



Prevention of allergy with diverse and healthy microbiota: an update

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Purpose of review

Microbiota consist of symbiotic microscopic neighbors that interact on and within our bodies in diverse and incompletely understood ways throughout our lifetime. Though various associations with allergic disease have been described, clear effective therapeutic interventions to prevent allergy have been elusive.

Recent findings

The human microbiome is influenced by multiple factors, including: mode of infant delivery (vaginal vs. cesarean section), breastfeeding, diet, presence of siblings and pets, exposure to antibiotics and other medications (particularly antacids), lifestyle, and developmental context. Microbial species promoting atopic responses and tolerance have been described. Specific microbiota likely act through distinct metabolic pathways to promote the health of their human hosts, optimally directing the developing immune system away from pro-allergic, Th2-dominated responses to more T-regulatory-influenced behaviors.

Summary

Evidence suggests that specific healthy infant microbiome signatures may influence development of some components of the allergic march of childhood by decreasing atopic dermatitis, asthma, and food allergy. Further understanding of factors that influence healthy microbiota may lead to specific strategies tailored for early intervention and disease prevention.

Keywords

allergy, asthma, atopic dermatitis, microbiome, microbiota, prevention

INTRODUCTION

The developing microbiome of childhood

Both inside and out, the human body is home to a microscopic pantheon. Our microbiota includes bacteria, archaea, fungi, protozoa, and viruses. Although the terms ‘microbiota’ and ‘microbiome’ are often used interchangeably, the term ‘microbiome’ refers to the combined genomes of these microorganisms, whereas the ‘microbiota’ describe the microorganisms themselves. The most commonly studied microbiota are bacteria that reside in the human intestinal tract. The composition and diversity of these gut bacteria play important roles in human health, from nutrient extraction to immune system modulation [1,2]. In particular, these bacteria produce short-chain fatty acids, such as acetate, propionate, and butyrate, which help to regulate metabolism and the immune system and protect against colonization by pathogens [3,4,5]. Shortly after birth, the intestinal tract is rapidly populated by bacteria from the environment, including the vaginal tract, skin, and breastmilk [6–9]. Differences in mode of delivery (vaginal delivery vs. cesarean section), diet, and antibiotic exposure

have all been linked to variation in gut bacterial composition and development of disease in children, including allergic and atopic disorders, obesity, and infection [10¹¹, 11¹², 12¹⁶, 17, 18¹⁹].

The intestinal tract of a vaginally delivered, breastmilk-fed infant born in a westernized country is initially colonized by facultative anaerobes, such as the genera *Enterococcus*, *Escherichia/Shigella*, and *Streptococcus* [20]. These bacteria consume oxygen, creating an anaerobic environment in which obligate anaerobes, such as *Bifidobacterium* spp., *Bacteroides* spp., and *Clostridium* spp. can proliferate as the

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KEY POINTS

- The microbiome influences the development of allergic disease, and we are just beginning to understand how specific microbiota relate to disease prevention and susceptibility.
- The developing microbiota is influenced by interactions with family members, siblings, pets, infections, antibiotics, antacids, and cultural influences.
- Greater specificity is needed to understand particular populations most likely to benefit from microbiome-targeted therapies, and in what settings the therapies will be most effective.

infant matures [20–22,23²²]. Although the bacterial composition of the gut is relatively dynamic in the first years of life, a notable shift occurs after the introduction of solid foods [23²²]. After the third year of life, the microbiome stabilizes and resembles the adult gut microbiome [24].

The skin microbiome may influence eczema development [25²¹] and varies by body site, with fungal organisms making up a significant proportion [26]. The infant skin is predominantly colonized by *Staphylococcus* spp. and *Streptococcus* spp., the former of which decreases in abundance over the first year as overall skin diversity increases. In individuals with atopic dermatitis, microbial diversity is diminished whereas *Staphylococcus aureus* abundance is enhanced [27]. Reintroduction of skin commensal bacteria has been shown to decrease *S. aureus* colonization and improve atopic dermatitis symptoms [28²²,29²²].

In children with rhinitis, the maturation of the nasal microbiome differs significantly from healthy controls over the first 18 months of life, with a decrease in diversity over time [30²¹]. Children with rhinitis were found to have greater abundance of the Oxalobacteraceae family (from the Proteobacteria phylum) and Aerococcaceae family (Firmicutes phylum), whereas healthy controls had greater abundance of the Corynebacteraceae family (Actinobacteria phylum).

The nasal microbiome can reflect disease control, and enrichment of *Prevotella buccalis*, *Dialister invisus*, *Gardnerella vaginalis*, and *Alkanindiges hongkongensis* has been associated with asthma exacerbations compared with nonexacerbated asthma and healthy controls in adults [31²¹]. Furthermore, in the upper airways of children with asthma, whether current or in remission, there is a greater abundance of *Staphylococcus* spp., as well as the genera *Dolosigranulum*, *Parvimonas*, *Corynebacterium*, and *Prevotella* [32²¹]. Controls, on the other

hand, have higher abundances of *Haemophilus* spp. and *Moraxella* spp. Children with severe asthma have an enrichment of *Bacteroides* spp., *Faecalibacterium* spp., and *Roseburia* spp. in their lower airways [33²¹].

As illustrated, there is a clear pattern for microbial acquisition after birth: the microbiomes at various body sites are initially more uniform, often reflecting early environmental exposures, and as they mature over time, they become more diverse. A common theme developing in the field of pediatric allergy is that early diversity is beneficial. Not all children acquire the same microbes, and the microbial composition at these body sites is often related to the development of allergic disease.

The gut microbiome in pediatric allergic disease

The atopic (allergic) march of childhood includes an association of genetic risk, atopic dermatitis, food allergy, asthma, and allergic rhinitis. Although still an emerging field, specific patterns within atopic microbiomes have developed, as summarized in Fig. 1. For example, the development of allergic disease (atopic dermatitis, allergic rhinitis, asthma, or food allergy) by 36 months of age was found to be associated with an increase in gut *Klebsiella* spp. and a decrease in *Bifidobacterium* spp. at 3 months of age in a Chinese cohort [34²¹]. Additionally, a Taiwanese twin-cohort study showed that children who developed allergic rhinitis, asthma, and atopic dermatitis had high abundance of species within the Lachnospiraceae family, particularly *Ruminococcus gnavus*. Transferring *R. gnavus* to mice resulted in the development of airway inflammation with an increase in interleukins (IL) IL-4, IL-5, and IL-13, indicating increased Th2 activity [35²¹]. Decreased intestinal microbiota diversity in infancy is associated with the development of allergic disease at school age [36]. Specific signatures have also been linked to the development of certain food allergies in childhood [37²¹,38]. For example, an enrichment of Lachnospiraceae, Streptococcaceae, and Leuconostocaceae has been associated with egg sensitization [37²¹], whereas milk allergy resolution has been associated with a greater abundance of *Clostridia* and *Firmicutes* [38]. There is speculation that low biodiversity and dysbiosis (microbial imbalance) cause decreased production of short-chain fatty acid and create a pro-inflammatory and Th2-weighted immune system [39]. One study showed that the microbiota transferred from allergic infants to mice led to the development of a Th17 inflammatory signature [10²²].

However, it can be difficult drawing direct lines between specific microbes and disease outcomes

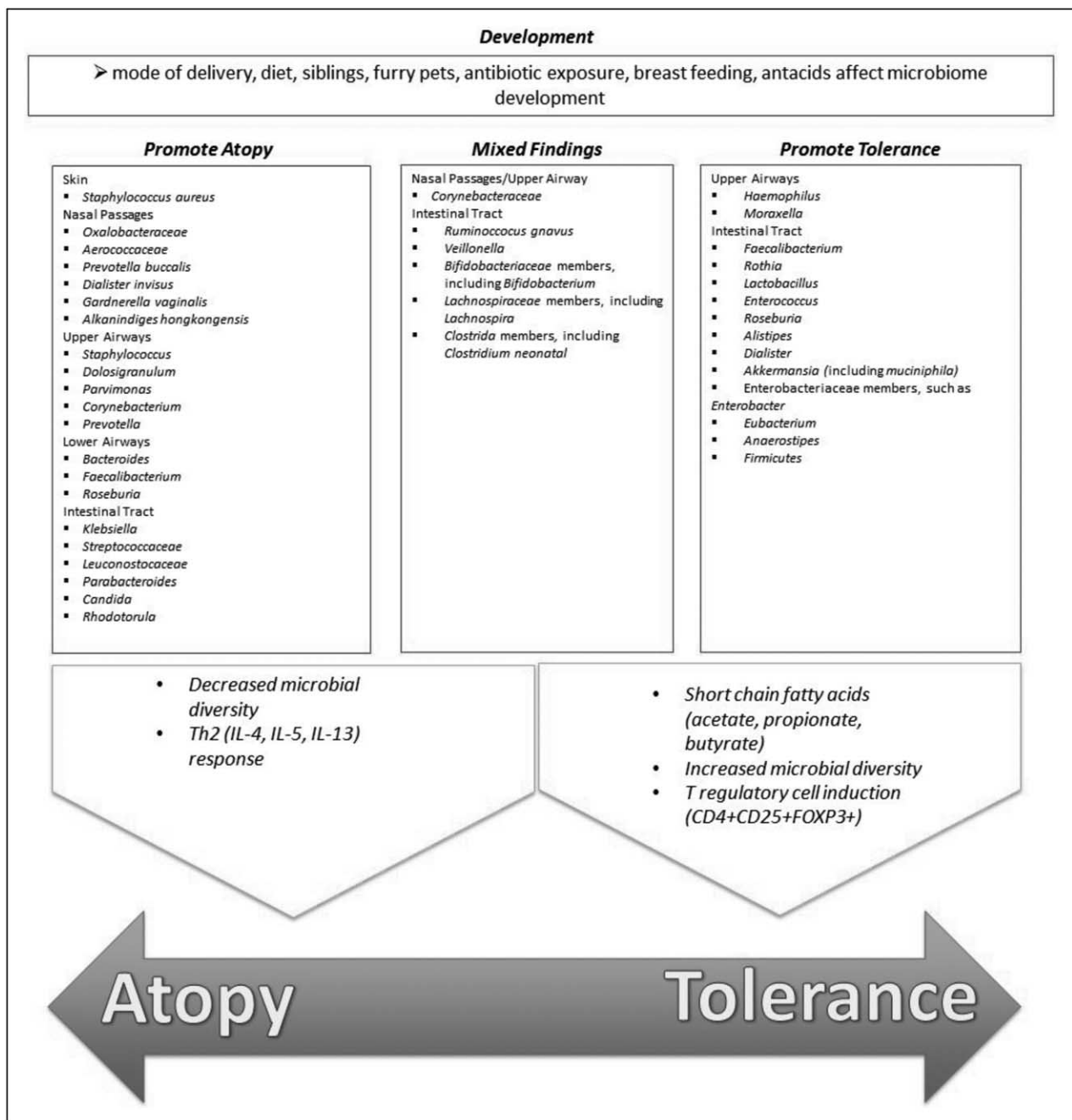


FIGURE 1. Microbiome development is influenced by several factors, resulting in establishment of a population, which influences health and disease during infancy over the lifetime. Particular microbial influences have been associated with atopic responses (asthma, allergic rhinitis, food allergy, and atopic dermatitis) whereas others have been associated with absence of these conditions and environmental tolerance.

because similar microorganisms have been reported to have different atopic effects in different studies. For instance, although a few studies show support for the association between *Lachnospira* abundance and allergy development, other studies have suggested *Lachnospira* may protect against allergy. In the Canadian Healthy Infant Longitudinal Development (CHILD) cohort, decreased *Lachnospira* and

increased *Clostridium neonatale* at 3 months were associated with the development of asthma at pre-school age [40]. Further studies of this Canadian cohort found that decreases of the genera *Lachnospira*, *Veillonella*, *Faecalibacterium*, and *Rothia* in the first 100 days of life were associated with the development of asthma. In addition, the transfer of these microbes to germ-free mice decreased airway

inflammation [41]. In another study of children from infancy to school age, children with IgE-associated allergic disease at 8 years of age had an enrichment of *Bifidobacterium* in their gut and a depletion of *Lachnospira*, *Lactobacillus* and *Enterococcus* compared with nonallergic children [42[¶]]. Other studies have shown opposite associations for *Veillonella* spp. and *Bifidobacterium* spp. A study of Danish children found that a higher abundance of *Veillonella* spp. but a lower abundance of *Bifidobacterium* spp. (along with *Roseburia*, *Faecalibacterium*, *Alisipes*, *Lachnospiraceae incertae sedis*, *Ruminococcus*, and *Dialister*) at age 1 were associated with increased risk of asthma at age 5 [43[¶]]. Regional, environmental, and industrial influences may explain some of the differences between study outcomes, along with individual variations in metabolic pathways and diet. In one study of rural Ecuadorian infants with atopic wheeze, dysbiosis was also found at age 3 months, similar to the Canadian Healthy Infant Longitudinal Development (CHILD) cohort with atopic wheeze. However, a different set of microorganisms, including fungi, were implicated, indicating geographic and population influences in dysbiosis [44[¶]]. Results may also be difficult to compare because many studies are only able to identify bacteria within a higher taxonomic rank (class, order, or family) rather than a lower taxonomic rank (genus, species), which contains fewer taxons but offers greater specificity. Consequently, it is unclear whether a small or large number of genera or species are associated with the outcome of interest.

Not only does the type of microbe matter, but also the maturity and diversity of entire microbial populations. Lower microbial maturity at 1 year of age was associated with development of asthma by age 5 [45,46]. Specific patterns and combinations may also provide potent immune influences. One example is seen in a United States cohort in which gut microbial composition at 3 months of age was associated with childhood atopy and asthma [45]. Infants at highest risk of developing asthma and atopy had depletions of *Bifidobacteria*, *Lactobacillus*, *Faecalibacterium*, and *Akkermansia*, as well as higher abundance of the fungi *Candida* and *Rhodotorula*. Interestingly, their fecal metabolome (total metabolites found in stool) had enriched pro-inflammatory metabolites, and when adult peripheral T cells were cultured in fecal water from these infants, there was an increase in CD4⁺ T cell IL-4 production and a decrease in abundance of CD4⁺CD25⁺FOXP3⁺ (Treg) cells. This finding is remarkable because IL-4 stimulates IgE production whereas Tregs play a role in downregulating the immune system and preventing autoimmunity. Therefore, increased IL-4 in the context of decreased Treg function would

be expected to drive allergic inflammation and sensitization.

The subject of atopic dermatitis, skin barrier function, and allergic sensitization is a growing area of interest given that the presence of severe atopic dermatitis is a risk factor for food allergy [47[¶]]. Specific perturbations in the gut microbiome may influence the development of atopic dermatitis. In Korean infants, depletion of the species *Akkermansia muciniphila*, *Ruminococcus gnavus*, and *Lachnospiraceae* bacterium 2_1_58FAA actually seems to decrease components of normal immune development, such as antigen processing and presentation through gene expression [48[¶]]. In a multicenter study, infants with atopic dermatitis by 18 months of age had lower levels of two Enterobacteriaceae genera and increased levels of *Parabacteroides* species. There were also decreased levels of lactate-utilizing, butyrate-producing *Eubacterium* spp. and *Anaerostipes* spp. [15[¶]]. Similar to the results of studies on the development of allergic disease, the development of atopic dermatitis specifically was also associated with reduced fecal microbiota diversity in infancy [49].

Prevention and treatment of allergic disease through the microbiome

A variety of interventions have been proposed to prevent and treat allergic disease. These include: diet changes, prebiotics and probiotics, decreased cesarean section (C-section) deliveries, vaginal bacterial transplantation after C-section, decreased antibiotic use, and decreased use of acid-suppressive medications in infancy [39,50^{¶¶},51^{¶¶},52,53]. Environmental exposures have also been implicated in the development of atopic disease [54,55[¶],56[¶]].

Dietary exposures associated with the prevention of allergic disease include consuming more breastmilk, ever consuming unpasteurized cow's milk, and dietary fiber. Breastmilk feeding, compared with formula feeding, has been associated with a more protective gut bacterial structure in infants [57] and may decrease risks for atopic dermatitis and asthma in early childhood, increase the likelihood of preschool eczema remission, and even protect against recurrent cough in adulthood [58–60,61[¶],62[¶]]. Ever consuming unpasteurized cow's milk has been associated with decreased risk of asthma, rhinoconjunctivitis, and environmental and food sensitization, though obvious safety concerns persist [63]. Dietary fermentable fiber also confers benefits. Mice fed a high-fiber diet had increased levels of short-chain fatty acids and were protected from allergic lung inflammation [52] and food allergy [64]. Depriving the gut microbiota of

dietary fiber leads to degradation of colonic mucus and increased susceptibility to pathogens [65], and as mentioned earlier, dietary co-factors may be a critical and often overlooked factor in microbiome health.

The administration of probiotics has been extensively investigated and found to have mixed effects in altering gut microbiome composition and preventing the development of allergic disease. *Lactobacillus* spp. supplementation has been shown to modify the gut microbiota of infants at high risk for asthma development [66[■]]. However, in another analysis, supplementation with a probiotic mixture to mothers in the last 6 weeks of pregnancy and to infants during the first year of life was associated with only minor and short-term differences in gut microbiota composition [67]. Although prenatal and postnatal supplementation with *Bifidobacteria* was found to be effective in preventing atopic dermatitis in a Japanese cohort [68], supplementation with *Lactobacillus rhamnosus* GG in the first 6 months of life was not found to prevent development of atopic dermatitis or asthma at 2 years of age in an United States cohort [69[■]]. Bacterial extracts, such as the immunostimulant OM-85, have been found to be effective in preventing wheezing attacks in young children [70]. Additionally, probiotic use to supplement oral immunotherapy has been explored [71,72[■]] and may be cost-effective [73[■]], but direct comparison of oral immunotherapy with and without probiotic supplementation requires further study.

C-section delivery has been associated with differences in gut microbiome composition compared with vaginal delivery [57] as well as with increased risk of asthma, autoimmunity (ulcerative colitis, celiac disease, juvenile idiopathic arthritis), and infection (laryngitis, lower respiratory tract infection, and gastroenteritis) [74]. The transfer of vaginal bacteria to babies born by C-section has been proposed to expose these infants to normal vaginal microbiota [53]. However, new evidence suggests that the exposure to the maternal vaginal flora may not be as important as exposure to maternal rectal microbiota during birth. One study profiling the microbiota of 42 mother–infant pairs showed that there was actually greater overlap between infant gut and maternal rectal – rather than vaginal – microbiota [75[■]].

Certain environmental exposures have also been shown to be associated with gut microbiome structure and development of allergies. Living with both siblings and furry pets has been found to affect gut composition in infants [56[■]] and increase microbiota diversity [76]. A landmark study of Amish and Hutterite children showed significantly lower

prevalence of asthma in the Amish compared to the Hutterites despite their common ancestry [54]. The Amish farms of Indiana use traditional farming practices on small family farms, whereas the Hutterite farms in South Dakota are more industrial. Farm dust endotoxin has been found to be protective against allergy development [77], and accordingly, Amish children – whose home dust endotoxin levels are almost seven times higher than those of Hutterite children – had a lower prevalence of asthma. Differences in the characteristics of the innate immune system between the groups included an increase in genes encoding anti-inflammatory enzymes and more monocytes with decreased expression of HLA-DR and increased expression of ILT3 (both indicating anti-inflammatory function) in Amish children [54].

H₂-antihistamines are sometimes used in infants for regurgitation, and there is evidence that they could be associated with allergy development. Histamine, a biogenic amine, is not only secreted by mammalian cells, but also by gut microbes [78[■]]. Histamine-2 receptor blockers have been found to lower the diversity of the gut microbiota of premature infants (also decreasing Firmicutes while increasing Enterobacteriaceae species) [79]. Some older studies have suggested that histamine enhances T helper 1-type responses [80,81]. Recent studies have shown that acid-suppressive medications, including H₂ blockers, used in the first 6 months of life are associated with subsequent development of allergic disorders, such as food and drug allergies, allergic rhinitis, anaphylaxis, and asthma [51[■]].

CONCLUSION

In reviewing the literature regarding the association between the gut microbiome and allergy development, a number of patterns have emerged. Reduced gut microbial diversity in infancy and inadequate colonization with beneficial microbes have been associated with the development of allergic disease. A number of factors could be responsible for intestinal microbial dysbiosis. These include infant delivery mode, diet, antibiotic exposure, acid-suppressive medications use, and environmental exposures. Studies of the use of probiotics to improve the microbiome have produced mixed results, and further investigations are needed to understand the importance of specific microbial patterns, prebiotics, developmental stages, and diet cofactors. Similarly, the relationship between allergy treatments and the gut microbiome deserves attention to determine if treatments have an actual effect on gut microbial composition and whether success is dependent on correcting the dysbiosis. Greater

understanding of dietary and environmental interventions is needed to help prevent disease in children at risk for developing allergies, with focus on the optimal timing, delivery, and context of therapies.

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Conflicts of interest

M.S. has a family member who is CEO of Altrix Medical. M.S. is a member of the Joint Task Force on Practice Parameters of the American Academy of Allergy, Asthma, and Immunology and the American College of Allergy, Asthma, and Immunology.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. LeBlanc JG, Milani C, de Giori GS, *et al.* Bacteria as vitamin suppliers to their host: a gut microbiota perspective. *Curr Opin Biotechnol* 2013; 24:160–168.
 2. Sassone-Corsi M, Raffatellu M. No vacancy: how beneficial microbes co-operate with immunity to provide colonization resistance to pathogens. *J Immunol* 2015; 194:4081–4087.
 3. Morrison DJ, Preston T. Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism. *Gut Microbes* 2016; 0976:1–12.
 4. Smolinska S, Groeger D, O'Mahony L. Biology of the microbiome 1: interactions with the host immune response. *Gastroenterol Clin North Am* 2017; 46:19–35.
- A review describing the current understanding of how the gut microbiome shapes mucosal immune response.
5. Jacobson A, Lam L, Rajendram M, *et al.* A gut commensal-produced metabolite mediates colonization resistance to salmonella infection. *Cell Host Microbe* 2018; 24:296.e7–307.e7.
- Mice with bacteroides species colonization were found to be resistant against *Salmonella enterica* by their production of the short-chain fatty acid propionate.
6. Pannaraj PS, Li F, Cerini C, *et al.* Association between breast milk bacterial communities and establishment and development of the infant gut microbiome. *JAMA Pediatr* 2017; 171:647–654.
- This prospective longitudinal study found that breastfed infants receive a significant proportion of their gut microbiome from mother's breastmilk (27.7%) and skin (10.3%) in the first 30 days of life, underscoring the importance of breastfeeding in the transfer of the microbiome.
7. Ferretti P, Pasolli E, Tett A, *et al.* Mother-to-infant microbial transmission from different body sites shapes the developing infant gut microbiome. *Cell Host Microbe* 2018; 24:133.e5–145.e5.
- The microbiome of 25 mother–infant pairs were sampled across multiple body sites, and the maternal gut microbiome was found to be most persistent in the infant gut.
8. Korpela K, Costea P, Coelho LP, *et al.* Selective maternal seeding and environment shape the human gut microbiome. *Genome Res* 2018; 28:561–568.
- Vaginally delivered babies were found to be mostly colonized by bacterial strains including Actinobacteria and Bacteroidia vertically transferred from their mothers, with environmental colonization occurring after the first year and into adulthood.
9. Asnicar F, Manara S, Zolfo M, *et al.* Studying vertical microbiome transmission from mothers to infants by strain-level metagenomic profiling. *mSystems* 2017; 2; pii: e00164-16.
- Using shotgun metagenomic sequencing and computational profiling, authors found that certain specific strains, such as *Bifidobacterium bifidum*, *Coprococcus comes*, and *Ruminococcus bromii* were vertically transmitted between mother and child.

10. Petrusdottir DH, Nordlander S, Qazi KR, *et al.* Early-life human microbiota associated with childhood allergy promotes the T helper 17 axis in mice. *Front Immunol* 2017; 8:1699.
- Mice inoculated with fecal samples from children of allergic heredity produced offspring with increased Th17-signature.
11. Tun HM, Bridgman SL, Chari R, *et al.*, Canadian Healthy Infant Longitudinal Development (CHILD) Study Investigators. Roles of birth mode and infant gut microbiota in intergenerational transmission of overweight and obesity from mother to offspring. *JAMA Pediatr* 2018; 172:368–377.
- This observational study of the Canadian Healthy Infant Longitudinal Development birth cohort found that children born to overweight mothers were more likely to be overweight and have a higher gut abundance of the Lachnospiraceae family.
12. Rifas-Shiman SL, Gillman MW, Hawkins SS, *et al.* Association of cesarean delivery with body mass index z score at age 5 years. *JAMA Pediatr* 2018; 172:777–779.
- In this study, controlling for confounders by studying siblings found that Cesarean section was not associated with increased BMI at age 5.
13. Stinson LF, Payne MS, Keelan JA. A critical review of the bacterial baptism hypothesis and the impact of cesarean delivery on the infant microbiome. *Front Med (Lausanne)* 2018; 5:135.
- A review and critical appraisal of the popular belief that Cesarean section causes dysbiosis.
14. Cassidy-Bushrow AE, Burmeister C, Havstad S, *et al.* Prenatal antimicrobial use and early-childhood body mass index. *Int J Obes (Lond)* 2018; 42:1–7.
- Prenatal antibiotic was found to be associated with increased BMI at age of 2 years.
15. Wopereis H, Sim K, Shaw A, *et al.* Intestinal microbiota in infants at high risk for allergy: effects of prebiotics and role in eczema development. *J Allergy Clin Immunol* 2018; 141:1334.e5–1342.e5.
- This clinical trial showed that a partially hydrolyzed infant formula with prebiotics produced gut microbiomes that more closely resembled that of breastfed infants.
16. Bentley JP, Burgner DP, Shand AW, *et al.* Gestation at birth, mode of birth, infant feeding and childhood hospitalization with infection. *Acta Obstet Gynecol Scand* 2018. [Epub ahead of print]
- A retrospective cohort study of 488 children found that Cesarean section, labor induction, and formula-feeding were associated with more infections in childhood.
17. Li R, Dee D, Li C-M, *et al.* Breastfeeding and risk of infections at 6 years. *Pediatrics* 2014; 134(Suppl):S13–S20.
18. Oosterloo BC, van Elburg RM, Rutten NB, *et al.* Wheezing and infantile colic are associated with neonatal antibiotic treatment. *Pediatr Allergy Immunol* 2018; 29:151–158.
- This prospective observational study found that the use of broad-spectrum antibiotics in the first week of life was associated with later development of wheezing.
19. Forbes JD, Azad MB, Vehling L, *et al.*, Canadian Healthy Infant Longitudinal Development (CHILD) Study Investigators. Association of exposure to formula in the hospital and subsequent infant feeding practices with gut microbiota and risk of overweight in the first year of life. *JAMA Pediatr* 2018; 172:e181161.
- A study of 1087 infants from a prospective pregnancy cohort that examined the association between breastfeeding, fecal microbiota, and risk of becoming overweight during infancy. At 3 months of age, exclusive formula feeding, as well as mixed breastmilk and formula feeding, were associated with an increased risk of being overweight by 12 months of age. Breastfeeding for less than 6 months was also associated with overweight status. This study suggests that breastfeeding may protect infants against becoming overweight through gut microbiota modification.
20. Bäckhed F, Roswall J, Peng Y, *et al.* Dynamics and stabilization of the human gut microbiome during the first year of life. *Cell Host Microbe* 2015; 17:690–703.
21. Eggesbø M, Moen B, Peddada S, *et al.* Development of gut microbiota in infants not exposed to medical interventions. *APMIS* 2011; 119:17–35.
22. Palmer C, Bik EM, DiGiulio DB, *et al.* Development of the human infant intestinal microbiota. *PLoS Biol* 2007; 5:e177.
23. de Muinck EJ, Trosvik P. Individuality and convergence of the infant gut microbiota during the first year of life. *Nat Commun* 2018; 9:2233.
- A longitudinal study of the fecal microbiota of 12 infants from whom daily stool samples were collected during the first year of life. This study identified that between 2 and 4 months of age, the infants' gut microbiotas became more similar to each other and had a bloom of *Bifidobacterium* species as well as a decline in abundance of Firmicutes. There was increasing divergence after the introduction of solid foods, roughly coinciding with the end of the 2–4-month period.
24. Yatsunenko T, Rey FE, Manary MJ, *et al.* Human gut microbiome viewed across age and geography. *Nature* 2012; 486:222–227.
25. Baurecht H, Rühlemann MC, Rodriguez E, *et al.* Epidermal lipid composition, barrier integrity, and eczematous inflammation are associated with skin microbiome configuration. *J Allergy Clin Immunol* 2018; 141:1668.e16–1676.e16.
- The skin microbiome was sequenced and compared between 10 children with atopic dermatitis and 10 healthy controls, with atopic dermatitis patients having increased abundance of staphylococcal species and decreased diversity, especially prominent at the sites of eczema.
26. Grice EA, Segre JA. The skin microbiome. *Nat Rev Microbiol* 2011; 9:244–253.

27. Kong HH, Oh J, Deming C, *et al.* Temporal shifts in the skin microbiome associated with disease flares and treatment in children with atopic dermatitis. *Genome Res* 2012; 22:850–859.
28. Nakatsuji T, Chen TH, Narala S, *et al.* Antimicrobials from human skin commensal bacteria protect against *Staphylococcus aureus* and are deficient in atopic dermatitis. *Sci Transl Med* 2017; 9:eaa4680.

The coagulase-negative *Staphylococcus* spp. isolated from the skin of individuals with atopic dermatitis was found to have decreased antimicrobial activity against *S. aureus* compared with controls, which points to a potential mechanism for how commensal microorganisms normally protect the body from pathogens and atopic disease.

29. Myles IA, Earland NJ, Anderson ED, *et al.* First-in-human topical microbiome transplantation with *Roseomonas mucosa* for atopic dermatitis. *JCI insight* 2018; 3; pii: 120608.

A phase I/II trial of ten adults and five pediatric patients with atopic dermatitis resulted in decreased disease severity, topical steroid requirement, and *S. aureus* burden whenever treated with *Roseomonas mucosa*, a microbe that had improved outcomes in atopic dermatitis mouse models in preclinical trials.

30. Ta LDH, Yap GC, Tay CJX, *et al.* Establishment of the nasal microbiota in the first 18 months of life: correlation with early-onset rhinitis and wheezing. *J Allergy Clin Immunol* 2018; 142:86–95.

Characterization of the nasal microbiome in 28 children with rhinitis, 34 children with rhinitis and wheeze, and 34 healthy controls in Singapore showed a difference in diversity and composition over the first 18 months of life in the three groups.

31. Fazlollahi M, Lee TD, Andrade J, *et al.* The nasal microbiome in asthma. *J Allergy Clin Immunol* 2018; 142:834.e2–843.e2.

Characterization of the nasal microbiome of 20 adult subjects with asthma, 31 with nonexacerbated asthma, and 21 healthy controls found an increase in Bacteroidetes and Proteobacteria taxa in asthmatic patients, with particular phyla and species differentiation based on level of asthma activity.

32. Kim B-S, Lee E, Lee M-J, *et al.* Different functional genes of upper airway microbiome associated with natural course of childhood asthma. *Allergy* 2018; 73:644–652.

A comparison of the upper airway microbiota found a positive association between airway reactivity and the abundance of *Staphylococcus* and *Streptococcus*, and a decrease in genes producing anti-inflammatory PGE₂ in asthmatic children.

33. Goldman DL, Chen Z, Shankar V, *et al.* Lower airway microbiota and mycobacteria in children with severe asthma. *J Allergy Clin Immunol* 2018; 141:808.e17–811.e17.

Bronchoscopic samples of 15 children with severe asthma showed certain significantly enriched bacteria genera including *Bacteroides*, *Faecalibacterium*, and *Roseburia* compared with that of 16 children without severe asthma, though differences in diversity were not observed.

34. Low JSY, Soh S-E, Lee YK, *et al.* Ratio of *Klebsiella/Bifidobacterium* in early life correlates with later development of paediatric allergy. *Benef Microbes* 2017; 8:681–695.

Characterization of the gut microbiome of 21 allergic children and 18 healthy controls in a Chinese cohort found decreased *Bifidobacteria* and increased *Klebsiella* at 3 months, with high *Klebsiella/Bifidobacterium* ratio associated with increased risk of developing allergies at age 3.

35. Chua H-H, Chou H-C, Tung Y-L, *et al.* Intestinal dysbiosis featuring abundance of *Ruminococcus gnavus* associates with allergic diseases in infants. *Gastroenterology* 2018; 154:154–167.

Characterization of the gut microbiota in a prospective twin cohort with 30 patients compared with 14 age-matched controls found increased Lachnospiraceae (*Ruminococcus gnavus*) in allergic children before symptom onset, and mice exposed to *R. gnavus* developed airway reactivity.

36. 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; 128:646.e1–652.e5.
37. Fazlollahi M, Chun Y, Grishin A, *et al.* Early-life gut microbiome and egg allergy. *Allergy* 2018; 73:1515–1524.

Characterization of the gut microbiome of 66 children with egg allergy and 75 children without allergy found greater diversity and increased abundance of Lachnospiraceae, Streptococcaceae, and Leuconostocaceae families in those with allergy, though there was no association between microbiota and egg allergy resolution by the age of eight.

38. Bunyavanich S, Shen N, Grishin A, *et al.* Early-life gut microbiome composition and milk allergy resolution. *J Allergy Clin Immunol* 2016; 138:1122–1130.
39. Simonyte Sjödin K, Vidman L, Rydén P, *et al.* Emerging evidence of the role of gut microbiota in the development of allergic diseases. *Curr Opin Allergy Clin Immunol* 2016; 16:390–395.
40. Stiemsma LT, Arrieta M-C, Dimitriu PA, *et al.* Shifts in Lachnospira and Clostridium sp. in the 3-month stool microbiome are associated with pre-school age asthma. *Clin Sci (Lond)* 2016; 130:2199–2207.
41. Arrieta M-C, Stiemsma LT, Dimitriu PA, *et al.* Early infancy microbial and metabolic alterations affect risk of childhood asthma. *Sci Transl Med* 2015; 7:307ra152.
42. Simonyte Sjödin K, Hammarström M-L, Rydén P, *et al.* Temporal and long-term gut microbiota variation in allergic disease: a prospective study from infancy to school age. *Allergy* 2018; 74:176–185.

Prospective longitudinal study of 93 children examining gut microbiota composition and its association with T-cell regulation and development of IgE-associated allergic disease at 8 years of age. This study identified bacterial genera whose consistent underrepresentation was associated with allergy, and also found that *Faecalibacterium* abundance was positively correlated with IL-10 mRNA levels in PBMCs in 8-year-olds.

43. Stokholm J, Blaser MJ, Thorsen J, *et al.* Maturation of the gut microbiome and risk of asthma in childhood. *Nat Commun* 2018; 9:141.

A prospective study following 700 children found that children born to asthmatic mothers were more likely to develop asthma at age 5 if their microbiomes were immature at age 1.

44. Arrieta MC, Arévalo A, Stiemsma L, *et al.* Associations between infant fungal and bacterial dysbiosis and childhood atopic wheeze in a nonindustrialized setting. *J Allergy Clin Immunol* 2017; 142:424.e10–434.e10.

A case–control study in rural Ecuador found that there was dysbiosis in the gut microbiome of children with atopic wheeze at age 3 months, though the dysbiosis involved different bacterial and fungal taxa compared with a previously described cohort of Canadian babies with atopic wheeze.

45. Fujimura KE, Sitarik AR, Havstad S, *et al.* Neonatal gut microbiota associates with childhood multisensitized atopy and T cell differentiation. *Nat Med* 2016; 22:1187–1191.
46. Abrahamsson TR, Jakobsson HE, Andersson AF, *et al.* Low gut microbiota diversity in early infancy precedes asthma at school age. *Clin Exp Allergy* 2014; 44:842–850.
47. Shaker M, Murray RGP, Mann JA. The ins and outs of an 'outside-in' view of allergies: atopic dermatitis and allergy prevention. *Curr Opin Pediatr* 2018; 30:576–581.

A review of the current understanding of how mechanisms causing atopic dermatitis such as breaks in the skin barrier, Th2 dysregulation, and skin dysbiosis, may also predispose the person to other allergic disorders.

48. Lee M-J, Kang M-J, Lee S-Y, *et al.* Perturbations of gut microbiome genes in infants with atopic dermatitis according to feeding type. *J Allergy Clin Immunol* 2018; 141:1310–1319.

Characterization of the gut microbiome in 63 infants with atopic dermatitis and 66 healthy controls at 6 months found significantly decreased gene expression related to immune development in the atopic dermatitis group.

49. Wang M, Karlsson C, Olsson C, *et al.* Reduced diversity in the early fecal microbiota of infants with atopic eczema. *J Allergy Clin Immunol* 2008; 121:129–134.
50. Huang YJ, Marsland BJ, Bunyavanich S, *et al.* The microbiome in allergic disease: current understanding and future opportunities—2017 PRACTALL document of the American Academy of Allergy, Asthma & Immunology and the European Academy of Allergy and Clinical Immunology. *J Allergy Clin Immunol* 2017; 139:1099–1110.

Joint initiative document outlining the current understanding of the microbiome's role in allergic disease and treatment, and continued gaps in knowledge.

51. Mitre E, Susi A, Kropp LE, *et al.* Association between use of acid-suppressive medications and antibiotics during infancy and allergic diseases in early childhood. *JAMA Pediatr* 2018; 20814:e180315.

This retrospective cohort study found an increased risk of developing allergic disease with the use of antacids (H2 blockers or PPIs) in the first 6 months.

52. Trompette A, Gollwitzer ES, Yadava K, *et al.* Gut microbiota metabolism of dietary fiber influences allergic airway disease and hematopoiesis. *Nat Med* 2014; 20:159–66.
53. Dominguez-Bello MG, De Jesus-Laboy KM, Shen N, *et al.* Partial restoration of the microbiota of cesarean-born infants via vaginal microbial transfer. *Nat Med* 2016; 22:250–253.
54. Stein MM, Hrusch CL, Gozdz J, *et al.* Innate immunity and asthma risk in Amish and Hutterite farm children. *N Engl J Med* 2016; 375:411–421.
55. O'Connor GT, Lynch SV, Bloomberg GR, *et al.* Early-life home environment and risk of asthma among inner-city children. *J Allergy Clin Immunol* 2018; 141:1468–1475.

Among the 442 high-risk inner city children followed in this study, higher house concentrations of cockroach, mouse, and cat allergens were associated with lower risk of developing asthma at age 7. Prenatal tobacco smoke exposure and higher maternal stress and depression in early life also increased the risk of asthma.

56. Tun HM, Konya T, Takaro TK, *et al.* CHILD Study Investigators. Exposure to household furry pets influences the gut microbiota of infants at 3-4 months following various birth scenarios. *Microbiome* 2017; 5:1–14.

Prenatal and postnatal exposure to pets in a 746-subject Canadian study were found to increase the abundance of *Oscillospira* spp. and *Ruminococcus* spp., two bacteria associated with decreased atopy and obesity.

57. Madan JC, Hoen AG, Lundgren SN, *et al.* Association of cesarean delivery and formula supplementation with the intestinal microbiome of 6-week-old infants. *JAMA Pediatr* 2016; 170:212–219.
58. Brew BK, Kull I, Garden F, *et al.* Breastfeeding, asthma, and allergy: a tale of two cities. *Pediatr Allergy Immunol* 2012; 23:75–82.
59. Luccioli S, Zhang Y, Verrill L, *et al.* Infant feeding practices and reported food allergies at 6 years of age. *Pediatrics* 2014; 134(Suppl):S21–S28.
60. Silvers KM, Frampton CM, Wickens K, *et al.* Breastfeeding protects against current asthma up to 6 years of age. *J Pediatr* 2012; 160:991.e1–996.e1.
61. Johansson EK, Bergström A, Kull I, *et al.* Prognosis of preschool eczema and factors of importance for remission. *Acta Derm Venereol* 2018; 98:630–635.

Swedish birth cohort study of 889 subjects who explored factors associated with remission and course of preschool eczema. Study found that exclusive breastfeeding for 4 or more months, as well as male sex, was positively associated with remission of eczema by school age.

62. Gerhart KD, Stern DA, Guerra S, *et al.* Protective effect of breastfeeding on recurrent cough in adulthood. *Thorax* 2018; 73:833–839.
 Prospective birth cohort study of 786 subjects evaluating infant feeding and recurrent cough in adulthood, which found that longer duration of breastfeeding reduced risk of recurrent cough, even with regards to smoking and other respiratory-related covariates.
63. Waser M, Michels KB, Bieli C, *et al.*, PARSIFAL Study team. Inverse association of farm milk consumption with asthma and allergy in rural and suburban populations across Europe. *Clin Exp Allergy* 2007; 37:661–670.
64. Tan J, McKenzie C, Vuillermin PJ, *et al.* Dietary fiber and bacterial SCFA enhance oral tolerance and protect against food allergy through diverse cellular pathways. *Cell Rep* 2016; 15:2809–2824.
65. Desai MS, Seekatz AM, Koropatkin NM, *et al.* A dietary fiber-deprived gut microbiota degrades the colonic mucus barrier and enhances pathogen susceptibility. *Cell* 2016; 167:1339.e21–1353.e21.
66. Durack J, Kimes NE, Lin DL, *et al.* Delayed gut microbiota development in high-risk for asthma infants is temporarily modifiable by *Lactobacillus* supplementation. *Nat Commun* 2018; 9:707.
 Supplementation of infants at high risk for asthma with *Lactobacillus* spp. during the first 6 months resulted in microbiome trajectories and meconium levels of anti-inflammatory lipids that were more similar to that of healthy controls, though the similarity waned 6 months after stopping treatment.
67. Rutten NB, Gorissen DM, Eck A, *et al.* Long term development of gut microbiota composition in atopic children: impact of probiotics. *PLoS One* 2015; 10:e0137681.
68. Enomoto T, Sowa M, Nishimori K, *et al.* Effects of bifidobacterial supplementation to pregnant women and infants in the prevention of allergy development in infants and on fecal microbiota. *Allergol Int* 2014; 63:575–585.
69. Cabana MD, McKean M, Caughey AB, *et al.* Early probiotic supplementation for eczema and asthma prevention: a randomized controlled trial. *Pediatrics* 2017; 140:e20163000.
 Supplementation of 92 high-risk infants with *Lactobacillus* spp. during the first 6 months of life did not result in a significant decrease in eczema, asthma, or rhinitis at 5 years.
70. Razi CH, Harmanci K, Abaci A, *et al.* The immunostimulant OM-85 BV prevents wheezing attacks in preschool children. *J Allergy Clin Immunol* 2010; 126:763–769.
71. Tang MLK, Ponsonby AL, Orsini F, *et al.* Administration of a probiotic with peanut oral immunotherapy: a randomized trial. *J Allergy Clin Immunol* 2015; 135:737.e8–744.e8.
72. Hsiao K-C, Ponsonby A-L, Axelrad C, *et al.* Long-term clinical and immunological effects of probiotic and peanut oral immunotherapy after treatment cessation: 4-year follow-up of a randomised, double-blind, placebo-controlled trial. *Lancet Child Adolesc Heal* 2017; 1:97–105.
 Follow-up study of combined probiotic and peanut oral immunotherapy (PPOIT) trial that showed lasting benefit of PPOIT.
73. Shaker MS. An economic analysis of a peanut oral immunotherapy study in children. *J Allergy Clin Immunol Pract* 2017; 5:1707–1716.
 An analysis of the cost-effectiveness of peanut oral immunotherapy in children.
74. Kristensen K, Henriksen L. Cesarean section and disease associated with immune function. *J Allergy Clin Immunol* 2016; 137:587–590.
75. Sakwinska O, Foata F, Berger B, *et al.* Does the maternal vaginal microbiota play a role in seeding the microbiota of neonatal gut and nose? *Benef Microbes* 2017; 8:763–778.
 Profiling the microbiota of 42 mother–infant pairs showed that there was greater overlap between infant gut and maternal rectal – rather than vaginal – microbiota.
76. 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; 9:15.
77. Schuijs M, Willart M, Vergote K. Farm dust and endotoxin protect against allergy through A20 induction in lung epithelial cells. *Science* 2015; 349:1106–1110.
78. Barcik W, Wawrzyniak M, Akdis CA, *et al.* Immune regulation by histamine and histamine-secreting bacteria. *Curr Opin Immunol* 2017; 48:108–113.
 A review of the current understanding of histamine's role in immunoregulation, including the finding of increased histamine-secreting bacteria in the gut of asthmatic subjects.
79. Gupta RW, Tran L, Norori J, *et al.* Histamine-2 receptor blockers alter the fecal microbiota in premature infants. *J Pediatr Gastroenterol Nutr* 2013; 56:397–400.
80. Jutel M, Watanabe T, Klunker S, *et al.* Histamine regulates T-cell and antibody responses by differential expression of H1 and H2 receptors. *Nature* 2001; 413:420–425.
81. Jutel M, Klunker S, Akdis M, *et al.* Histamine upregulates Th1 and down-regulates Th2 responses due to different patterns of surface histamine 1 and 2 receptor expression. *Int Arch Allergy Immunol* 2001; 124:190–192.