life and protection against atopic symptoms.^{39–41} A prospective cohort study including 123 infants was conducted to evaluate the relationship between early life diet and the development of FA.⁴⁰ The results show that an infant diet rich in fruits, vegetables, and homemade foods is associated with lower rates of FA by 2 years of age. It was theorized that higher fruit and vegetable intake is protective because of the beneficial anti-inflammatory effects of nutrients found in these foods, such as β -carotenes, folate, oligosaccharides, and vitamin C. The benefit of homemade foods was attributed to higher overall micronutrient content, because food processing is known disrupt this. These effects were not allergen-specific, because the differences were significant regardless of the food that the child was sensitized to.⁴⁰ In older children, adherence to a Mediterranean diet also has been shown to reduce wheeze and hay fever symptoms,^{42,43} suggesting that the protection of a healthy diet against atopy is not limited to the first few years of life. Importantly, delayed introduction or avoidance of potentially allergenic foods no longer is recommended to decrease the risk of FA because the efficacy of this strategy is not well supported.⁴⁴ Taking the opposite approach by early introduction of potentially allergenic food into the infant diet has proved effective in reducing the risk of peanut allergy, but further research on other common allergens is needed.²²

High-sugar and high-fat diets also have been associated with an increased risk of atopic disease in both children and adults.^{18,45} This association may be moderated by the gut microbiome, epigenetic changes, or interaction of both. A case-control study, which linked atopic disease to high-sugar and high-fat intake in children, also found that atopic disease risk was associated with significant differences in the gut microbiome.¹⁸ Recent literature review provides further evidence of the modulatory role of the gut in allergic disease, concluding that the gut microbiome is 1 likely factor to explain the protective effect of breastfeeding against FA.¹⁹ These findings suggest

that mediators, such as the gut microbiome, are important in explaining the link between diet and FA. Epigenetic changes also may be an important explanation of the link between high-sugar and high-fat diets and FA. It has been demonstrated that diet can activate epigenetic changes directly in early life, which can result in modifications of gut mucosal immunity.^{46,47} These early-life modifications might be a causal factor in the development of atopic disease because, once induced, epigenetic changes can have long-term consequences. For example, transiently high glucose levels have been implicated in causing persistent glucose intolerance via epigenetic changes in the nuclear factor (NF)- κ B gene.⁴⁸ The NF- κ B gene regulates gene expression in the immune system, and its specific relationship to atopic disease is still being elucidated.⁵ Similar mechanisms of epigenetic dysregulation in this or other genes induced by dietary intake could underlie the development of FA.

Epigenetic mechanisms and the gut microbiome may influence the development of atopic disease both separately and through interaction with one another. A review by Paparo and colleagues⁴⁶ explains that dietary differences have been associated with differences in the metabolic outputs of the gut microbiome and that these metabolic outputs then go on to influence epigenetic changes in host immune cells, such as macrophages and DCs. A focus on multistep causal pathways, such as this one, will be important as more work is done to further clarify the pathogenesis of FA and other atopic conditions.

Some of the most influential gut microbial outputs to be identified are short-chain fatty acids (SCFAs), which may help explain how the microbes in the gut interact with diet to modulate allergic responses. SCFAs are produced by commensal bacteria in the gut through fermentation of undigested dietary carbohydrates.⁴⁹ Higher adherence to the Mediterranean diet is associated with higher levels of fecal SCFA,⁵⁰ which can be attributed the Mediterranean diet's high levels of undigestible complex carbohydrates and fiber.⁵¹ SCFAs are used by colonic epithelial cells for energy, having epigenetic influence on immune tolerance in the gut by modulating tight junction proteins, mucus production, and several types of adaptive (T cells and B cells) and innate (macrophages, neutrophils, and DCs) immune cells.^{52–67}

The 4 major SCFA groups are acetate, propionate, butyrate, and valerate. Butyrate has been well documented as playing a modulatory role in the gut by strengthening epithelial barrier function⁴⁹ and promoting numerous immune tolerance mechanisms.⁴ In a murine model, higher acetate and butyrate levels observed in mice fed a high-fiber diet were associated with increased numbers of CD103⁺ DCs, which promote the growth of Tregs, protecting against FA.⁵¹ A prospective cohort study of 139 children in Sweden demonstrated a consistent association between SCFA levels and FA.^{58,59} They found that lower fecal butyrate and valerate levels at 1 year were associated with both current FA at 1 year and development of FA by 4 years.^{58,59} In addition to explaining the mechanisms by which the diet has an impact on risk of atopy, SCFAs show early promise as a treatment of allergic disease, because oral butyrate supplementation can inhibit allergic responses in mice.⁴ Taken together, these findings support that SCFAs, butyrate in particular, may be 1 link to explain associations between dietary intake and FA development, helping to elucidate why Mediterranean diet-like, fiber-rich diets confer protection against FA.^{40,51,60}

Link Between Diet and Colonization of Protective Bacterial Species Within the Gut

Genetically similar individuals living in different environments have been demonstrated to have significantly different rates of atopic disease, including higher rates of atopic disease in African American children compared with African children living in African countries.⁶¹ This emphasizes the importance of environmental factors, such as diet

and urbanization, in the development of atopic disease. There is evidence that the protective effect of living in Africa may be explained by the beneficial effect of high-fiber diets and rural living on the gut microbiome. For example, the abundance of the *Prevotella* genus in the gut has been associated with agrarian diets rich in fruits and vegetables, whereas westernized diets abundant in fat and protein tend to be dominated by *Bacteroides*.⁶² *Prevotella* abundance also positively correlates with living in rural environments, and this association has been attributed to higher dietary intake of complex carbohydrates in rural populations.⁶³ Although these findings have begun to explain the association between environmental factors and atopic disease, members of the *Prevotella* genus have been associated with both inflammatory conditions^{66,67} and health-promoting, anti-inflammatory effects.^{50,63,68–71} These inconsistencies highlight the necessity of species and strain specific analysis in fully understanding the effects of this genus on the gut microbiome and atopic disease.⁶⁷ Evidence of a link to atopic disease at lower taxonomic levels may offer more clarity, and it is already available in some cases, like *Prevotella copri*.

P copri is a species within the *Prevotella* genus that is necessary for the breakdown of complex polysaccharides.⁷² There is evidence that diet influences *P copri* at both the species and strain levels. De Filippis and colleagues⁶² demonstrated that different strains of *P copri* are found in individuals with different dietary patterns. *P copri* strains from vegans and individuals with agrarian-like diets demonstrated higher potential for complex fiber breakdown than the *P copri* strains found in individuals with high-fat and high-protein diets. In short, the high-fiber-consuming people had high-fiber-consuming *P copri*.⁶² Another study in young children had similar results, demonstrating an inverse association between levels of *P copri* in the gut and dietary intake of sugar and saturated fat.¹⁸ This same study found significantly reduced levels of *P copri* in children with atopic disease compared with healthy children,¹⁸ and another showed that succinate, a metabolite of *P copri*, is present at lower levels in infants who go on to develop atopic disease.⁷³ Maternal *P copri* during gestation also may be protective, because 1 study demonstrated significantly lower levels of this species in mothers whose infants later have FA.⁷⁴ Taken together, these results suggest that it is possible that the diet and the environment select the gut microbes and that the gut microbes go on to select the disease. *P copri*, and the most protective strains within it, appear to thrive in the settings of a healthy diet and closer contact with natural environments, where they can in turn protect against atopic disease, such as FA. Conversely, poor diet and altered microbial exposure in urban settings, combined with a lack of protective factors from *P copri*, may result in poor control of sugar metabolism, setting the stage for atopic disease.¹⁸

Other bacterial genera and species in the gut also have been implicated in the development of atopic disease. A study in 38 South African toddlers aged 12 months to 36 months found no significant differences in the gut microbiota of healthy children compared with those with FA.⁷⁵ Investigation of a larger sample ($n = 83$) from the same population of toddlers, however, found many significant differences in the gut microbiota between healthy children and those AD.¹⁸ This is notable when discussing FA because it so often is comorbid with AD, with evidence that up to a third of children with AD also suffer from FA.^{76,77} Another study examining 79 Chinese infants 2 months to 11 months old did find significant differences in the gut microbiota of healthy infants compared with those with FA.⁷⁸ Both studies found that the gut microbiota of healthy infants/toddlers have increased *Streptococcus* and decreased *Faecalibacterium* and *Clostridium cluster XIVa* compared with those with AD¹⁸ or FA.⁷⁸ Toddlers with AD, however, had decreased *Prevotella* and increased *Blautia*, *Bacteroides*, *Lachnospiraceae*, and *Clostridium cluster XI*.^{18,78} Although the conflicts in these findings could be

attributed to any number of factors, they may indicate that the gut microbiome exerts its influence on FA differently in the first year of life while the immune system is forming.

Role of Probiotics in Modulating Gut Microbiome and Preventing Food Allergy

Resolution of allergic disease has been described on reintroduction of commensal microbes to the gut microbiome, but the role of probiotics in FA is incompletely understood.⁵ Probiotic supplements most commonly include the *Lactobacillus* and *Bifidobacterium* phyla, which are found at higher levels in nonallergic children.⁷⁹ Their presence also has been shown to confer protection against atopic disease and correct gut dysbiosis in both animals and humans.^{5,80–83}

There are many mechanisms by which probiotics interact with the gut microbiome that may confer protection against allergic disease. These include direct interactions with the gut epithelial cells to strengthen the epithelial barrier, competition with pathogenic microbes via depletion of nutrients, production of acid, creation of antimicrobial metabolites, and interactions with the immune system to promote tolerogenic responses.^{5,83,84} By adhering strongly to the gut epithelium and taking up space and nutrients, probiotics block adhesion of pathogenic bacteria and strengthen barrier function to prevent pathogen invasion.^{85–87} Probiotics containing lactic acid bacteria, such as species contained within *Lactobacillus* and *Bifidobacterium*, also have been demonstrated to harm pathogens directly through secretion of antimicrobial substances and signaling peptides that promote further colonization of antipathogenic bacteria.^{88,89} Probiotics also can be immunomodulatory, with evidence of bacterial metabolites, such as SCFAs and biotransformed bile acids acting as ligands in cell signaling mechanisms.⁹⁰ Although the precise nature of probiotics in inducing immune tolerance is not well understood, it has been demonstrated that effective probiotics tend to reduce the allergenic T_H2 profile to restore T_H1/T_H2 balance.⁵

Probiotic supplementation shows early promise as a safe and effective strategy for both treatment and prevention of atopic disease, including FA. *Lactobacillus* species, in particular, have been demonstrated to mitigate FA.⁵ Despite considerable variation in the species, strains, and combinations used during these investigations, the benefits of *Lactobacillus* on improving allergic symptoms have been fairly consistent.⁵ For example, a randomized controlled trial of 62 children with peanut allergy demonstrated that concurrent administration of a *Lactobacillus* probiotic with peanut oral immunotherapy (OIT) resulted in sustained unresponsiveness to peanut allergens in 82.1% of the treated group versus 3.6% of patients receiving a placebo.⁹¹ The trial did not include groups treated with probiotic or OIT alone, so it is not possible to conclusively determine their individual impact. The results of a similar study that administered OIT alone, however, showed only a 50% sustained unresponsiveness rate,⁹² suggesting that the probiotic may have significantly boosted efficacy. Although there is some literature that proposes solutions like the inclusion of probiotics in foods to combat allergic disease,⁷⁹ Paparo and colleagues argue that the evidence is not yet robust enough to recommend probiotics for treatment or prevention of atopy.⁹³ Further investigation is needed to determine the most beneficial probiotic dose, delivery, and types of bacteria, but such research has significant potential to create actionable solutions for FA.

CLINICS CARE POINTS

- A low species richness of gut microbiota at 3 months of age is associated with increased likelihood of FA by 1 year of age.¹⁵

- Each quartile increase in the ratio of *Enterobacteriaceae/Bacteroidaceae* increases a child's risk of developing food sensitization 2-fold.¹⁵
- Breastfeeding currently is recommended for the possible prevention of allergic diseases, including FA.¹⁹
- Early infant feeding patterns have a significant effect on the composition of the infant gut microbiome.²³
- Breastfeeding is a major source of beneficial bacterial species, including *Bifidobacteria*, *Lactobacilli*, and *Enterobacteriaceae*.¹⁹
- Adherence to a Mediterranean diet during lactation and gestation has been found to protect against the subsequent development of allergic disease and FA.³³
- An infant diet rich in fruits, vegetables, and homemade foods is associated with lower rates of FA by 2 years of age.⁴⁰
- In older children, adherence to a Mediterranean diet also has been shown to reduce wheeze and hay fever symptoms.^{42,43}
- High-sugar and high-fat diets also have been associated with an increased risk of atopic disease in both children and adults.^{18,45}
- Lower levels of SCFA groups (specifically, butyrate, and valerate) at 1 year of age are associated with development of FA by 4 years of age.^{58,59}
- Certain bacterial species, including *Prevotella* have been found to protect against the development of FA and are associated with diets rich in fruits and vegetables.⁶²
- Resolution of allergic disease has been described on reintroduction of commensal microbes to the gut microbiome.⁵

SUMMARY

In conclusion, the infant gut microbiome has a significant impact on a child's overall gut health and predisposition for FA. The development of an individual's gut microbiome begins as early as gestation. Environmental factors contributing to gut dysbiosis from that time forward can exert influence over microbiota composition and overall species richness. Although breastfeeding is not correlated directly with lower risk for FA development, infants who are breastfed have been found to have a higher diversity of gut microbiota and possess particular bacterial species that serve a protective role against the development of FA.^{19,24} Additionally, studies suggest that when lactating mothers and table-fed infants adhere to a Mediterranean diet, there is a lower risk of developing atopic disease, including FA.³³ Diet also has been correlated with a higher abundance of *Prevotella* species of bacteria, which has been shown to serve as a protective factor against inflammation and the development of atopic disease.⁶³ Recent studies suggest that reintroducing commensal microbes via probiotics potentially can confer protection against atopic disease when these commensal bacteria are lost during gut dysbiosis.⁵ Further research is necessary to better understand the timeline for gut dysbiosis in early infancy and the commensal microbes necessary to protect against FA. This area of research is promising for the development of therapeutic targets for protection against FA in early infancy.

DISCLOSURE

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