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Role of the Microbiome in Allergic Disease Development

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Abstract

Purpose of Review: Evidence suggests that the microbiome of the skin, gastrointestinal tract and airway contribute to health and disease. As we learn more about the role that the microbiota plays in allergic disease development, we can develop therapeutics to alter this pathway.

Recent Findings: Epidemiologic studies reveal that an association exists between environmental exposures which alter the microbiota, and developing atopic dermatitis, food allergy and/or asthma. In fact, samples from the skin, gastrointestinal tract and respiratory tract, reveal distinct microbiotas compared to healthy controls, with microbial changes (dysbiosis) often preceding the development of allergic disease. Mechanistic studies have confirmed that microbes can either promote skin, gut and airway health by strengthening barrier integrity, or they can alter skin integrity and damage gut and airway epithelium.

Summary: In this review, we will discuss recent studies that reveal the link between the microbiota and immune development, and we will discuss ways to influence these changes.

Keywords

Microbiome; Asthma; Food Allergy; Atopic Dermatitis; Immune Development

INTRODUCTION

The prevalence of allergic disease continues to increase in the developed world leading to an increase in the number of children diagnosed with respiratory allergies such as rhinitis and asthma, food allergy, and/or atopic dermatitis. The hygiene hypothesis suggests that individuals from larger households have lower rates of allergic rhinitis and asthma. The advent of sophisticated methods to detect bacteria has resulted in numerous studies investigating the association between bacteria and allergic disease. Associations between the microbiota and exposures (cesarean deliveries, formula feeding, prebiotic or probiotic use, high fat and low fiber diets, and antibiotic use during infancy), and the eventual development

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of allergic disease suggests that the human microbiota plays a central role in the regulation of this process. (1–5)

This review summarizes the current literature linking the microbiota and allergic diseases, and reviews experimental data suggesting potential mechanisms between the two. In addition, the authors will discuss clinical evidence that early interventions may alter the microbiome and may decrease development of allergic disease. Because findings differ for each of the three main allergic diseases, atopic dermatitis, food allergy, and asthma will be reviewed individually.

ATOPIC DERMATITIS

The skin microbiome is comprised of bacteria, fungi, viruses and archaeal communities, with bacteria (the microbiota) being the most widely studied. Healthy skin consists of a diverse community of microbes that has differing communities depending on the sampling site. *Propionibacterium* species predominate in sebaceous sites while *Corynebacterium* and *Staphylococcus* species are found in moist microenvironments.(6, 7) When changes in this "healthy microbiome" occur, allergic sensitization can ensue.

Infant Skin Microbiome

Early skin colonization of infants consists of four main genera: *Staphylococcus*, *Streptococcus*, *Lactobacillus* and *Propionibacterium*.(8) However, in infants with atopic dermatitis (AD), an increased prevalence of *Staphylococcus aureus* with a decrease in the commensal microbes, *Propionibacterium*, *Streptococcus*, *Acinetobacter*, *Corynebacterium*, and *Prevotella*, has been observed. (8–13) These changes in bacterial composition can impair the skin's ability to prevent overgrowth of harmful bacteria. For example, coagulase negative commensal bacteria, including *S. epidermidis*, *S. hominis*, and *S. lugdunensis*, secrete antimicrobials that limit *S. aureus* overgrowth and biofilm formation. In individuals with AD the prevalence of these protective bacteria is decreased which can disrupt this protective process.(14) Despite evidence that an overgrowth of *S. aureus* precedes the development of atopic dermatitis, (15) colonization with other species of Staphylococcus is associated with lower risk of atopic dermatitis by one year of age, demonstrating that mechanistic pathways influencing AD development can be species specific. (16)

Skin Microbiota and Atopic Dermatitis

Regardless of the timing of presentation, numerous studies have shown that over 90% of patients with atopic dermatitis have *Staphylococcus aureus* colonization.(17) Furthermore, the proportion of *S. aureus* relative to other commensals increases during flares, with higher density associated with more severe AD. (12, 18, 19) Mechanistic studies investigating the association between the presence of *S. aureus* and AD severity have shown that *S. aureus* affects atopic dermatitis in several ways. *S. aureus* activates protease receptors to disrupt the epidermal barrier of patients with AD or mice with filaggrin loss of mutation functions.(20, 21). In addition, *S. aureus* releases endotoxins and enterotoxins which stimulate mast cells and cause inflammation and dysregulation of keratinocytes. *S. aureus* also upregulates production of type 2 cytokines such as TSLP, IL-4 and IL-13.(20) High IL-4 and IL-13

deplete keratinocyte-produced antimicrobial peptides (AMPs) needed to control pathogenic organisms, thereby allowing further destruction by pathogenic bacteria. Ultimately, TLR2-mediated sensing of *S. aureus* is impaired in Langerhans cells from AD skin causing a cycle of keratinocyte dysregulation and disruption of the skin microbiome.(22) In healthy skin, *Staphylococcus epidermidis* activates TLR2, which promotes tight junction protein expression and induces keratinocyte-derived AMPs secretion; therefore when *S. aureus* is the predominating species colonizing the skin this protective process is less effective. (23, 24) In addition, coagulase negative bacteria including *S. epidermidis*, *S. hominis*, and *S. lugdunensis* secrete antimicrobials that limit *S. aureus* overgrowth and biofilm formation. (25) While most studies point to *S. aureus* preceding the overgrowth of atopic dermatitis, one recent study did not find a high prevalence of *S. aureus* in lesional skin of infants with AD, (16) suggesting that longitudinal studies are needed to determine if *S. aureus* or other microbes play a role in AD development.

Gut Microbiome and Atopic Dermatitis

A diminished diversity of the gut microbiome also shares a relationship with atopic dermatitis. For example, antibiotic use in the first two years of life is associated with an increased risk of atopic dermatitis, suggesting a link between changing the GI microbiota and skin immunity. (1, 8) Additionally, other evidence demonstrates a lack of *Bacteroides* diversity or a high prevalence of C*lostridium difficile* colonization by one year of age is associated with atopic dermatitis development by 2 years of age. (26–28) One explanation for this difference is that individuals with atopic dermatitis are missing mucin producing bacteria which provides food for the commensal bacteria of the gut. If this nutrition is lacking it is possible that pathogenic bacteria overgrowth occurs instead. (29) Furthermore, often times a lower abundance of *Bifidobacterium* is present in the intestine of these individuals, suggesting that immune mechanisms are activated differently if more than one allergic disease is present. (30) Interestingly, the gut microbiota of infants with atopic dermatitis changes if they have concomitant food allergy. The fecal microbiota of those with both atopic dermatitis and food allergy contained more *Escherichia coli* and *Bifidobacterium pseudocatenulatum*, and less *Bifidobacterium breve*, *Bfidobacterium adolescentis*, *Faecalibacterium prausnitzii*, and *Akkermansia muciniphila* than children who had atopic dermatitis without food allergy. (9) Understanding the mechanisms behind this difference will help improve methods of prevention and treatment.

Treatment

Recent treatments for atopic dermatitis address the microbiota of the skin, with *S. aureus* as the main target. Emollients and anti-inflammatory medications are initially used to improve the epidermal barrier and prevent *S. aureus* from predominating. Antimicrobials are then used to directly combat *S. Aureus*. (8) New treatment strategies aim to add helpful bacteria to the skin rather than eliminate unwanted microorganisms. For example, the addition of topical *Roseomonas mucosa* and *Vitreoscilla filiformis* bacterial lysate has been shown to improve inflammation and severity of eczema. (31) Additionally, autologous microbiome transplant of *S. hominis* and *S. epidermidis* has also been efficacious in controlling *S. aureus* overgrowth. (32)

Improving the gut microbiome has been another target in the treatment of atopic dermatitis. Supplementation with probiotics and prebiotics is one intervention being assessed. Some success has been seen with probiotics. Prenatal and post-natal administration of the probiotics *Bifidobacterium breve* M-16V and *Bifidobacterium longum* BB536 reduced the risk of developing atopic dermatitis during the first 18 months of life. (33, 34) Additionally, prenatal and post-natal treatment with *Lactobacillus* combined with *Bifidobacterium* reduced the risk of developing atopic dermatitis.(35) However, other studies have found conflicting results for probiotic use. For example, a recent randomized controlled trial administered *Lactobacillus rhamnosus* to children with a parental history of asthma for the first 6 mo of life. (36) Compared to those who received placebo, supplementation did not prevent the development of eczema or asthma by 2 years of age, suggesting that *Bifidobacterium* may play a larger role in allergic sensitization than *Lactobacillus*.

FOOD ALLERGY

Method of Delivery

The gut microbiome is mostly comprised of *E. Coli* and enterococcus species immediately after birth.(37) These microbes provide an oxygen rich environment for *Bifidobacterium*, *Lactobacillus*, *Bacteroides*, and *Clostridium* to proliferate. In infants born by cesarean section, *Clostridium* predominates over *Bifidobacterium* species, while the inverse is observed with vaginal deliveries.(38) Furthermore, infants born by cesarean section are colonized by maternal skin and hospital derived microbes, (39) suggesting that method of delivery may play a role in the early development of the microbiota and potentially the development of food allergy.

The Early Microbiome and Breastfeeding

Breastfed infants have less overall gut diversity within the first few weeks of life and are mostly colonized by *Bifidobacterium*. (40) An increased prevalence of C*lostridium* species compared to *Bifidobacterium* species at 3 weeks of age is associated with developing a food allergy in the first year of life. (40, 41) Furthermore, decreased *Bifidobacterium* and *Lactobacillus* species at 1–2 months of age increases the risk of developing allergies by 5 years of age. (42, 43) One possible explanation for this link between bacteria and decreased food allergy is that *Bifidobacterium* releases SCFAs (butyrate and propionate) and lowers stool pH, thereby creating an unfavorable environment for pathogenic bacteria. In mouse studies, non-digestible oligosaccharides and SCFAs decrease IgE mediated basophil degranulation and reduce the development of food allergies, further supporting a link between high levels of *Bifidobacterium* and food allergy. (44) Interestingly, formula is lacking *Bifidobacterium* further suggesting that early exposure to specific bacteria through the diet is key to food allergy prevention.(45)

Maternal Diet

Maternal diet may influence the infant microbiota and development of food allergy. The presence of *Prevotella* in maternal stool is associated with a decreased risk of their infant developing food allergy. (46) *Prevotella* is less prevalent in the Western world and is a microbe know for fermenting fiber and producing SCFAs. Maternal diets high in fat and

fiber are associated with lower risk of food allergy development in offspring and this risk was further decreased if the mother's stool contained *Prevotella copri*. Furthermore, *P. copri* is more prevalent in women from larger households and in women who did not receive antibiotics during pregnancy, two known protective associations in the development of allergic diseases. (46) Additionally, maternal peanut ingestion during pregnancy and lactation paired with early infant introduction to peanut allergen was shown to be associated with a decreased risk of sensitization to peanut allergen compared to early infant diet introduction alone.(47) However, another study found increased sensitization in offspring of mothers who consumed peanuts during pregnancy. (48) Insufficient data exists at this time to recommend a modification of the maternal diet during pregnancy to reduce the risk of food allergy.

Infant Diet

When considering introduction of solid foods, the benefits of SCFAs have been demonstrated. In a subset study of 301 children in the Protection Against Allergy Study in Rural Environments, the consumption of yogurt, fish, vegetables, and fruits within the first year of life was found to be associated with increased butyrate in stool samples by one year of age. In those children with butyrate and propionate levels over the 95th percentile, decreased sensitization to food allergens was discovered between the ages of 3 to 6 years of age.(4) Furthermore, another cohort study out of the United Kingdom found that diets rich in fruits, vegetables, and home prepared foods (as opposed to commercial infant foods) were associated with lower rates of food allergy by age 2 years of age. (49) These data could be secondary to the production of SCFAs by commensal bacteria, but more evidence is needed. Animal studies are currently underway and will help define mechanisms between bacteria and food allergy. (50)

Early food introduction to a diverse range of foods has been linked to lower incidence of food allergy.(49, 51, 52) The most substantial study supporting this is The Learning Early About Peanut Allergy trial, which revealed that introducing peanut allergen into an infant's diet at 4–6 months of age reduced the incidence of peanut allergy. (51, 53) Interestingly, infants with *Staphylococcus* skin colonization were more likely to develop allergy suggesting that skin colonization may also contribute to allergic sensitization. In addition to early introduction of peanut, cheese consumption is associated with a reduced risk for food allergy, potentially due to its microbial composition and/or its relatively high content of SCFAs.(4) Further research is needed to delineate the relationship between specific foods and microbial development.

Gastrointestinal Microbiota and Food Allergy

The microbiota of the GI tract changes over the first three years of life, with the neonatal and infant microbiota influenced by method of delivery, breastfeeding, and solid food introduction as discussed above. (54, 55) Microbiota differences have been observed in patients with established food allergy, and they differ based on the food allergen studied. For example, studies report a higher prevalence of *Lachnospiraceae*, *Streptococcaceae*, and *Leuconostocaceae* in children with egg allergy (56), and an increase in *Lachnospiraceae* and *Ruminocaceae* in those with milk allergy.(57) Interestingly, further differences exist between

those who have resolution of their allergy. An observational study investigating the microbiota of 226 infants between 3–16 months of age with milk allergy found that the presence of *Clostridia* and *Firmicutes* in the gut was associated with resolution of milk allergy by 8 years of age.(58) Further studies are needed to determine if specific species of these bacteria could be used to treat food allergy.

Studies investigating the mechanisms between food allergy and the microbiota have found that symbiotic bacteria have been shown to assist in intestinal integrity and immune system development/regulation. For example, commensal bacteria induce intestinal T-cells to differentiate into T-regulatory cells (59, 60) and the SCFAs, butyrate and propionate, drive T-regulatory differentiation (61, 62) and decrease pro-inflammatory mediator production from dendritic cells.(61) In addition, high fiber diets have been shown to protect mice from developing peanut sensitization due to the increase in fiber fermenting anaerobic bacteria producing SCFA which increase T-regulatory cells and dendritic cell tolerogenesis.(63)

As discussed above, numerous studies have demonstrated an association between the microbiome and the development of food allergy. Further mechanistic studies are needed to help us better understand how these bacteria lead to food allergy in some, but not all, infants.

Treatment

Despite our lack of understanding of these underlying mechanisms, studies investigating various treatment modalities have been performed. Treatments that intervene with the microbiome include prebiotics, probiotics, synbiotics, and fecal microbiota transplantation. The benefit of adding prebiotics to mimic human milk in formula-fed infants to decrease food allergy has not been demonstrated. In regard to probiotics, *Lactobacillus rhamnosus* supplementation in children with milk allergy has been shown to reduce the development of other allergic diseases and hasten resolution of milk allergy.(64) Use of this same supplement alongside oral desensitization to peanut resulted in a majority of participants achieving tolerance, however the study lacked a probiotic only and oral immunotherapy only groups for comparison.(65) Recent reviews of probiotics in food allergy concluded that insufficient data exists to recommend probiotic supplementation at this time. (66) Based on these data, the World Allergy Organization has suggested that probiotics can be used in certain high-risk populations making it clear that its recommendations are based on low-quality evidence.(67) Further research is needed in this area. Synbiotics and fecal microbiota transfers trials are still in their infancy and have yet to produce reliable results. Currently the use of partially hydrolyzed infant formula with added synbiotics compared to regular infant formula is being investigated. Fecal microbiota transfer studies in murine models have revealed that colonization of milk sensitized, germ-free mice with bacteria from healthy infant stool decreased the systemic allergic response compared to uncolonized mice.(68) In humans, fecal microbiota transfers have been studied in irritable bowel disease and *Clostridium difficile* infection (69, 70) however data for peanut allergy treatment with fecal microbiota transfers are still undergoing several phase 1 clinical trials (NCT02960074).

ASTHMA

The early work of Bisgaard et al. showed that bacterial colonization of the hypopharynx at one month of age was associated with early wheeze and the subsequent development of asthma.(71) Furthermore, they found that early colonization with *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Haemophilus influenzae* was associated with increased levels of total IgE and blood eosinophil counts (71). The same group demonstrated that bacterial infections of the airway were associated with acute episodes of wheeze in children, independent of viral infection, (72) suggesting bacteria could be an early predictive marker or a causal factor in the development of wheeze and childhood asthma.

Environmental Impact

It has now been well established that a child's environment can influence health outcomes. Multiple studies have found that children raised in the setting of rural farm communities have a decreased likelihood of developing asthma (73–79). Furthermore, some studies have looked into specific exposures, finding that pig farming, farm milk consumption (80), and time spent working in animal sheds and barns are protective (78). Meanwhile sheep farming, hare/rabbit farming, and hay feed exposure increased the risk of developing asthma (78). Endotoxin levels found in the dust near these farming environments have been the focus of studies examining the differences between these various farm-related exposures. In comparing the rural farm environment of Indiana Amish versus South Dakota Hutterite children, it was found that endotoxin levels were 6.8 times greater in dust from the homes of the Amish community. (73) Interestingly, the prevalence of asthma in the Amish cohort of children was 4 times lower than that of the Hutterite. The exposure to greater microbial diversity, found in various farming communities, seems to exhibit protection from the development of asthma. It has been suggested by many that the early-in-life exposure to higher levels of environment-specific endotoxins plays a significant role in innate immunity activation and its ability to suppress inflammatory responses (73, 78, 79). While the knowledge that certain farm exposures protect against asthma development is helpful, it is not a practical solution to raise all children on farms. A recent study investigated the mechanisms behind this exposure finding that mice exposed to dust from Amish farms have less airway hyper-reactivity and eosinophilia. Furthermore, knocking out steps in innate immunity pathways eliminated these protective effects, demonstrating that high endotoxin exposure is needed to develop innate immune responses. (75)

Method of Delivery

With an increase in the number of caesarian sections being performed in industrialized countries coinciding with an increase in asthma prevalence, method of delivery has become an area of interest in regard to the neonatal microbiome. Multiple studies have found an association between delivery via caesarian section and childhood asthma, with a recent meta-analysis finding that caesarian section increased the risk of childhood asthma by 20% (81). The microbiota within the nares, skin, and oral cavity are different between caesarian and vaginally delivered neonates.(82) Furthermore, neonates born via caesarian section showed greater nasopharyngeal microbiota instability longitudinally as well as decreased abundance of *Corynebacterium* and *Dolosigranulum* (83), bacteria associated with an

absence of wheeze or asthma. Not only is the nasopharyngeal microbiota affected but the gut microbiota also appears to play a role in early airway immune responses. Independent of intrapartum antibiotic administration, vaginally delivered infants have a higher abundance of *Bifidobacterium* and *E. coli* with a lower abundance of *Staphylococcus* and *Klebsiella*. The same study also found that the composition of the GI microbiota at one week of life was associated with the number of respiratory infections reported in infants over the first year of life, suggesting that both the respiratory and gut microbiota play a role in asthma development. (84) However, other studies have found that while mode of delivery was associated with different patterns of microbiota in the neonate, when the microbiota was sampled again at 6 weeks of age, the differences no longer remained (82). Further investigations are needed to determine if this early difference in the microbiome at birth is associated with long term outcomes of asthma.

Breastfeeding

Many studies have shown a beneficial association between breastfeeding and respiratory health (85–89). Infants exclusively breastfeed for the first six weeks of life have a more stable microbiota profile comprised mainly of *Dolosigranulum* and *Corynebacterium*. Breastfeeding for a longer period of time (3 months) was also associated with prolonged elevated abundance of *Dolosigranulum* and *Corynebacterium*, thereby providing greater microbiota stability to the developing airway (90). In addition, breastfeeding is associated with fewer parent-reported respiratory infections (91, 92), suggesting that this prolonged microbiota stability is stimulating immune system development.

Airway Microbiome and Asthma

Whether a causal relationship exists between the airway microbiota and asthma remains unknown. However, multiple studies have attempted to map out the upper airway microbiota in order to investigate a possible relationship between dysbiosis and respiratory illness, wheeze, and asthma. Prospective cohort studies have found that six dominant genera make up the upper airway microbiota, ranging from early childhood through late adolescence. Throughout this time period the dominant genera in the upper airway microbiota are *Moraxella*, *Streptococcus*, *Corynebacterium*, *Alloiococcus*, *Haemophilus*, and *Staphylococcus* (93–95). Alterations in the development of the upper airway microbiota are associated with an increased risk of upper respiratory tract infections (URIs) during the first few years of life. (95, 96) Increases in the abundance of *Streptococcus* and *Haemophilus* (97) is associated with RSV bronchiolitis, while RV bronchiolitis is associated with an increased abundance of *Haemophilus* and *Moraxella*. (98) (91, 93, 99, 100). In contrast, a high abundance of *Corynebacterium* confers protective effects leading to stabilization of airway microbiota and milder disease, (90, 91, 93, 100, 101) suggesting that bacteria play an active role in the immune responses to infection. In a study of the upper and lower airway microbiome and transcriptome, it was suggested that in the nasal airway of non-asthmatics, *Corynebacterium* negatively interacted with genes that promoted inflammation and therefore conferred protection (100). The relationship between *Moraxella* and respiratory illness remains ill-defined with studies showing conflicting data. While some are associating its abundance with microbial stability and lack of respiratory illness(91), others are finding that a microbial profile dominated by *Moraxella* correlates with increased instances of

respiratory illness and asthma exacerbations(71, 94). Murine models do support a detrimental role, as colonization with *Moraxella* led to strong inflammatory responses and elevated neutrophilic infiltrates (102, 103). In another study, isolated strains of *Moraxella* from nasal secretions of asthmatics were utilized for inoculation of airway epithelial cell cultures. It was found that *Moraxella* isolates increased epithelial damage as well as gene expression of pro-inflammatory cytokines(94). These studies point to the importance of understanding the evolution of early life airway microbiota and identifying a 'critical window' in which intervention could alter the trajectory of respiratory health. Further supporting these findings, neonatal mice exhibited a two-week window following birth in which microbial exposure and diversity correlated with stabilization of the lung microbiota. Dysregulation of the microbiota in the time window led to sustained susceptibility to allergic airway inflammation into adulthood (104). Additional studies are still needed to confirm whether distinct microbiota profiles trigger harmful responses in the upper airway.

Treatment

While numerous studies are underway, few interventions have been published. Administration of *Lactobacillus reuteri* to mice attenuated recruitment of airway eosinophils and prevented allergen-induced airway hyperresponsiveness.(105) In infants, one recent study examined third trimester supplementation with fish oil and high dose Vitamin D. (106) At one month of age, the infant airway microbiota contained fewer bacteria associated with asthma development compared to placebo matched controls. Interestingly, the vaginal microbiota was not altered in this study, suggesting that prenatal supplementation does not harm the maternal microbiota. Randomized control trials with long-term follow-up are needed to determine if these early interventions prevent allergic diseases during childhood.

CONCLUSIONS

A growing body of evidence links the skin, gut, and respiratory microbiota with allergic diseases. Commensal bacteria is associated with "healthy" immune development, while a higher abundance of pathogenic bacteria is associated with weakened mucosal protection and the upregulation of inflammatory cytokines (Figure 1). However, studies describing the timing behind these microbial changes and immune development are lacking, and the ideal moment to intervene before detrimental immune changes occur is needed. Once this "window of opportunity" is determined, better methods to prevent allergic disease can be achieved.

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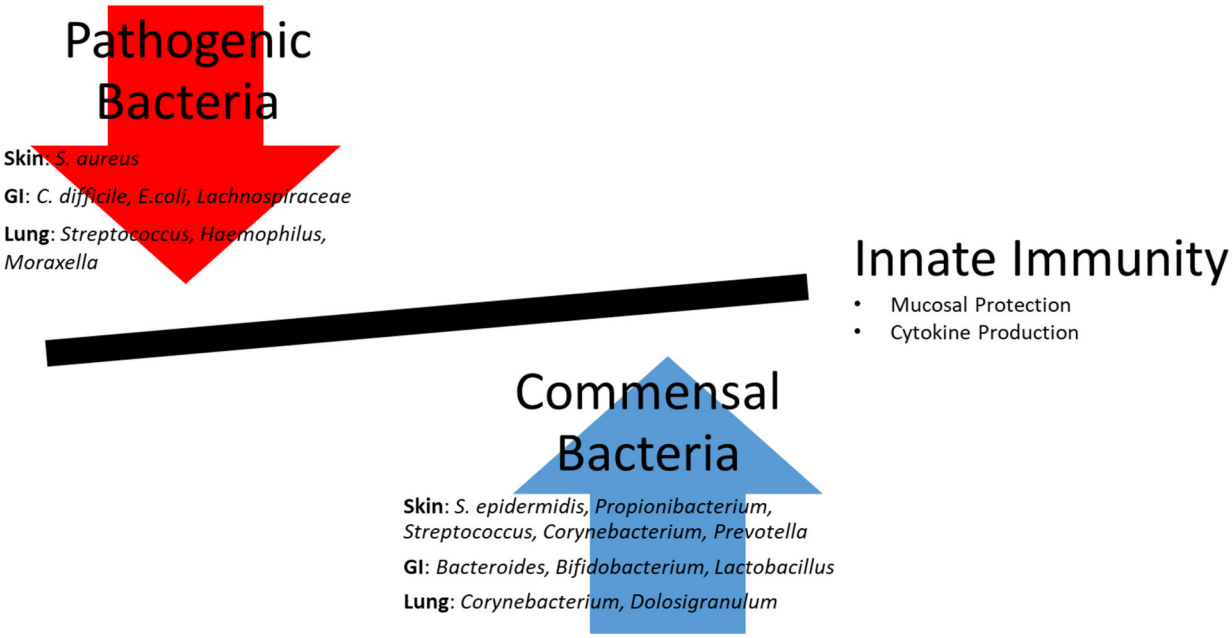

Figure 1:

An increase in pathogenic bacteria is associated with a decrease in innate immune responses including a decrease in mucosal protection and an upregulation of inflammatory cytokines leading to an increase in allergic sensitization. In contrast, an increase in commensal bacteria is associated with activation of innate immunity and prevention of allergic sensitization.