HHS Public Access

Author manuscript

Pediatr Clin North Am. Author manuscript; available in PMC 2016 December 01.

Published in final edited form as:

Pediatr Clin North Am. 2015 December ; 62(6): 1479–1492. doi:10.1016/j.pcl.2015.07.007.

Gut Microbiome and the Development of Food Allergy and Allergic Disease

Benjamin T. Prince, MD[1,2], **Mark J. Mandel, PhD**[3], **Kari Nadeau, MD, PhD**[4], and **Anne Marie Singh, MD**[1,2]

[1]Department of Pediatrics, Division of Allergy and Immunology, Ann & Robert H. Lurie Children's Hospital of Chicago, Northwestern University, Chicago, Illinois

[2]Department of Medicine, Division of Allergy and Immunology, Northwestern Feinberg School of Medicine, Northwestern University, Chicago, Illinois

[3]Department of Microbiology-Immunology, Northwestern Feinberg School of Medicine, Northwestern University, Chicago, Illinois

[4]Department of Pediatrics, Division of Allergy, Immunology, and Rheumatology, Stanford University School of Medicine, Stanford, California

Abstract

The prevalence of food allergy and other allergic diseases continues to rise within the industrialized world, yet the cause of this epidemic remains elusive. Environmental factors such as microbial exposures have more recently been implicated as one possible driving factor behind the increasing burden of allergic disease. The impact of gut microbiome on human development, nutritional needs, and disease has become evident with advances in our ability to study these complex communities of microorganisms, and there is a growing appreciation for the role of the microbiome in immune regulation. Several studies have examined associations between changes in the commensal microbiota and the development of asthma, allergic rhinitis, and asthma, but far less have evaluated the impact of the microbiome on the development of food allergy. In this article we review the human gastrointestinal microbiome, focusing on the theory and evidence for its role in the development of IgE-mediated food allergy and other allergic diseases.

Keywords

Microbiome; Gut Microbiota; Commensal Flora; Food Allergy; Asthma; Allergic Rhinitis; Eczema; Allergy; Allergic Disease

Address correspondence to Anne Marie Singh, MD, Ann & Robert H. Lurie Children's Hospital of Chicago, Northwestern University, Department of Allergy & Immunology, 225 E. Chicago Avenue #60, Chicago, IL 60611, USA. Tel: +1-312-227-6010; Fax: +1-312-227-9401; anne-singh@northwestern.edu.

Conflicts of Interest/Corporate Sponsors: None

Introduction

Food allergy, defined as an adverse, immune-mediated reaction to a food that is reproducible upon a subsequent exposure,[1] affects nearly 5% of all adults[2] and up to 8% of children in the United States.[3] Recent data from the US Centers for Disease Control and Prevention (CDC) have found that the prevalence among children 0 to 17 years increased by 50% from 1999 to 2011.[4] Even prior to this increase in prevalence, food allergies were the leading cause of anaphylaxis in patients presenting to the emergency department in the US.[5] Studies have also shown that a diagnosis of food allergy results in a significantly lower quality of life.[6–8] Despite the increase in prevalence, the life-threatening potential, and the disease burden of food allergies, the cause of this epidemic remains elusive.

One of the leading theories to explain this modern day allergy epidemic was introduced by Strachan in 1989 as the hygiene hypothesis. In his hypothesis, Strachan proposed that a larger family size was protective against allergic disease because of early life exposure to sibling infections.[9] However, since its introduction, others have revisited this idea, suggesting that that changes in early life viral and bacterial exposures and intestinal colonization patterns in western countries have contributed to the failure to induce and maintain tolerance, a state of unresponsiveness to harmless antigens.[10,11]

The Human Microbiome

It has been estimated that the human gut is populated with up to 100 trillion microbes.[12] Rough estimates are that the microbiota (previously termed flora or microflora) contain on the order of 150-fold more genes than are encoded in the human genome.[13] The ancient symbiotic relationship between multicellular animals and resident microbes has shaped the evolution of our immune system into its present state.[14] Although the composition of the microbiota changes substantially from infancy to adulthood, the majority of organisms come from the four phyla Actinobacteria, Bacteroidetes, Firmicutes, and Proteobacteria.[15]

The advent of high-throughput DNA deep sequencing technologies has revolutionized the ability to characterize microbial diversity and compare this diversity across organs and individuals. Sequencing of diagnostic regions of the 16S rRNA gene sequence provides a robust method to identify the bacteria present in a sample. Because clinical samples can be sequenced directly, organisms are identified even if they cannot yet be cultured, and the resulting 16S rRNA sequence provides a reference for known bacterial taxa (i.e., species) and for novel ones.[16,17] This bacterial census provides information on specific taxa that are present; loss of specific taxa and alterations in the community structure are associated with disease progression (e.g., infection by *Clostridium difficile*).[18] Beyond 16S data, genome sequencing from microbial communities (i.e., metagenomics) can enable functional studies, identify gene categories that influence the host, and reveal conservation at the level of gene function even in cases where those genes are derived from unrelated organisms.[19,20] Much current work is aimed at extending these techniques to understand gene expression at the RNA (transcriptional profiling) and protein (proteomics) levels, and to understand how microbial communities affect the flux of metabolites (metabolomics) in the host.[21]

The Microbiome and Immune Development

Early microbial colonization plays an important role the development of both the innate and the adaptive immune systems, [22] and there are several proposed mechanisms to explain how alterations in microbiome could lead to the development of allergic disease. Experimental, germ-free (gnotobiotic) mouse models have demonstrated that gut-associated lymphoid tissues (GALT) fail to develop when microbial colonization is delayed, leading to a Th2 skewed immune response.[23] Secretory IgA produced by resident B cells in GALT tissue may also promote oral tolerance by binding allergens in the gut and preventing their uptake.[24] Microbial colonization has been shown to be important in the development of Th1[25,26] and regulatory T cells (Tregs),[27–31] which are necessary to maintain immunologic balance and promote tolerance. Microbiota may also influence epigenetic modifications of genes. It is known that various forms of epigenetic changes, such as DNA methylation and histone modifications play an important role in immune development and regulation,[32] and microbial metabolites butyrate and propionate have been shown to have inhibitory effects on histone deacetylases that may promote the development of peripherally induced Tregs.[33,34] Lastly, the gut microbiota plays a significant role in the development and maintenance of barrier function[35,36] and it is thought that a breakdown of this epithelial barrier may lead to allergic sensitization.[37,38]

The impact of the microbiome on human development, nutritional needs, and even psychological variations has become evident with advances in our ability to study these complex communities of microorganisms.[39,40] There is also a growing appreciation for the role of the microbiome in immune regulation, and it is plausible that changes in the commensal microbiota may influence the development of food allergy and other allergic diseases.[36] When considering various determinants that may influence the unique bacterial families that constitute the microbiome, there are several factors to consider, including: environmental setting, mode of delivery, birth order, antibiotic exposure, and diet.[41] In this review, we will explore the relationship between the gastrointestinal microbiota and IgE-mediated food allergy and other allergic diseases.

The Influence of the Microbiome in Allergic Disease

The potential impact of the microbiome on allergic disease was first studied in Europe using cross-sectional surveys to examine the prevalence of allergic diseases in children. The authors found that children living in farming environments had a significantly decreased frequency of hay fever, asthma and eczema compared to children living in urban areas.[42,43] This relationship was further explored in the GABRIELA and PARSIFAL cohorts, which confirmed previous observations that children living on farms had decreased rates of allergic disease compared to urban children.[44,45] Although most studies have focused on the impact of postnatal environmental exposure, there is increasing evidence that prenatal exposure may also be important.[46–48] Epidemiological studies examining the effect of prenatal exposures on the development of allergic disease have shown that maternal exposure to farming environments during pregnancy is associated with decreased rates of asthma, allergic rhinitis and eczema in their children.[49,50]

Animal Exposure

Recent studies suggest that the protective association between farming and the development of allergic disease may be due to differences in microbial exposure. Using single-strand conformational polymorphism DNA analysis to examine house dust in the same GABRIELA and PARSIFAL cohorts, Ege *et al.* found that the diversity of microbial exposure was inversely associated with the prevalence of asthma even after controlling for farming status.[51] Moreover, investigators examining the gut microbiota in children using 16S rDNA sequencing have shown that decreased microbial diversity early in life is associated with the development of asthma,[52] allergic rhinitis,[53] and atopic dermatitis.[54] Similarly, pet ownership has also been shown to increase the diversity of the microbial composition of house dust[55] and infant fecal samples,[56] and early life pet ownership has been associated with a decreased risk for asthma and other atopic diseases.[57–59] Specifically, several studies have shown that infants who develop allergic disease later in life tended to have less *Bacteroides, Bifidobacteria* and *Enterococci*, but more *Clostridiae* comprising their microbiome early in life (Table 1).[54,60–62] It appears that a diverse microbial exposure both perinatally and early in life modifies both the innate[49] and adaptive[63] immune system resulting in a significantly decreased risk of allergic disease.

Mode of Delivery

Another factor that has been implicated in altering the human microbiome is birth by Caesarean-section. Instead of traveling through the birth canal where colonization by maternal microbiota would typically occur, the baby is delivered through a sterile surface.[64] Subsequently, delivery by Caesarean-section has been shown to delay the development of the gut microbiota and shape its colonization to patterns similar to the maternal skin.[65] Studies examining the impact of this difference in microbiome and the development of allergic disease have found that children born by Caesarean-section had decreased microbial diversity and reduced Th1 responses during the first two years of life.[26] Other studies have shown an association between Caesarean-section delivery and the development of asthma, allergic rhinitis, and eczema.[62,66–68] Specifically, the microbiome of babies born by Caesarean-section showed a reduced abundance of *Bacteroides*, *B*ifidobacteria, and *E. coli* but increased amounts of *Klebsiella*, *Enterobacter*, *Enterococcus*, and clostridia (Table 1).[26,62,69,70]

Birth Order and Family Size

An observation that infants with higher numbers of siblings had a decreased incidence of allergic disease was one driving principles behind Strachan's proposal of the initial hygiene hypothesis.[9] Since then, several studies have reproduced the inverse relationship between sibling number and asthma, allergic rhinitis, and eczema.[71] This association was initially thought to arise from an increased exposure to infections during childhood. There is now evidence that birth order and family size may also mediate their protective effects through alterations in the gut microbiome.[70] Penders and colleagues showed that infants with an increased number of older siblings had decreased colonization rates of clostridia and increased rates of *Lactobacillus* and *Bacteroides.* Moreover, colonization with clostridia was associated with an increased risk of developing atopic dermatitis (Table 1).[70]

Antibiotic Exposure

It is well known that early life antibiotic exposure can influence an infant's microbiome. Data from a population-based study done by the CDC from 2003–2004 reported that 32% of laboring women received intrapartum antibiotics for group B Streptococcus infection prevention, maternal pyrexia, prematurity, and other factors.[72] One of the most frequent reasons for early antibiotic use is prematurity, and it has been shown that bacterial microbiota colonization can be delayed in children who have a prolonged neonatal hospital course.[73] Studies using qPCR and 16S rRNA sequencing to specifically examine microbiome changes in preterm infants as a result of perinatal antibiotic exposure have found that infants receiving antibiotics had a lower bacterial diversity and higher abundance of *Enterobacter*.[74,75] Similar studies on full term infants receiving perinatal antibiotics also showed that antibiotic treatment as associated with less bacterial diversity along with higher proportions of *Proteobacteria* and *Enterobacteriaceae* and lower proportions of *Bifidobacterium* and *Lactobacillus* (Table 1).[76,77] When considering the relationship between the development of allergic disease and early-life antibiotic exposure, there appears to be an association between both prenatal[78,79] and postnatal[79–81] antibiotic exposure and asthma. It should be noted, however, that many studies might be confounded by an increased treatment of respiratory infections at an early age when manifestations of asthma may be indistinguishable from infection.[82,83] There may also be an association between postnatal but not prenatal antibiotic exposure and the development of atopic dermatitis,[84] but a significant relationship between early-life antibiotic use and allergic rhinitis has not been established.[85,86]

Diet

A final area that has been shown to have significant effects on the microbiome is diet.[87] One specific dietary aspect that has been extensively studied in regard to its effects on gut microbial composition and the development of allergic disease is bottle versus breast-feeding. It has been demonstrated that breast milk may contain small oligosaccharides that promote the colonization of beneficial bacteria such as *B*ifidobacteria,[88] Most studies over the last 30 years, however, have only shown minor differences in gut microbiota between breast and formula-fed infants.[69] One of the most reproducible differences between breast and formula-fed infants is that formula fed infants have higher amounts of *Clostridium difficile* that make up their gut microbiome.[89–92] Some studies also suggest that *Bacteroides*, *Enterococci*, and *Enterobacteriaceae* may be more common in the microbiome of formula fed infants, where staphylococci tend to be more prevalent in breast fed infants (Table 1).[69] When evaluating the impact of breast-feeding on the development of allergic disease, breast-fed infants appear to have a lower rate of early wheezing and asthma, but this affect seems to diminish with age.[93–96] Studies examining the association between breast-feeding and the development of allergic rhinitis and eczema have been inconclusive, though there may a protective effect for eczema in high risk infants.[95,97]

More generally, it is well known that westernized countries have a higher prevalence of allergic disease,[98] and modern western diets have been associated with differences in the gut microbiome.[87] Studies have also shown that differences in consumption of animal fat, carbohydrates, and fiber can cause changes in gut microbiota that can have profound affects

on the immune system.[99,100] A Recent study further demonstrated that microbial metabolism of dietary fiber and subsequent production of short-chain fatty acids influenced Th2 inflammation and allergic airway disease in mice.[101] Work directly addressing the influence of dietary factors and the development of allergic disease in humans are lacking however.

The Influence of the Microbiome in Food Allergy

In contrast to other allergic diseases, there is significantly less literature specifically evaluating the impact of the microbiome on the development of food allergy, and a majority of studies have been done using mouse models. Gnotobiotic and antibiotic treated mice that are reconstituted with well-characterized populations of gut microbiota can provide a particularly useful insight into the role that the microbiome plays in the maintenance of oral tolerance.[23,102,103]

Murine Models

One of the first studies investigating the impact of the gut microbiota on oral tolerance induction showed that gnotobiotic mice had Th2 skewing and increased IL-4 production with OVA challenge that was abrogated with intestinal microbiota reconstitution of the bacteria *Bifidobacterium infantis*.[23] The authors demonstrated that the *Bifidobacterium* reconstitution was only effective when performed during the neonatal period, but not in older mice suggesting that there may be a window of time during immune development in which the commensal microbiota plays an important regulatory role.[23] In a similar gnotobiotic mouse model, antibiotic treated mice were shown to have an increased susceptibility to peanut sensitization characterized by increased peanut specific IgE and anaphylactic symptoms with peanut challenge.[102,103] Moreover, colonizing antibiotic-treated mice with a Clostridia-enriched microbiota, which has been previously shown to induce colonic Tregs,[28,104] confers a food allergy protective phenotype in an IL-22 dependent mechanism by affecting intestinal barrier function and reducing the amount of peanut allergen in the bloodstream after intragastric gavage.[103] Another study demonstrated that colonization of gnotobiotic mice with *Bifidobacterium* spp. and *Bacteroides* spp. from the fecal microbiota of healthy infants was protective in a mouse model of cow's milk allergy.[105] Commensal microbiota may also impact the development of food allergy is through its activation of toll-like receptors (TLR) of intestinal epithelial cells (IECs).[106] TLR4 deficient mice have been shown to have a Th-2 skewed immune response and an increased susceptibility to food allergy that is abrogated with a TLR9 ligand.[102] Furthermore, peripheral blood mononuclear cells (PBMCs) from food allergic patients were shown to have a negative effect on barrier function of IECs *in vitro* that was prevented with TLR9 activation.[107] Finally, a specific microbiota signature was recently linked to mice carrying a gain-of-function mutation in the IL-4 receptor α chain that results in an increased susceptibility to oral allergic sensitization and anaphylaxis.[108] The authors demonstrate that germ-free, wild-type mice reconstituted with this microbiota rendered these animals more prone to developing food allergy.

Human Studies

There have been a few epidemiological studies that have examined the relationship between environmental factors that are known to alter the gut microbiome and food allergy. One important aspect to consider in many of these studies is how the diagnosis of food allergy is established. Many studies rely on self-reported diagnosis of food allergy or evidence of IgE sensitization with either skin-prick testing (SPT) or serology, which is notoriously inaccurate compared to the gold standard of oral food challenge (OFC).[109,110]

Mode of delivery has been the most widely studied environmental factor thought to contribute to the development of food allergy. Overall, there is evidence that Caesarean-section delivery increases the risk of developing IgE sensitization to food allergens,[111] but studies utilizing OFC proven food allergy have shown mixed results.[112–115] Although several studies have addressed the effect of farming environment and animal exposure on the development of other allergic diseases, far less have examined this environmental exposure and food allergy. In an Australian infant cohort of 5276 infants, J.J. Koplin *et al.* found that the presence of a dog in the home was inversely associated with the diagnosis of egg allergy at 1 year of age (aOR 0.72),[115] however, this is the only study with OFC confirmed food allergy and more research needs to be done.[116] The same authors used this infant cohort to also examine the influence of birth order on food allergy and found that children with older siblings had a significantly reduced risk of egg allergy at 1 year of age.[115] Similar results have been found in studies evaluating siblingship size and cow milk allergy (CMA).[114] Antibiotic exposure has shown conflicting results when assessed as a risk factor for developing food allergy. Although one study found that both pre and postnatal antibiotic exposure was associated with an increased risk of CMA,[117] other studies have not demonstrated a statistically significant association.[112,115,118] A final area that has been evaluated in association with the development of food allergy is bottle versus breast-feeding. Aside from the fact that many studies that have examined this relationship rely on the presence of sensitization as a marker for food allergy, another obstacle in interpreting this literature is that the extent and duration of breast-feeding varies substantially between studies. Considering these limitations, there is insufficient data at this time to suggest whether breast-feeding is a protective factor in the development of food allergy.[95,119,120]

Only a few studies have assessed the specific microbiota within the human gut that have been associated with the development of food allergy. Using conventional culturing techniques, a Spanish cohort of 46 patients with CMA demonstrated a greater total bacterial count and more anaerobes in the feces of allergic patients at diagnosis compared to matched controls, but no difference in the percentage of bacterial species.[121] In a follow-up study of the same patient cohort, the authors better characterize the fecal microbiota using 10 fluorescent *in situ* hybridization and find that CMA patients had significantly more *Clostridium coccoides* and *Atopobium* cluster species compared to non-allergic controls, but there were no differences in *Bifidobacteria, Lactobacilli,* or *Bacteroides* genera.[122] Using 16SrRNA sequencing, a separate study found increased levels of *Clostridium sensu stricto* and *Anaerobacter* but decreased levels of *Bacteroides* and *Clostridium* XVIII in the feces of 17 Chinese infants with IgE mediated food allergy.[123] Finally, using 16S rRNA sequencing to examine the gut microbiota in cohort of Canadian infants, M.B. Azad *et al.* showed that

the 12 infants with food sensitization on skin prick testing had increased amounts of *Enterobacteriaceae* and less *Bacteroidaceae* in their feces.[124]

Conclusions

Early microbial colonization plays an important role the development of both the innate and the adaptive immune systems, and there are several proposed mechanisms to explain how alterations in microbiome could lead to the development of allergic disease. Although some studies have identified notable relationships between the gastrointestinal microbiota and the development of asthma, allergic rhinitis, and eczema, specific studies examining the microbiome in human food allergy are lacking. Animal models suggest that the microbiome, particularly early in life, may play a crucial role in the susceptibility to food sensitization and food allergy, however, more work is required to confirm these findings. As technology and knowledge of the microbiome advances, discoveries in food allergy and atopic disease will likely provide insight into primary prevention and treatment strategies.

References

1. Boyce JA, Assa'ad A, et al. NIAID-Sponsored Expert Panel, . Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. 2010; 126:S1–58.10.1016/j.jaci.2010.10.007
2. Sicherer SH, Sampson HA. Food allergy: Epidemiology, pathogenesis, diagnosis, and treatment. Journal of Allergy and Clinical Immunology. 2014; 133(2):291–307. e5. [PubMed: 24388012]
3. Gupta RS, Springston EE, Warrier MR, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. Pediatrics. 2011; 128(1):e9–17.10.1542/peds.2011-0204 [PubMed: 21690110]
4. Jackson KD, Howie LD, Akinbami LJ. Trends in allergic conditions among children: United States, 1997–2011. NCHS Data Brief. 2013; (121):1–8. [PubMed: 23742874]
5. Yocum MW, Khan DA. Assessment of patients who have experienced anaphylaxis: a 3-year survey. Mayo Clin Proc. 1994; 69(1):16–23. [PubMed: 7903730]
6. Lieberman JA, Sicherer SH. Quality of life in food allergy. Current Opinion in Allergy and Clinical Immunology. 2011; 11(3):236–242.10.1097/ACI.0b013e3283464cf0 [PubMed: 21464708]
7. Flokstra-de Blok BMJ, Dubois AEJ, Vlieg-Boerstra BJ, et al. Health-related quality of life of food allergic patients: comparison with the general population and other diseases. Allergy. 2010; 65(2): 238–244.10.1111/j.1398-9995.2009.02121.x [PubMed: 19796214]
8. Shemesh E, Annunziato RA, Ambrose MA, et al. Child and parental reports of bullying in a consecutive sample of children with food allergy. Pediatrics. 2013; 131(1):e10–7.10.1542/peds.2012-1180 [PubMed: 23266926]
9. Strachan DP. Hay fever, hygiene, and household size. BMJ. 1989; 299(6710):1259–1260. [PubMed: 2513902]
10. Wold AE. The hygiene hypotheslis revised: is the rising frequency of allergy due to changes in the intestinal flora? Allergy. 1998; 53(s46):20–25. [PubMed: 9825991]
11. Mutius von E. Allergies, infections and the hygiene hypothesis--the epidemiological evidence. Immunobiology. 2007; 212(6):433–439.10.1016/j.imbio.2007.03.002 [PubMed: 17544828]
12. Ley RE, Peterson DA, Gordon JI. Ecological and evolutionary forces shaping microbial diversity in the human intestine. Cell. 2006; 124(4):837–848.10.1016/j.cell.2006.02.017 [PubMed: 16497592]
13. Qin J, Li R, Raes J, et al. A human gut microbial gene catalogue established by metagenomic sequencing. Nature. 2010; 464(7285):59–65.10.1038/nature08821 [PubMed: 20203603]

14. McFall-Ngai M, Hadfield MG, Bosch TC, et al. Animals in a bacterial world, a new imperative for the life sciences. Proceedings of the National Academy of Sciences. 2013; 110(9):3229–3236.10.1073/pnas.1218525110/-/DCSupplemental
15. Wopereis H, Oozeer R, Knipping K, Belzer C, Knol J. The first thousand days - intestinal microbiology of early life: establishing a symbiosis. Pediatr Allergy Immunol. 2014; 25(5):428–438.10.1111/pai.12232 [PubMed: 24899389]
16. Morgan XC, Huttenhower C. Human microbiome analysis. PLoS computational biology. 201210.1371/journal.pcbi.1002808.s001
17. Ivanov II, Atarashi K, Manel N, et al. Induction of intestinal Th17 cells by segmented filamentous bacteria. Cell. 2009; 139(3):485–498.10.1016/j.cell.2009.09.033 [PubMed: 19836068]
18. Schubert AM, Rogers MAM, Ring C, et al. Microbiome data distinguish patients with Clostridium difficile infection and non-C. difficile-associated diarrhea from healthy controls. MBio. 2014; 5(3):e01021–14.10.1128/mBio.01021-14 [PubMed: 24803517]
19. Turnbaugh PJ, Hamady M, Yatsunenko T, et al. A core gut microbiome in obese and lean twins. Nature. 2009; 457(7228):480–484.10.1038/nature07540 [PubMed: 19043404]
20. Hehemann J-H, Correc G, Barbeyron T, Helbert W, Czjzek M, Michel G. Transfer of carbohydrate-active enzymes from marine bacteria to Japanese gut microbiota. Nature. 2010; 464(7290):908–912.10.1038/nature08937 [PubMed: 20376150]
21. Waldram A, Holmes E, Wang Y, et al. Top-down systems biology modeling of host metabotype-microbiome associations in obese rodents. J Proteome Res. 2009; 8(5):2361–2375.10.1021/pr8009885 [PubMed: 19275195]
22. Renz H, Brandtzaeg P, Hornef M. The impact of perinatal immune development on mucosal homeostasis and chronic inflammation. Nat Rev Immunol. 2012; 12(1):9–23.10.1038/nri3112 [PubMed: 22158411]
23. Sudo N, Sawamura S, Tanaka K, Aiba Y, Kubo C, Koga Y. The requirement of intestinal bacterial flora for the development of an IgE production system fully susceptible to oral tolerance induction. J Immunol. 1997; 159(4):1739–1745. [PubMed: 9257835]
24. Berin MC. Mucosal antibodies in the regulation of tolerance and allergy to foods. Semin Immunopathol. 2012; 34(5):633–642.10.1007/s00281-012-0325-9 [PubMed: 22777546]
25. Mazmanian SK, Liu CH, Tzianabos AO, Kasper DL. An immunomodulatory molecule of symbiotic bacteria directs maturation of the host immune system. Cell. 2005; 122(1):107–118.10.1016/j.cell.2005.05.007 [PubMed: 16009137]
26. Jakobsson HE, Abrahamsson TR, Jenmalm MC, et al. Decreased gut microbiota diversity, delayed Bacteroidetes colonisation and reduced Th1 responses in infants delivered by caesarean section. Gut. 2014; 63(4):559–566.10.1136/gutjnl-2012-303249 [PubMed: 23926244]
27. Round JL, Mazmanian SK. Inducible Foxp3+ regulatory T-cell development by a commensal bacterium of the intestinal microbiota. Proceedings of the National Academy of Sciences. 2010; 107(27):12204–12209.10.1073/pnas.0909122107/-/DCSupplemental
28. Atarashi K, Tanoue T, Shima T, et al. Induction of colonic regulatory T cells by indigenous Clostridium species. Science. 2011; 331(6015):337–341.10.1126/science.1198469 [PubMed: 21205640]
29. Geuking MB, Cahenzli J, Lawson MAE, et al. Intestinal bacterial colonization induces mutualistic regulatory T cell responses. Immunity. 2011; 34(5):794–806.10.1016/j.immuni.2011.03.021 [PubMed: 21596591]
30. Lochner M, Berard M, Sawa S, et al. Restricted microbiota and absence of cognate TCR antigen leads to an unbalanced generation of Th17 cells. The Journal of Immunology. 2011; 186(3):1531–1537.10.4049/jimmunol.1001723 [PubMed: 21178008]
31. Smith PM, Howitt MR, Panikov N, et al. The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. Science. 2013; 341(6145):569–573.10.1126/science.1241165 [PubMed: 23828891]
32. Obata Y, Furusawa Y, Hase K. Epigenetic modifications of the immune system in health and disease. Immunol Cell Biol. 201510.1038/icb.2014.114

33. Arpaia N, Campbell C, Fan X, et al. Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. Nature. 2013; 504(7480):451–455.10.1038/nature12726 [PubMed: 24226773]
34. Furusawa Y, Obata Y, Fukuda S, et al. Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. Nature. 2013; 504(7480):446–450.10.1038/nature12721 [PubMed: 24226770]
35. Kabat AM, Srinivasan N, Maloy KJ. Modulation of immune development and function by intestinal microbiota. Trends Immunol. 2014; 35(11):507–517.10.1016/j.it.2014.07.010 [PubMed: 25172617]
36. Hooper LV, Littman DR, Macpherson AJ. Interactions between the microbiota and the immune system. Science. 2012; 336(6086):1268–1273. [PubMed: 22674334]
37. Kalliomaki M, Isolauri E. Role of intestinal flora in the development of allergy. Current Opinion in Allergy and Clinical Immunology. 2003; 3(1):15–20.10.1097/01.all.0000053262.39029.a1 [PubMed: 12582309]
38. Chahine BG, Bahna SL. The role of the gut mucosal immunity in the development of tolerance versus development of allergy to food. Current Opinion in Allergy and Clinical Immunology. 2010; 10(4):394–399.10.1097/ACI.0b013e32833982ab [PubMed: 20629265]
39. Yatsunenko T, Rey FE, Manary MJ, et al. Human gut microbiome viewed across age and geography. Nature. 2012; 486(7402):222–227.10.1038/nature11053 [PubMed: 22699611]
40. Diaz Heijtz R, Wang S, Anuar F, et al. Normal gut microbiota modulates brain development and behavior. Proc Natl Acad Sci USA. 2011; 108(7):3047–3052.10.1073/pnas.1010529108 [PubMed: 21282636]
41. Rook GAW, Raison CL, Lowry CA. Microbial “old friends,” immunoregulation and socioeconomic status. Clin Exp Immunol. 2014; 177(1):1–12.10.1111/cei.12269 [PubMed: 24401109]
42. Ehrenstein Von OS, Mutius von E, Illi S, Baumann L, Bohm O, Kries von R. Reduced risk of hay fever and asthma among children of farmers. Clin Exp Allergy. 2000; 30(2):187–193. [PubMed: 10651770]
43. Riedler J, Braun-Fahrlander C, Eder W, et al. Exposure to farming in early life and development of asthma and allergy: a cross-sectional survey. Lancet. 2001; 358(9288):1129–1133.10.1016/S0140-6736(01)06252-3 [PubMed: 11597666]
44. Alfven T, Braun-Fahrlander C, Brunekreef B, et al. Allergic diseases and atopic sensitization in children related to farming and anthroposophic lifestyle--the PARSIFAL study. Allergy. 2006; 61(4):414–421.10.1111/j.1398-9995.2005.00939.x [PubMed: 16512802]
45. Genuneit J, Strachan DP, Buchele G, et al. The combined effects of family size and farm exposure on childhood hay fever and atopy. Pediatr Allergy Immunol. 2013; 24(3):293–298.10.1111/pai.12053 [PubMed: 23551831]
46. Jimenez E, Marin ML, Martin R, et al. Is meconium from healthy newborns actually sterile? Res Microbiol. 2008; 159(3):187–193.10.1016/j.resmic.2007.12.007 [PubMed: 18281199]
47. DiGiulio DB, Romero R, Amogan HP, et al. Microbial prevalence, diversity and abundance in amniotic fluid during preterm labor: a molecular and culture-based investigation. PLoS ONE. 2008; 3(8):e3056.10.1371/journal.pone.0003056.s006 [PubMed: 18725970]
48. Gosalbes MJ, Llop S, Valles Y, Moya A, Ballester F, Francino MP. Meconium microbiota types dominated by lactic acid or enteric bacteria are differentially associated with maternal eczema and respiratory problems in infants. Clin Exp Allergy. 2013; 43(2):198–211.10.1111/cea.12063 [PubMed: 23331561]
49. Ege MJ, Bieli C, Frei R, et al. Prenatal farm exposure is related to the expression of receptors of the innate immunity and to atopic sensitization in school-age children. J Allergy Clin Immunol. 2006; 117(4):817–823.10.1016/j.jaci.2005.12.1307 [PubMed: 16630939]
50. Douwes J, Cheng S, Travier N, et al. Farm exposure in utero may protect against asthma, hay fever and eczema. European Respiratory Journal. 2008; 32(3):603–611.10.1183/09031936.00033707 [PubMed: 18448493]
51. Mutius von E. Exposure to Environmental Microorganisms and Childhood Asthma. The new england journal of medicine. 2011:1–9.

52. Abrahamsson TR, Jakobsson HE, Andersson AF, Bjorksten B, Engstrand L, Jenmalm MC. Low gut microbiota diversity in early infancy precedes asthma at school age. Clin Exp Allergy. 2014; 44(6):842–850.10.1111/cea.12253 [PubMed: 24330256]
53. Bisgaard H, Li N, Bonnelykke K, et al. Reduced diversity of the intestinal microbiota during infancy is associated with increased risk of allergic disease at school age. J Allergy Clin Immunol. 2011; 128(3):646–52. e1–5.10.1016/j.jaci.2011.04.060 [PubMed: 21782228]
54. Abrahamsson TR, Jakobsson HE, Andersson AF, Bjorksten B, Engstrand L, Jenmalm MC. Low diversity of the gut microbiota in infants with atopic eczema. J Allergy Clin Immunol. 2012; 129(2):434–40. 440.e1–2.10.1016/j.jaci.2011.10.025 [PubMed: 22153774]
55. Fujimura KE, Johnson CC, Ownby DR, et al. Man's best friend? The effect of pet ownership on house dust microbial communities. J Allergy Clin Immunol. 2010; 126(2):410–2. 412.e1–3.10.1016/j.jaci.2010.05.042 [PubMed: 20633927]
56. Azad MB, Konya T, Maughan H, et al. Infant gut microbiota and the hygiene hypothesis of allergic disease: impact of household pets and siblings on microbiota composition and diversity. Allergy Asthma Clin Immunol. 2013; 9(1):15.10.1186/1710-1492-9-15 [PubMed: 23607879]
57. Ownby DR, Johnson CC, Peterson EL. Exposure to dogs and cats in the first year of life and risk of allergic sensitization at 6 to 7 years of age. JAMA. 2002; 288(8):963–972. [PubMed: 12190366]
58. Litonjua AA, Milton DK, Celedon JC, Ryan L, Weiss ST, Gold DR. A longitudinal analysis of wheezing in young children: the independent effects of early life exposure to house dust endotoxin, allergens, and pets. J Allergy Clin Immunol. 2002; 110(5):736–742.10.1067/mai.2002.128948 [PubMed: 12417882]
59. Wegienka G, Johnson CC, Havstad S, Ownby DR, Nicholas C, Zoratti EM. Lifetime dog and cat exposure and dog- and cat-specific sensitization at age 18 years. Clin Exp Allergy. 2011; 41(7):979–986.10.1111/j.1365-2222.2011.03747.x [PubMed: 21668818]
60. Kalliomaki M, Kirjavainen P, Eerola E, Kero P, Salminen S, Isolauri E. Distinct patterns of neonatal gut microflora in infants in whom atopy was and was not developing. J Allergy Clin Immunol. 2001; 107(1):129–134.10.1067/mai.2001.111237 [PubMed: 11150002]
61. Bjorksten B, Sepp E, Julge K, Voor T, Mikelsaar M. Allergy development and the intestinal microflora during the first year of life. J Allergy Clin Immunol. 2001; 108(4):516–520.10.1067/mai.2001.118130 [PubMed: 11590374]
62. van Nimwegen FA, Penders J, Stobberingh EE, et al. Mode and place of delivery, gastrointestinal microbiota, and their influence on asthma and atopy. J Allergy Clin Immunol. 2011; 128(5):948–55. e1–3.10.1016/j.jaci.2011.07.027 [PubMed: 21872915]
63. Stern DA, Riedler J, Nowak D, et al. Exposure to a farming environment has allergen-specific protective effects on TH2-dependent isotype switching in response to common inhalants. J Allergy Clin Immunol. 2007; 119(2):351–358.10.1016/j.jaci.2006.10.013 [PubMed: 17140649]
64. Biasucci G, Rubini M, Riboni S, Morelli L, Bessi E, Retetangos C. Mode of delivery affects the bacterial community in the newborn gut. Early Hum Dev. 2010; 86 (Suppl 1):13–15.10.1016/j.earlhumdev.2010.01.004 [PubMed: 20133091]
65. Dominguez-Bello MG, Costello EK, Contreras M, et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proceedings of the National Academy of Sciences. 2010; 107(26):11971–11975.10.1073/pnas.1002601107/-/DCSupplemental
66. Thavagnanam S, Fleming J, Bromley A, Shields MD, Cardwell CR. A meta-analysis of the association between Caesarean section and childhood asthma. Clin Exp Allergy. 2008; 38(4):629–633.10.1111/j.1365-2222.2007.02780.x [PubMed: 18352976]
67. Guibas GV, Moschonis G, Xepapadaki P, et al. Conception via in vitro fertilization and delivery by Caesarean section are associated with paediatric asthma incidence. Clin Exp Allergy. 2013; 43(9):1058–1066.10.1111/cea.12152 [PubMed: 23957341]
68. Pistiner M, Gold DR, Abdulkerim H, Hoffman E, Celedon JC. Birth by cesarean section, allergic rhinitis, and allergic sensitization among children with a parental history of atopy. J Allergy Clin Immunol. 2008; 122(2):274–279.10.1016/j.jaci.2008.05.007 [PubMed: 18571710]
69. Adlerberth I, Wold AE. Establishment of the gut microbiota in Western infants. Acta Paediatr. 2009; 98(2):229–238.10.1111/j.1651-2227.2008.01060.x [PubMed: 19143664]

70. Penders J, Gerhold K, Stobberingh EE, et al. Establishment of the intestinal microbiota and its role for atopic dermatitis in early childhood. J Allergy Clin Immunol. 2013; 132(3):601–607. e8.10.1016/j.jaci.2013.05.043 [PubMed: 23900058]
71. Karmaus W, Botezan C. Does a higher number of siblings protect against the development of allergy and asthma? A review. J Epidemiol Community Health. 2002; 56(3):209–217. [PubMed: 11854343]
72. Verani JR, McGee L, Schrag SJ. Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention (CDC). Prevention of perinatal group B streptococcal disease--revised guidelines from CDC, 2010. MMWR Recomm Rep. 2010; 59(RR-10):1–36. [PubMed: 21088663]
73. Bennet R, Eriksson M, Nord CE, Zetterstrom R. Fecal bacterial microflora of newborn infants during intensive care management and treatment with five antibiotic regimens. Pediatr Infect Dis. 1986; 5(5):533–539. [PubMed: 3763418]
74. Greenwood C, Morrow AL, Lagomarcino AJ, et al. Early empiric antibiotic use in preterm infants is associated with lower bacterial diversity and higher relative abundance of Enterobacter. J Pediatr. 2014; 165(1):23–29.10.1016/j.jpeds.2014.01.010 [PubMed: 24529620]
75. Arboleya S, Sanchez B, Milani C, et al. Intestinal Microbiota Development in Preterm Neonates and Effect of Perinatal Antibiotics. J Pediatr. 2015; 166(3):538–544.10.1016/j.jpeds.2014.09.041 [PubMed: 25444008]
76. Fouhy F, Guinane CM, Hussey S, et al. High-throughput sequencing reveals the incomplete, short-term recovery of infant gut microbiota following parenteral antibiotic treatment with ampicillin and gentamicin. Antimicrob Agents Chemother. 2012; 56(11):5811–5820.10.1128/AAC.00789-12 [PubMed: 22948872]
77. Tanaka S, Kobayashi T, Songjinda P, et al. Influence of antibiotic exposure in the early postnatal period on the development of intestinal microbiota. FEMS Immunol Med Microbiol. 2009; 56(1): 80–87.10.1111/j.1574-695X.2009.00553.x [PubMed: 19385995]
78. Stensballe LG, Simonsen J, Jensen SM, Bonnelykke K, Bisgaard H. Use of antibiotics during pregnancy increases the risk of asthma in early childhood. J Pediatr. 2013; 162(4):832–838. e3.10.1016/j.jpeds.2012.09.049 [PubMed: 23140881]
79. Murk W, Risnes KR, Bracken MB. Prenatal or early-life exposure to antibiotics and risk of childhood asthma: a systematic review. Pediatrics. 2011; 127(6):1125–1138.10.1542/peds. 2010-2092 [PubMed: 21606151]
80. Ong M-S, Umetsu DT, Mandl KD. Consequences of antibiotics and infections in infancy: bugs, drugs, and wheezing. Ann Allergy Asthma Immunol. 2014; 112(5):441–445. e1.10.1016/j.anai. 2014.01.022 [PubMed: 24631182]
81. Sun W, Svendsen ER, Karmaus WJJ, Kuehr J, Forster J. Early-life antibiotic use is associated with wheezing among children with high atopic risk: a prospective European study. J Asthma. 2015:1–6.10.3109/02770903.2014.999284 [PubMed: 25137342]
82. Wickens K, Ingham T, Epton M, et al. The association of early life exposure to antibiotics and the development of asthma, eczema and atopy in a birth cohort: confounding or causality? Clin Exp Allergy. 2008; 38(8):1318–1324.10.1111/j.1365-2222.2008.03024.x [PubMed: 18727794]
83. Cullinan P, Harris J, Mills P, et al. Early prescriptions of antibiotics and the risk of allergic disease in adults: a cohort study. Thorax. 2004; 59(1):11–15. [PubMed: 14694239]
84. Tsakok T, McKeever TM, Yeo L, Flohr C. Does early life exposure to antibiotics increase the risk of eczema? A systematic review. Br J Dermatol. 2013; 169(5):983–991.10.1111/bjd.12476 [PubMed: 23782060]
85. Harris JM, Mills P, White C, Moffat S, Newman Taylor AJ, Cullinan P. Recorded infections and antibiotics in early life: associations with allergy in UK children and their parents. Thorax. 2007; 62(7):631–637.10.1136/thx.2006.072124 [PubMed: 17289862]
86. Kummeling I, Stelma FF, Dagnelie PC, et al. Early life exposure to antibiotics and the subsequent development of eczema, wheeze, and allergic sensitization in the first 2 years of life: the KOALA Birth Cohort Study. Pediatrics. 2007; 119(1):e225–31.10.1542/peds.2006-0896 [PubMed: 17200248]

87. Maslowski KM, Mackay CR. Diet, gut microbiota and immune responses. Nat Immunol. 2011; 12(1):5–9.10.1038/ni0111-5 [PubMed: 21169997]

88. Zivkovic AM, German JB, Lebrilla CB, Mills DA. Human milk glycobiome and its impact on the infant gastrointestinal microbiota. Proc Natl Acad Sci USA. 2011; 108 (Suppl 1):4653–4658.10.1073/pnas.1000083107 [PubMed: 20679197]

89. Benno Y, Sawada K, Mitsuoka T. The intestinal microflora of infants: composition of fecal flora in breast-fed and bottle-fed infants. Microbiol Immunol. 1984; 28(9):975–986. [PubMed: 6513816]

90. Tullus K, Aronsson B, Marcus S, Mollby R. Intestinal colonization with Clostridium difficile in infants up to 18 months of age. Eur J Clin Microbiol Infect Dis. 1989; 8(5):390–393. [PubMed: 2502403]

91. Penders J, Thijs C, Vink C, et al. Factors influencing the composition of the intestinal microbiota in early infancy. Pediatrics. 2006; 118(2):511–521.10.1542/peds.2005-2824 [PubMed: 16882802]

92. Azad MB, Konya T, Maughan H, et al. Gut microbiota of healthy Canadian infants: profiles by mode of delivery and infant diet at 4 months. Canadian Medical Association Journal. 2013; 185(5):385–394.10.1503/cmaj.130147 [PubMed: 23401405]

93. Silvers KM, Frampton CM, Wickens K, et al. Breastfeeding protects against current asthma up to 6 years of age. J Pediatr. 2012; 160(6):991–6. e1.10.1016/j.jpeds.2011.11.055 [PubMed: 22289356]

94. Guibas GV, Xepapadaki P, Moschonis G, et al. Breastfeeding and wheeze prevalence in pre-schoolers and pre-adolescents: the Genesis and Healthy Growth studies. Pediatr Allergy Immunol. 2013; 24(8):772–781.10.1111/pai.12169 [PubMed: 24298900]

95. Matheson MC, Allen KJ, Tang MLK. Understanding the evidence for and against the role of breastfeeding in allergy prevention. Clin Exp Allergy. 2012; 42(6):827–851.10.1111/j.1365-2222.2011.03925.x [PubMed: 22276526]

96. Dogaru CM, Nyffenegger D, Pescatore AM, Spycher BD, Kuehni CE. Breastfeeding and childhood asthma: systematic review and meta-analysis. Am J Epidemiol. 2014; 179(10):1153–1167.10.1093/aje/kwu072 [PubMed: 24727807]

97. Blattner CM, Murase JE. A practice gap in pediatric dermatology: does breast-feeding prevent the development of infantile atopic dermatitis? J Am Acad Dermatol. 2014; 71(2):405–406.10.1016/j.jaad.2014.01.868 [PubMed: 25037796]

98. Devereux G. The increase in the prevalence of asthma and allergy: food for thought. Nat Rev Immunol. 2006; 6(11):869–874.10.1038/nri1958 [PubMed: 17063187]

99. Wu GD, Chen J, Hoffmann C, et al. Linking long-term dietary patterns with gut microbial enterotypes. Science. 2011; 334(6052):105–108.10.1126/science.1208344 [PubMed: 21885731]

100. Thorburn AN, Macia L, Mackay CR. Diet, metabolites, and “western-lifestyle” inflammatory diseases. Immunity. 2014; 40(6):833–842.10.1016/j.immuni.2014.05.014 [PubMed: 24950203]

101. Trompette A, Gollwitzer ES, Yadava K, et al. Gut microbiota metabolism of dietary fiber influences allergic airway disease and hematopoiesis. Nat Med. 2014; 20(2):159–166.10.1038/nm.3444 [PubMed: 24390308]

102. Bashir MEH, Louie S, Shi HN, Nagler-Anderson C. Toll-like receptor 4 signaling by intestinal microbes influences susceptibility to food allergy. J Immunol. 2004; 172(11):6978–6987.10.4049/jimmunol.172.11.6978 [PubMed: 15153518]

103. Stefka AT, Feehley T, Tripathi P, et al. Commensal bacteria protect against food allergen sensitization. Proc Natl Acad Sci USA. 2014; 111(36):13145–13150.10.1073/pnas.1412008111 [PubMed: 25157157]

104. Atarashi K, Tanoue T, Oshima K, et al. Treg induction by a rationally selected mixture of Clostridia strains from the human microbiota. Nature. 2013; 500(7461):232–236.10.1038/nature12331 [PubMed: 23842501]

105. Rodriguez B, Prioult G, Hacini-Rachinel F, et al. Infant gut microbiota is protective against cow’s milk allergy in mice despite immature ileal T-cell response. FEMS Microbiol Ecol. 2012; 79(1):192–202.10.1111/j.1574-6941.2011.01207.x [PubMed: 22029421]

106. de Kivit S, Tobin MC, Forsyth CB, Keshavarzian A, Landay AL. Regulation of Intestinal Immune Responses through TLR Activation: Implications for Pro-and Prebiotics. Front Immunol. 2014; 5:60.10.3389/fimmu.2014.00060 [PubMed: 24600450]

107. de Kivit S, Tobin MC, DeMeo MT, et al. In vitro evaluation of intestinal epithelial TLR activation in preventing food allergic responses. Clin Immunol. 2014; 154(2):91–99.10.1016/j.clim.2014.07.002 [PubMed: 25058467]
108. Noval Rivas M, Burton OT, Wise P, et al. A microbiota signature associated with experimental food allergy promotes allergic sensitization and anaphylaxis. J Allergy Clin Immunol. 2013; 131(1):201–212.10.1016/j.jaci.2012.10.026 [PubMed: 23201093]
109. McGowan EC, Keet CA. Prevalence of self-reported food allergy in the National Health and Nutrition Examination Survey (NHANES) 2007–2010. J Allergy Clin Immunol. 2013; 132(5):1216–1219. e5.10.1016/j.jaci.2013.07.018 [PubMed: 23992749]
110. Keet CA, Wood RA, Matsui EC. Limitations of reliance on specific IgE for epidemiologic surveillance of food allergy. J Allergy Clin Immunol. 2012; 130(5):1207–1209. e10.10.1016/j.jaci.2012.07.020 [PubMed: 22964106]
111. Koplin J, Allen K, Gurrin L, Osborne N, Tang MLK, Dharmage S. Is caesarean delivery associated with sensitization to food allergens and IgE-mediated food allergy: a systematic review. Pediatr Allergy Immunol. 2008; 19(8):682–687.10.1111/j.1399-3038.2008.00731.x [PubMed: 19076564]
112. Eggesbo M, Botten G, Stigum H, Nafstad P, Magnus P. Is delivery by cesarean section a risk factor for food allergy? Journal of Allergy and Clinical Immunology. 2003; 112(2):420–426.10.1067/mai.2003.1610 [PubMed: 12897751]
113. Eggesbo M, Botten G, Stigum H, Samuelsen SO, Brunekreef B, Magnus P. Cesarean delivery and cow milk allergy/intolerance. Allergy. 2005; 60(9):1172–1173.10.1111/j.1398-9995.2005.00857.x [PubMed: 16076303]
114. Metsala J, Lundqvist A, Kaila M, Gissler M, Klaukka T, Virtanen SM. Maternal and perinatal characteristics and the risk of cow's milk allergy in infants up to 2 years of age: a case-control study nested in the Finnish population. Am J Epidemiol. 2010; 171(12):1310–1316.10.1093/aje/kwq074 [PubMed: 20472571]
115. Koplin JJ, Dharmage SC, Ponsonby AL, et al. Environmental and demographic risk factors for egg allergy in a population-based study of infants. Allergy. 2012; 67(11):1415–1422.10.1111/all.12015 [PubMed: 22957661]
116. Campbell BE, Lodge CJ, Lowe AJ, Burgess JA, Matheson MC, Dharmage SC. Exposure to "farming" and objective markers of atopy: a systematic review and meta-analysis. Clin Exp Allergy. 2015; 45(4):744–757.10.1111/cea.12429 [PubMed: 25270644]
117. Metsala J, Lundqvist A, Virta LJ, Kaila M, Gissler M, Virtanen SM. Mother's and offspring's use of antibiotics and infant allergy to cow's milk. Epidemiology. 2013; 24(2):303–309.10.1097/EDE.0b013e31827f520f [PubMed: 23348066]
118. Mai XM, Kull I, Wickman M, Bergstrom A. Antibiotic use in early life and development of allergic diseases: respiratory infection as the explanation. Clin Exp Allergy. 2010; 40(8):1230–1237.10.1111/j.1365-2222.2010.03532.x [PubMed: 20545711]
119. Luccioli S, Zhang Y, Verrill L, Ramos-Valle M, Kwegyir-Afful E. Infant feeding practices and reported food allergies at 6 years of age. Pediatrics. 2014; 134 (Suppl 1):S21–8.10.1542/peds.2014-0646E [PubMed: 25183751]
120. McGowan EC, Bloomberg GR, Gergen PJ, et al. Influence of early-life exposures on food sensitization and food allergy in an inner-city birth cohort. J Allergy Clin Immunol. 2015; 135(1):171–178.10.1016/j.jaci.2014.06.033 [PubMed: 25129677]
121. Thompson-Chagoyan OC, Vieites JM, Maldonado J, Edwards C, Gil A. Changes in faecal microbiota of infants with cow's milk protein allergy--a Spanish prospective case-control 6-month follow-up study. Pediatr Allergy Immunol. 2010; 21(2 Pt 2):e394–400.10.1111/j.1399-3038.2009.00961.x [PubMed: 19889194]
122. Thompson-Chagoyan OC, Fallani M, Maldonado J, et al. Faecal microbiota and short-chain fatty acid levels in faeces from infants with cow's milk protein allergy. Int Arch Allergy Immunol. 2011; 156(3):325–332.10.1159/000323893 [PubMed: 21720179]
123. Ling Z, Li Z, Liu X, et al. Altered fecal microbiota composition associated with food allergy in infants. Appl Environ Microbiol. 2014; 80(8):2546–2554.10.1128/AEM.00003-14 [PubMed: 24532064]

124. Azad MB, Konya T, Guttman DS, et al. Infant gut microbiota and food sensitization: associations in the first year of life. Clin Exp Allergy. 2015; 45(3):632–643.10.1111/cea.12487 [PubMed: 25599982]

Key Points

- Early microbial colonization plays an important role in the development of both the innate and the adaptive immune systems, and there are several proposed mechanisms to explain how alterations in microbiome could lead to the development of allergic disease.
- Although some studies have identified notable relationships between the gastrointestinal microbiota and the development of asthma, allergic rhinitis, and eczema, specific studies examining the microbiome in human food allergy are lacking.
- As technology and knowledge of the microbiome advances, discoveries in food allergy and atopic disease will likely provide insight into primary prevention and treatment strategies.

Table 1

Summary of various early-life environmental exposures and specific gut microbiota associated with the development of allergic disease

Exposure	Bacteria	Risk
Less Animal Exposure	↓ *Bacteroides, Bifidobacteria, and Enterococci* ↑ *Clostridiae*	↑ Asthma, Allergic Rhinitis, and Eczema +/− Food Allergy
Delivery by Caesarean-section	↓ *Bacteroides, Bifidobacteria, and E. coli* ↑ *Klebsiella, Enterobacter, Enterococcus*	↑ Asthma, Allergic Rhinitis, and Eczema +/− Food Allergy
Decreased Siblingship	↑ Clostridia, *Lactobacillus, and Bacteroides*	↑ Eczema (Clostridia) ? Asthma, Allergic Rhinitis, and Food Allergy
Perinatal Antibiotic Use	↓ *Bifidobacteria and Lactobacillus* ↑ *Proteobacteria and Enterobacteriaceae*	↑ Asthma and Eczema +/− Food Allergy – Allergic Rhinitis
Bottle Feeding	↓ *Staphylococcus* ↑ *Clostridium difficile, Bacteroides, Enterococci, and Enterobacteriaceae*	↑ Asthma and Eczema (high-risk pts.) +/− Food Allergy and Allergic Rhinitis