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CME Review

# The microbiome of the nose

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**Key Messages**

- The nasal microbiome is a diverse community of microorganisms that can be found throughout the nose and sinuses.
- Bacteria in the nose and nasal microbiome profiles can be detected shortly after birth.
- *Staphylococcus aureus* is a key pathogenic bacterium in chronic rhinosinusitis with nasal polyps; however, this may dependent on the phenotype and severity of disease.
- Probiotics can potentially improve clinical efficacy of immunotherapies and antihistamines in treatment plans of allergic rhinitis, but this requires further evidence.

**Instructions**

Credit can now be obtained, free for a limited time, by reading the review article and completing all activity components. Please note the instructions listed below:

- Review the target audience, learning objectives and all disclosures.
- Complete the pre-test.
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**Overall Purpose**

Participants will be able to demonstrate increased knowledge of the clinical treatment of allergy/asthma/immunology and how new information can be applied to their own practices.

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**Learning Objectives**
At the conclusion of this activity, participants should be able to:

- Describe the relationship between the nasal microbiome, chronic rhinosinusitis and allergic rhinitis
- Discuss clinical trials examining the potential clinical benefits of probiotic treatments in chronic rhinosinusitis and allergic rhinitis

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**Target Audience**
Physicians involved in providing patient care in the field of allergy/asthma/immunology

**Accreditation**
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## Introduction of the Microbiome

The human body harbors 10 trillion to 100 trillion microorganisms, vastly outnumbering the quantity of human cells.[1] The microbes and their genomes located within a particular area are defined as the microbiome. Microbiomes can be found in all different types of hosts, such as plants, animals, and humans. Research into the human microbiome surged in the late 2000s with the launch of the Human Microbiome Project.[1] This project aimed to identify and characterize microorganisms located on environmentally exposed surfaces. The human microbiome has been suggested to play an important role in disease development and overall health of the host.[2,3] Dysfunctional or imbalance of microbial composition (dysbiosis) can potentially affect inflammatory conditions, including inflammatory bowel disease, obesity, and allergic disease.[4]

In humans, bacterial communities live in areas with external exposure such as the skin, gastrointestinal tract, mouth, upper airways, and lungs.[5] Human cells possess approximately 21,000 protein-encoding genes, whereas the human microbiome encompasses at least 3 million protein-encoding genes.[6,7] Proteins produced by microbes may interact with human cells and potentially function in altering barrier protection to the external environment. The microbiota, which is the community of fungi, parasites, viruses, and bacteria, may increase mucosal barrier function through pathogen exclusion and activation of the innate and adaptive immune system.[8,9] In the gastrointestinal tract, microorganisms play a role in regulating T cells and dendritic cells.[10,11] Whether similar immune modulation occurs in the nose is undetermined. Respiratory tract immunity may be connected to immunomodulatory activities seen in the gastrointestinal tract through the common mucosal immune system hypothesis.[12] This hypothesis suggests that antigens in the gastrointestinal track stimulate local lymphoid cells, which may migrate to other submucosal sites in the upper and lower airways.[12] Antigens are thought to be collected by Peyer's patches and delivered to antigen-presenting cells.[13] Naïve T and B cells become sensitized to the antigen located in the Peyer's patch and migrate to the bloodstream to be distributed to the gut, urinary, and respiratory tracts.[13] This review focuses primarily on the nasal microbiome and its impact on allergic rhinitis (AR). Because of the limited data on AR and the nasal microbiome, we briefly discuss the nasal microbiome influence on chronic rhinosinusitis (CRS). This review also addresses the potential role for probiotic therapeutic interventions for these respiratory diseases (Table 1).

## The Hygiene, Biodiversity, and Microflora Hypotheses

The hygiene hypothesis relationship with allergy originated in Canada during the 1970s. Gerrard et al[14] observed a decreased prevalence of allergic disease in the Metis community in Northern Saskatchewan compared with the Caucasian population in central Saskatchewan.[14] In 1989, Strachan proposed the hygiene hypothesis while observing an inverse association between allergic disease and children with larger families.[15] This study suggested that unhygienic contact through older siblings may allow for protection against AR.[15] The hygiene hypothesis was supported by an observational self-report–based study conducted in children ages 9 through 11 years from East and West Germany.[16] Atopic sensitization and reported AR were significantly greater in children from West Germany compared with East Germany.[16] Less hygienic living conditions in early childhood may have allowed for the transmission of infections that was thought to prevent the development of allergic disease. This concept was reinforced by examining the relationship of rural living conditions and atopic diseases. Early life exposure to farming-based environments was linked with decreased atopic frequency in children.[17] As new articles and ideas have emerged, the hygiene hypothesis was updated to suggest that T helper type 1 (Th1) cells may have reduced stimulation with hygienic living conditions, thus potentially leading to an imbalance of T helper type 2 (Th2) cells.[18] The hygiene hypothesis is still often discussed in the context of the development of allergic disease and atopy.

The biodiversity hypothesis is a more recent concept largely made popular by the Human Microbiome Project. The biodiversity hypothesis suggests the importance of microbial variety during human development to allow for an enriched and diverse microbiome.[19] This notion does not directly refute or contradict the hygiene hypothesis but instead builds on the original concept of infants lacking exposure to critical environmental contacts. Recent evidence indicates that asthma in children may be associated with decreased nasal microbiome diversity.[20] Depner et al[20] analyzed the bacterial diversity from 68 nose and 327 throat swabs from children ages 6 to 12.[20] This study observed an association of asthma in children with decreased nasal bacterial diversity.[20] Likewise, a Swedish study demonstrated that increased biodiversity in the gut was associated with protection from allergic disease in early life.[21] The biodiversity hypothesis mainly focuses on the interaction of the gut microbiome because of the diversity and quantity of microorganisms found in the gastrointestinal tract.

The microflora hypothesis expands on the concepts of both the hygiene and biodiversity hypotheses. The microflora hypothesis proposes a possible disruption to immunity because of interaction with a dysbiotic microbiota.[22] The microbiota in the gut may function in a modulator role for the immune system.[10,11] Evidence that supports this concept examines the use of antibiotics in young children and the development of allergic disease. The International Study of Asthma and Allergies in Childhood performed a survey-based study that spanned across 29 countries to observe the development of allergic disease in children ages 6 to 7 years.[23] Foliaki et al[23] reported that antibiotic use within 1 year of birth was associated with an increased risk of symptoms for asthma, eczema, and rhinoconjunctivitis.[23] Although several hypotheses have been suggested, the exact mechanism of how the microbiome functions in allergic disease development is not yet fully understand.

## Microbiome of the Nose in Healthy Individuals

The nasal cavity is an important interface to the external environment. During inspiration, the airways are exposed to pollutants, aeroallergens, microbes, and fungal spores. The human respiratory tract is organized into 2 distinct sections: the upper respiratory tract (URT) and the lower respiratory tract. The URT encompasses the anterior nares, vestibule, inferior turbinate, middle turbinate, superior turbinate, sinuses, nasopharynx, and the section of the larynx located above the vocal cord. The nose is inhabited by a wide variety of potential pathogenic and harmless bacteria.[24-27] This diverse nature may be attributable to localized factors (temperature and humidity) and position in the respiratory tract. Yan et al[24] observed that the anterior nares had decreased levels of microbiome biodiversity in comparison with the middle meatus and sphenoethmoidal recesses.[24] However, no significant differences were noted in biodiversity between the middle meatus and sphenoethmoidal recesses, which differ in location, but both have ciliated pseudo-stratified columnar epithelium.[24] In contrast, the anterior nares are lined with keratinized squamous epithelium and sebaceous glands that produce sebum,[26] and this may have an impact on bacterial diversity.[24] However, a recent study did not detect any significant differences in bacterial diversity from the middle meatus, inferior turbinate, and anterior nares from healthy individuals.[28]

The microbiome of the anterior nares in healthy adults has been observed to be dominated by 3 phyla: Actinobacteria, Firmicutes, and Proteobacterai.[25] In 2014, Zhou et al[26] examined the anterior nares of 236 healthy adults, using a nasal swab.[26] The anterior nares can

**Table 1**
Characteristics of Clinical Trials That Examined the Efficacy of Probiotics in Treating Allergic Rhinitis and Chronic Rhinosinusitis

| Year | Author | Design | Disease | Participants | Probiotic strains (dosage) | Treatment arms | Duration |
|---|---|---|---|---|---|---|---|
| 2017 | Dennis-Wall et al[58] | Parallel double-blind, randomized, placebo-controlled study | SAR | 173 adults (18-60 years) | *Lactobacillus gasseri* KS-13, *Bifidobacterium bifidum* G9-1, *Bifidobacterium longum* MM-2 ($3 \times 10^9$ CFU/day) | I. Oral probiotics<br>II. Oral placebo | 8 weeks |
| 2017 | Mårtensson et al[63] | Crossover, double-blind, randomized, sham-controlled study | CRSsNP | 20 adults (21-80 years) | 13 Honeybee lactic acid bacteria (2 doses to each nostril twice a day—$1 \times 10^9$ CFU/dose) | I. Nasal probiotic spray<br>II. Nasal sham spray | 2 weeks |
| 2016 | Jerzynska et al[59] | Prospective double-blind, randomized, placebo-controlled study | SAR | 100 children (5-12 years) | *Lactobacillus rhamnosus GG* (Once per day) | I. 5-Grass SLIT tablet 300 IR with vitamin D 1,000 IU<br>II. 5-Grass SLIT tablet 300 IR with oral probiotic<br>III. 5-Grass SLIT tablet 300 IR with oral placebo | 5 months |
| 2016 | Xu et al[56] | Parallel double-blind, randomized, placebo controlled study | PAR | 158 patients | *Clostridium butyricum* (2 capsules of 420 mg twice per day) | I. Oral probiotic<br>II. Oral probiotic with SCIT[a]<br>III. SCIT[a]<br>IV. Oral placebo | 12 months |
| 2014 | Lin et al[55] | Parallel double-blind, randomized, placebo-controlled study | PAR | 60 children (6-13 years) | *Lactobacillus paracasei* HF.A00232 ($5 \times 10^9$ CFU/daily) | I. Levocetirizine with oral placebo[b]<br>II. Levocetirizine with oral probiotic[b] | 12 weeks |
| 2013 | Singh A et al[57] | Parallel double-blind, randomized, placebo-controlled study | SAR | 20 adults (20-65 years) | *Bifidobacterium lactis* NCC2818 ($4 \times 10^9$ CFU/day) | I. Oral probiotic<br>II. Oral placebo | 8 weeks |
| 2009 | Mukerji et al[61] | Prospective, double-blind, randomized, placebo-controlled study | CRS | 77 patients (16-69 years) | *Lactobacillus rhamnosus* R0011 (Twice daily—500 million active cells/tablet) | I. Oral probiotic<br>II. Oral placebo | 8 weeks |
| 2005 | Ishida et al[54] | Double-blind, randomized, placebo-controlled study | PAR | 49 adults | *Lactobacillus acidophilus* L-92 ($3 \times 10^{10}$ CFU/day) | I. Oral probiotic<br>II. Oral placebo | 8 weeks |

Abbreviations: CFU, colony-forming unit; CRS, chronic rhinosinusitis; CRSsNP, chronic rhinosinusitis without nasal polyps; IR, index of reactivity; IU, International Unit, PAR, perennial allergic rhinitis; SAR, seasonal allergic rhinitis; SLIT, sublingual immunotherapy.

[a] For first 6 months, then injected placebo for last 6 months.

[b] Levocetirizine used as rescue treatment for last 4 weeks.

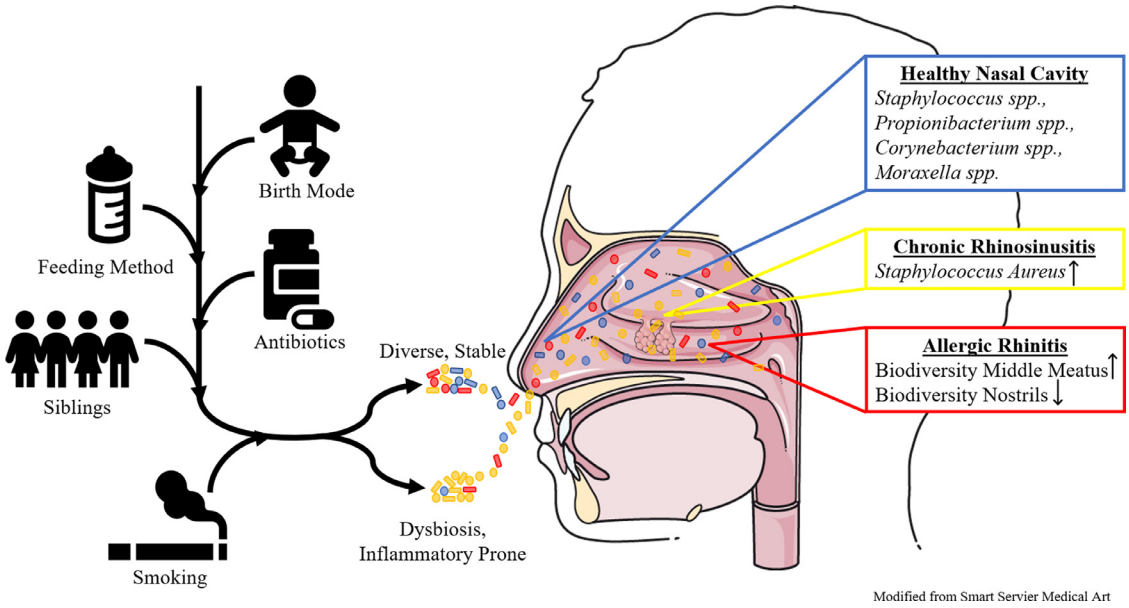


**Figure 1.** Environmental factors and characteristic species of the nasal microbiome. Factors that may alter the nasal microbiome during development include mode of delivery, feeding method, siblings, antibiotic treatments, and exposure to smoke.[3,31] These influences can shape the nasal microbiome community to be more prone to the development of inflammation or dysbiosis. Nose and polyp images were obtained and modified from Servier Medical Art under a Creative Commons Attribution 3.0 Unported license (https://creativecommons.org/licenses/by/3.0).

generally be further classified into 4 distinct genus profiles through an abundance of *Staphylococcus*, *Propionibacterium*, *Corynebacterium*, or *Moraxella*.[26] The middle meatus has been examined by Ramakrishnan et al[27] in 28 healthy adults. These areas possessed rich diverse bacterial communities, with the most abundant microorganisms being *Staphylococcus aureus, Staphylococcus epidermidis,* and *Propionibacterium acnes*.[27] The adult nasal microbiome in healthy individuals is better characterized than unhealthy disease states. The timing and stages of nasal microbiome development require further research.

Newborns were previously believed to be completely free of microorganisms while in utero, and microbiome development began on departing the womb. This belief has been challenged in the past decade. Jiménez et al[29] demonstrated that treating pregnant mice orally with genetically labeled bacteria resulted in the bacterium transferring to the meconium of the offspring.[29] This was supported in humans by Rautava et al,[30] who demonstrated that the consumption of probiotics during pregnancy altered the Toll-like receptor genes in the meconium of neonates compared with controls.[30] These studies suggests that colonization of the gut begins before birth. Typical factors that may impact the development of the microbiome include mode of birth, breastfeeding, environmental exposures, antibiotics, and smoke inhalation (Fig 1).[3,31]

Development of the nasal microbiome may begin before parturition; microorganisms can be detected in healthy neonates' nasopharyngeal tissue minutes after birth, regardless of delivery mode.[32] Biesbroek et al[33] also examined the URTs of 60 healthy infants at 1.5, 6, 12, and 24 months post-birth.[33] Eight microbiota profiles were identified from nasopharyngeal swab, with the earliest detected at 1.5 months of age.[33] Biesbroek et al[33] also observed that early colonization of *Moraxella*, and *Corynebacterium* in combination with *Dolosigranulum* were associated with stability in the microbiota profile.[33] In 2015, a similar prospective study identified distinct nasal microbiota profiles within the first 3 months of life when analyzing nasal swabs from 48 healthy infants biweekly. Mika et al[34] also observed seasonal differences in the microbiota profiles, with increases of *Corynebacterium* and *Pasteurellaceae* in the summer and winter months, respectively.[34] Both studies observed a relatively high abundance of *Staphylococcus* and *Corynebacterium* in the nasal microbiota during early life.[33,34] Both bacterial species are common colonizers of breast milk and adult human skin.[35,36] This suggest that skin contact and breastfeeding may help shape the nasal microbiota.

## Allergic Rhinitis and the Microbiome of the Nose

AR is an immunoglobulin (Ig)E-mediated inflammatory disease of the nasal passageway that results in symptoms such as sneezing, rhinorrhea, and nasal congestion. In Canada, AR affects approximately 25% of the population, and its prevalence is increasingly globally.[37] AR has been demonstrated to have a negative impact on social life, sleep, and productivity.[37,38] AR can be divided into 2 broad subcategories: perennial AR (PAR) and seasonal AR (SAR). Perennial AR is characterized by AR symptoms throughout the entire year. Common allergens include house dust mites, cat and dog dander, molds, and fungus. Seasonal AR symptomatically responds to environmental pollens (grass, trees, weeds), and nasal symptoms correlate with specific pollen seasons. The nasal microbiome could potentially function in an important role of AR barrier protection and immune regulation of localized responses.

A limited number of studies have attempted to characterize the nasal microbiome of patients suffering from AR. One recent study evaluated the sinonasal microbiome during the changing of pollen seasons. Choi et al[39] examined 20 SAR participants and 19 nonallergic individuals with endoscopically guided swabs from the middle meatus and vestibule before and during the pollen season.[39] The SAR participants had increased bacterial diversity within the pollen season and a positive correlation with increased nasal eosinophils in the middle meatus compared with nonallergic participants.[39] Before the pollen season, study groups showed no significant differences.[39] Likewise, no changes in biodiversity were observed within participants before and during the pollen season.[39] These results are counterintuitive, because increased bacterial diversity is often associated with a healthy microbiome, as suggested by the biodiversity and microflora hypotheses.[21,23] Likewise, Lal et al[40] compared the microbiome of

middle meatus and inferior meatus in healthy AR and CRS participants.[40] This study did not reproduce an increased biodiversity in AR participants.[40] This may be a result of a small sample size and performing their study outside of the pollen season. Ruokolainen et al[41] examined the prevalence of allergic disease along with both skin and nasal microbiota in 180 children, ages 7 to 11, from Finnish and Russian Karelia, which have relatively identical climatic and geographic features.[41] Russian Karelia is mainly a rural environment, whereas Finnish Karelia is more of a modernized area. AR, atopic eczema, atopic sensitization, asthma, and self-reported rhinitis were 3-fold to 10-fold more common in children from Finnish Karelia.[41] Bacterial and fungal populations in the nasal mucosa had a significantly greater diversity among Russian participants compared with Finnish subjects.[41] These data suggest that early-life exposure to environmental microbes may influence the development of allergic diseases. The mechanism of dysbiosis for AR is currently inconclusive.

## Dysfunction of the Nasal Microbiome in Chronic Rhinosinusitis

CRS is defined as an inflammatory disease of the nasal cavity and sinuses, with sinonasal symptoms for 12 weeks or greater.[42] Nasal congestion, rhinorrhea, loss of smell, and pressure in the sinus area are common examples of CRS symptoms. CRS can be further classified into CRS with or without nasal polyps, which may express different immunological characteristics. Both Th1-predominated inflammation and Th2-mediated inflammation are commonly characterized in CRS without nasal polyps and CRS with nasal polyps, respectively.[42] CRS affects approximately 3% to 5% and 12.5% of the population in Canada and United States, respectively.[43,44] CRS may reduce quality of life in patients by decreasing productivity and sleep.[45] Typical therapeutic interventions for CRS include nasal and oral corticosteroids regimens along with consideration toward antibiotics and nasal irrigation.[42] Patients who do not respond to medications may require surgical intervention to clear inflamed tissue and mucus from the sinonasal cavity.

The relationship between CRS and the nasal microbiome has been investigated to understand which microorganism might influence CRS. No consistent patterns of 1 specific microbe has been observed in all CRS patients. However, dysbiosis or decreased biodiversity of bacteria species may play a role in disease severity. One bacterial species that potentially functions in the development of CRS is *S aureus*. *S aureus* is a gram-positive bacterium that potentially can be pathogenic or commensal. Colonization of the nasal cavity and sinus with *S aureus* may be associated with the presence of nasal polyps or disease severity of CRS.[46] However, *S aureus* is not observed in the nasal or sinonasal microbiomes of all individuals suffering from CRS.[47] CRS patients have a wide detection rate of *S aureus,* ranging from 15% to 70%, which may be caused by the variance in the disease severity and nasal polyp phenotype.[47] This variance was evident in a study performed by Zhang et al.,[46] who examined 376 adult CRS participants' levels of *S aureus* and *Pseudomonas aeruginosa* from endoscopically guided sinus swab cultures.[46] Participants colonized with *S aureus* had 1.9 times increased odds of possessing nasal polyps when compared with *P aeruginosa*–colonized participants.[46] In 2014, Choi et al[48] performed a metagenomics analysis on nasal lavage samples from 3 groups: CRS with nasal polyps (n = 5), CRS without nasal polyps (n = 3), and non-CRS controls (n = 3).[48] The CRS participants had decreased bacterial diversity while having a greater abundance of bacteria compared with non-CRS controls.[48] Choi et al also reported *S aureus* to be significantly increased in CRS participants with nasal polyps compared with CRS participants without nasal polyps.[48] Feazel et al[49] also observed an increased amount of *S aureus* and lower microbial diversity in CRS participants and CRS participants with the co-morbidity of asthma.[49] *S aureus* has also been suggested to function in the development of nasal polyps in CRS. Increased abundance of *S aureus* has been observed in CRS participants with nasal polyps compared with CRS participants without nasal polyps.[50] However, a recent study did not observe a difference in bacterial composition of the nares or maxillary when comparing 23 CRS participants with nasal polyps with 19 CRS participants without nasal polyps.[51] The nasal microbiome may be clinically relevant in CRS, and *S aureus* may have a functional role in the development of CRS.

## Probiotic Interventions

Probiotics are defined by the World Health Organization as "live microorganisms which when administered in adequate amounts can confer a health benefit in the host."[52] The use of probiotics in history revolves around the beneficial properties of fermented milk. In the early 1900s, Elie Metchnikoff suggested the positive advantage of bacteria in fermented milk and the potential health benefits to humans.[52] Probiotics can be suggested by physicians as a part of the treatment plan for gastrointestinal diseases such as irritable bowel syndrome, diarrhea, and *Clostridium difficile* infection. In the early 2000s. Kalliomaki et al[53] examined the role of *Lactobacillus rhamnosus* in the prevention of atopic disease.[53] In a double-blind, randomized, placebo-controlled study, a total of 82 placebo- and 77 *L rhamnosus*–receiving mothers, who had at least 1 first-degree relative or partner with atopic disease, were treated for 2 to 4 weeks before the expected delivery date.[53] The infants were also treated for 6 months after birth with the matching treatment.[53] The frequency of atopic eczema at 2 years of age was reduced by half in the probiotic group compared with placebo.[53] One limitation of this study includes environmental exposures, which were not reported. The use of probiotics as a treatment for atopic disease is still very controversial.

## Probiotics in Perennial and Seasonal Allergic Rhinitis

Probiotic treatments may be clinically beneficial for individuals suffering from AR. One common area of probiotic research has been focused on treating house dust mite–induced AR. Ishida et al[54] performed a double-blind, randomized, placebo-controlled study that involved 49 participants with PAR receiving either *Lactobacillus acidophilus* 92 in fermented milk or milk without lactic acid bacteria.[54] They reported that administration of *L acidophilus* 92 significantly improved nasal symptom scores in PAR participants.[54] A separate 12-week double-blind, placebo-controlled study randomized 60 PAR children (ages 6-13) into 2 groups: levocetirizine with placebo and levocetirizine with *Lactobacillus paracasei* (*L paracasei*).[55] Analysis indicated improvement in pediatric rhinoconjunctivitis quality-of-life questionnaires scores and a significant improvement in nasal itching and sneezing scores in the *L paracasei* group compared with placebo.[55] Probiotic combination therapy with standard AR treatments has been examined for dust mite–specific subcutaneous immunotherapy (SCIT).[56] Xu et al[56] examined this therapeutic option by comparing 4 treatment arms: placebo, *Clostridium butyricum*, SCIT, and SCIT with *C butyricum.*[56] After 6 months, the SCIT and SCIT with *C butyricum* groups were treated with placebo (saline) instead of dust mite extract until the end of the study.[56] Nasal symptoms were markedly reduced in the SCIT and SCIT with *C butyricum* arms compared with placebo.[56] Furthermore, combination therapy enhanced the efficacy of SCIT by improving nasal symptom scores, decreasing specific IgE and Th2 cytokines.[56] Probiotics as a complementary treatment for PAR appears to be a promising concept, yet many questions remain unanswered, such as dosage and length of treatment.

The SAR probiotic interventions have shown some promise for relief of clinical symptoms. In a double-blind, randomized, placebo-controlled study during the grass pollen season, 10 participants suffering from grass-induced AR were introduced orally to *Bifidobacterium lactis* over an 8-week period.[57] Compared with placebo, total

nasal symptom scores significantly improved while interleukin (IL)-5, IL-13, and tumour necrosis factor alpha were significantly decreased.[57] Likewise, Dennis-Wall et al[58] reported an improvement in mini–rhinoconjunctivitis quality-of-life questionnaires scores in probiotic-treated (*Lactobacillus gasseri, Bifidobacterium bifidum, Bifidobacterium longum*) individuals compared with placebo over an 8-week period during the spring.[58] Similar to PAR, combination therapy of sublingual immunotherapy (SLIT) and probiotics has been examined for SAR. A 5-month prospective, double-blind, randomized, placebo-controlled trial was conducted in 100 children (ages 5-12 years) to examine the efficacy of 5-grass SLIT 300 IR tablets given with vitamin D, placebo, or *L rhamnosus*, and a control group not receiving SLIT.[59] Jerzynska et al[59] observed a decrease in symptom-medication score in all groups treated with SLIT.[59] They also demonstrated a significant increase of CD4+CD25+Fox3+ cells in the children receiving SLIT with *L rhamnosus* compared with children treated with SLIT and vitamin D.[59] A systemic review of the probiotics in the treatment of AR by Güvenç et al[60] concluded that significant evidence suggests beneficial clinical and immunologic effects of probiotics.[60] The previously described probiotic clinical trials relied on oral dosing, and research into direct nasal probiotics is scarce. Modulating the intestinal microbiome may be more complicated because the probiotic species must survive the high acidity of the gastric acid in the stomach.

## Chronic Rhinosinusitis and Probiotics

Probiotic treatments have been suggested as an intervention option for CRS; however, recent probiotic therapeutics literature has not supported this concept. No significant clinical improvements were observed in sinonasal quality of life scores during a double-blind, randomized, placebo-controlled trial using an oral intervention of *L rhamnosus* in 77 CRS participants.[61] The impact of probiotic administration directly to the site of action for CRS is currently being investigated. In 2016, Mårtensson et al[62] examined the safety profile of delivering honeybee lactic acid bacteria (HLAB) directly into the nasal passage, using a spray.[62] This administration of topical treatment did not produce any symptoms, or change in inflammatory biomarkers of the nasal cavity, and did not alter commensal bacteria.[62] This suggests that nasal administration of HLAB probiotics are safe and well-tolerated, and it may provide an alternative method of delivery to alter the nasal microbiome. However, nasal administration of HLAB in 21 CRS participants with nasal polyps did not reduce nasal symptoms or inflammatory markers.[63] Probiotic treatments for CRS are not currently clinically recommended.

## Conclusion

The microbiome is a complex community of microorganisms that can act in a symbiotic relationship similar to a healthy organ in the body. The nasal microbiome may be influenced by several environmental factors, such as geographical locations, type of delivery, and hygiene. Dysbiosis has been linked to increased risk of diseases such as inflammatory bowel disease, obesity, and allergies.[2-4] The role of the nasal microbiome in SAR, PAR, and CRS requires more evidence to fully understand the mechanisms that may be involved. Furthermore, evidence is clearly lacking examining the difference in the nasal microbiomes of AR patients and healthy controls. Probiotic treatments have shown some promise, yet the mechanism of action is not well understood. Future studies should continue to examine the nasal microbiome to determine whether an individualized treatment would be required to alleviate dysbiosis and nasal symptoms. Larger studies are required to determine the true efficacy behind probiotic treatments and examine nasal probiotics as a possible technique to reduce clinical symptoms for AR, CRS, and other respiratory diseases. Combination therapies have displayed some benefit for treatment of AR but require further support. In addition, a combination of probiotic and immunotherapy may be a more practical approach to help improve the efficacy of the current treatments on the market and potentially allow for enhanced care for allergic diseases.

## References


[1] Turnbaugh PJ, Ley RE, Hamady M, Fraser-Liggett CM, Knight R, Gordon JI. The human microbiome project. *Nature*. 2007;449(7164):804–810.
[2] Cho I, Blaser MJ. The human microbiome: At the interface of health and disease. *Nat Rev Genet*. 2012;13(4):260.
[3] Arrieta M-C, Stiemsma LT, Amenyogbe N, Brown EM, Finlay B. The intestinal microbiome in early life: Health and disease. *Front Immunol*. 2014;5:427.
[4] DeGruttola AK, Low D, Mizoguchi A, Mizoguchi E. Current understanding of dysbiosis in disease in human and animal models. *Inflamm Bowel Dis*. 2016;22(5):1137–1150.
[5] Human Microbiome Project Consortium THMP. Structure, function and diversity of the healthy human microbiome. *Nature*. 2012;486(7402):207–214.
[6] Qin J, Li R, Raes J, et al. A human gut microbial gene catalogue established by metagenomic sequencing. *Nature*. 2010;464(7285):59–65.
[7] Human Genome Sequencing Consortium I. Finishing the euchromatic sequence of the human genome. *Nature*. 2004;431(7011):931–945.
[8] van Baarlen P, Troost F, van der Meer C, et al. Human mucosal *in vivo* transcriptome responses to three lactobacilli indicate how probiotics may modulate human cellular pathways. *Proc Natl Acad Sci U S A*. 2011;108(Suppl 1):4562–4569.
[9] Campeotto F, Suau A, Kapel N, et al. A fermented formula in pre-term infants: Clinical tolerance, gut microbiota, down-regulation of faecal calprotectin and up-regulation of faecal secretory IgA. *Br J Nutr*. 2011;105(12):1843–1851.
[10] Di Giacinto C, Marinaro M, Sanchez M, Strober W, Boirivant M. Probiotics ameliorate recurrent Th1-mediated murine colitis by inducing IL-10 and IL-10-dependent TGF-beta-bearing regulatory cells. *J Immunol*. 2005;174(6):3237–3246.
[11] Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. *Cell*. 2014;157(1):121–141.
[12] Mestecky J. The common mucosal immune system and current strategies for induction of immune responses in external secretions. *J Clin Immunol*. 1987;7(4):265–276.
[13] Kudsk KA. Current aspects of mucosal immunology and its influence by nutrition. *Am J Surg*. 2002;183(4):390–398.
[14] Gerrard JW, Geddes CA, Reggin PL, Gerrard CD, Horne S. Serum IgE levels in white and metis communities in Saskatchewan. *Ann Allergy*. 1976;37(2):91–100.
[15] Strachan DP. Hay fever, hygiene, and household size. *BMJ*. 1989;299(6710):1259–1260.
[16] von Mutius E, Martinez FD, Fritzsch C, Nicolai T, Roell G, Thiemann HH. Prevalence of asthma and atopy in two areas of West and East Germany. *Am J Respir Crit Care Med*. 1994;149(2):358–364.
[17] Riedler J, Braun-Fahrländer 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.
[18] Okada H, Kuhn C, Feillet H, Bach JF. The "hygiene hypothesis" for autoimmune and allergic diseases: An update. *Clin Exp Immunol*. 2010;160(1):1–9.
[19] Ruokolainen L, Fyhrquist N, Haahtela T. The rich and the poor: Environmental biodiversity protecting from allergy. *Curr Opin Allergy Clin Immunol*. 2016;16(5):421–426.
[20] Depner M, Ege MJ, Cox MJ, et al. Bacterial microbiota of the upper respiratory tract and childhood asthma. *J Allergy Clin Immunol*. 2017;139(3):826–834.
[21] Sjögren YM, Jenmalm MC, Böttcher MF, Björkstén B, Sverremark-Ekström E. Altered early infant gut microbiota in children developing allergy up to 5 years of age. *Clin Exp Allergy*. 2009;39(4):518–526.
[22] Noverr MC, Huffnagle GB. The "microflora hypothesis" of allergic diseases. *Clin Exp Allergy*. 2005;35(12):1511–1520.
[23] Foliaki S, Pearce N, Björkstén B, et al. Antibiotic use in infancy and symptoms of asthma, rhinoconjunctivitis, and eczema in children 6 and 7 years old: International Study of Asthma and Allergies in Childhood Phase III. *J Allergy Clin Immunol*. 2009;124(5):982–989.
[24] Yan M, Pamp SJ, Fukuyama J, et al. Nasal microenvironments and interspecific interactions influence nasal microbiota complexity and *S. aureus* carriage. *Cell Host Microbe*. 2013;14(6):631–640.
[25] Bassis CM, Tang AL, Young VB, Pynnonen MA. The nasal cavity microbiota of healthy adults. *Microbiome*. 2014;2:27.
[26] Zhou Y, Mihindukulasuriya KA, Gao H, et al. Exploration of bacterial community classes in major human habitats. *Genome Biol*. 2014;15(5):R66.
[27] Ramakrishnan VR, Feazel LM, Gitomer Ir D SA, Robertson CE, Frank DN. The microbiome of the middle meatus in healthy adults. *PLoS One*. 2013;8(12):e85507.
[28] Biswas K, Hoggard M, Jain R, Taylor MW, Douglas RG. The nasal microbiota in health and disease: Variation within and between subjects. *Front Microbiol*. 2015;9:134.
[29] Jiménez E, Marín ML, Martín R, et al. Is meconium from healthy newborns actually sterile. *Res Microbiol*. 2008;159(3):187–193.
[30] Rautava S, Collado MC, Salminen S, Isolauri E. Probiotics modulate host-microbe interaction in the placenta and fetal gut: A randomized, double-blind, placebo-controlled trial. *Neonatology*. 2012;102(3):178–184.

[31] Man WH, de Steenhuijsen Piters WAA, Bogaert D. The microbiota of the respiratory tract: Gatekeeper to respiratory health. *Nat Rev Microbiol*. 2017;15(5):259–270.
[32] 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. *Proc Natl Acad Sci U S A*. 2010;107(26):11971–11975.
[33] Biesbroek G, Tsivtsivadze E, Sanders EAM, et al. Early respiratory microbiota composition determines bacterial succession patterns and respiratory health in children. *Am J Respir Crit Care Med*. 2014;190(11):1283–1292.
[34] Mika M, Mack I, Korten I, et al. Dynamics of the nasal microbiota in infancy: A prospective cohort study. *J Allergy Clin Immunol*. 2015;135(4):905–912.e11.
[35] Hunt KM, Foster JA, Forney LJ, et al. Characterization of the diversity and temporal stability of bacterial communities in human milk. *PLoS One*. 2011;6(6):e21313.
[36] Grice EA, Segre JA. The skin microbiome. *Nat Rev Microbiol*. 2011;9(4):244–253.
[37] Keith PK, Desrosiers M, Laister T, Schellenberg RR, Waserman S. The burden of allergic rhinitis (AR) in Canada: Perspectives of physicians and patients. *Allergy Asthma Clin Immunol*. 2012;8(1):7.
[38] Benninger MS, Benninger RM. The impact of allergic rhinitis on sexual activity, sleep, and fatigue. *Allergy Asthma Proc*. 2009;30(4):358–365.
[39] Choi CH, Poroyko V, Watanabe S, et al. Seasonal allergic rhinitis affects sinonasal microbiota. *Am J Rhinol Allergy*. 2014;28(4):281–286.
[40] Lal D, Keim P, Delisle J, et al. Mapping and comparing bacterial microbiota in the sinonasal cavity of healthy, allergic rhinitis, and chronic rhinosinusitis subjects. *Int Forum Allergy Rhinol*. 2017;7(6):561–569.
[41] Ruokolainen L, Paalanen L, Karkman A, et al. Significant disparities in allergy prevalence and microbiota between the young people in Finnish and Russian Karelia. *Clin Exp Allergy*. 2017;47(5):665–674.
[42] Akdis CA, Bachert C, Cingi C, et al. Endotypes and phenotypes of chronic rhinosinusitis: A PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology. *J Allergy Clin Immunol*. 2013;131(6):1479–1490.
[43] Chen Y, Dales R, Lin M. The epidemiology of chronic rhinosinusitis in Canadians. *Laryngoscope*. 2003;113(7):1199–1205.
[44] Halawi AM, Smith SS, Chandra RK. Chronic rhinosinusitis: Epidemiology and cost. *Allergy Asthma Proc*. 2013;34(4):328–334.
[45] Alt JA, DeConde AS, Mace JC, Steele TO, Orlandi RR, Smith TL. Quality of life in patients with chronic rhinosinusitis and sleep dysfunction undergoing endoscopic sinus surgery. *JAMA Otolaryngol Neck Surg*. 2015;141(10):1.
[46] Zhang Z, Adappa ND, Doghramji LJ, Chiu AG, Cohen NA, Palmer JN. Different clinical factors associated with *Staphylococcus aureus* and *Pseudomonas aeruginosa* in chronic rhinosinusitis. *Int Forum Allergy Rhinol*. 2015;5(8):724–733.
[47] Lin A, Busaba NY. *Staphylococcus aureus* and endoscopic sinus surgery. *Curr Opin Otolaryngol Head Neck Surg*. 2006;14(1):19–22.
[48] Choi EB, Hong SW, Kim DK, et al. Decreased diversity of nasal microbiota and their secreted extracellular vesicles in patients with chronic rhinosinusitis based on a metagenomic analysis. *Allergy*. 2014;69(4):517–526.
[49] Feazel LM, Robertson CE, Ramakrishnan VR, Frank DN. Microbiome complexity and *Staphylococcus aureus* in chronic rhinosinusitis. *Laryngoscope*. 2012;122(2):467–472.
[50] Ramakrishnan VR, Feazel LM, Abrass LJ, Frank DN. Prevalence and abundance of *Staphylococcus aureus* in the middle meatus of patients with chronic rhinosinusitis, nasal polyps, and asthma. *Int Forum Allergy Rhinol*. 2013;3(4):267–271.
[51] Thunberg U, Söderquist B, Hugosson S. Bacterial findings in optimised sampling and characterisation of *S. aureus* in chronic rhinosinusitis. *Eur Arch Otorhinolaryngol*. 2017;274(1):311–319.
[52] Mackowiak PA. Recycling metchnikoff: Probiotics, the intestinal microbiome and the quest for long life. *Front Public Health*. 2013;1:52.
[53] Kalliomäki M, Salminen S, Arvilommi H, Kero P, Koskinen P, Isolauri E. Probiotics in primary prevention of atopic disease: A randomised placebo-controlled trial. *Lancet*. 2001;357(9262):1076–1079.
[54] Ishida Y, Nakamura F, Kanzato H, et al. Clinical effects of *Lactobacillus acidophilus* strain L-92 on perennial allergic rhinitis: A double-blind, placebo-controlled study. *J Dairy Sci*. 2005;88(2):527–533.
[55] Lin WY, Fu LS, Lin HK, Shen CY, Chen YJ. Evaluation of the effect of *Lactobacillus paracasei* (HF.A00232) in children (6–13 years old) with perennial allergic rhinitis: A 12-week, double-blind, randomized, placebo-controlled study. *Pediatr Neonatol*. 2014;55(3):181–188.
[56] Xu LZ, Yang LT, Qiu SQ, et al. Combination of specific allergen and probiotics induces specific regulatory B cells and enhances specific immunotherapy effect on allergic rhinitis. *Oncotarget*. 2016;7(34):54360–54369.
[57] Singh A, Hacini-Rachinel F, Gosoniu M, et al. Immune-modulatory effect of probiotic *Bifidobacterium lactis* NCC2818 in individuals suffering from seasonal allergic rhinitis to grass pollen: An exploratory, randomized, placebo-controlled clinical trial. *Eur J Clin Nutr*. 2013;67(10):161–167.
[58] Dennis-Wall JC, Culpepper T, Nieves C, et al. Probiotics ( *Lactobacillus gasseri* KS-13, *Bifidobacterium bifidum* G9-1, and *Bifidobacterium longum* MM-2) improve rhinoconjunctivitis-specific quality of life in individuals with seasonal allergies: A double-blind, placebo-controlled, randomized trial. *Am J Clin Nutr*. 2017;105(3):758–767.
[59] Jerzynska J, Stelmach W, Balcerak J, et al. Effect of *Lactobacillus rhamnosus* GG and vitamin D supplementation on the immunologic effectiveness of grass-specific sublingual immunotherapy in children with allergy. *Allergy Asthma Proc*. 2016;37(4):324–334.
[60] Güvenç IA, Muluk NB, Mutlu FŞ, et al. Do probiotics have a role in the treatment of allergic rhinitis? A comprehensive systematic review and meta-analysis. *Am J Rhinol Allergy*. 2016;30(5):157–175.
[61] Mukerji SS, Pynnonen MA, Kim HM, Singer A, Tabor M, Terrell JE. Probiotics as adjunctive treatment for chronic rhinosinusitis: A randomized controlled trial. *Otolaryngol Neck Surg*. 2009;140(2):202–208.
[62] Mårtensson A, Greiff L, Lamei SS, et al. Effects of a honeybee lactic acid bacterial microbiome on human nasal symptoms, commensals, and biomarkers. *Int Forum Allergy Rhinol*. 2016;6(9):956–963.
[63] Mårtensson A, Abolhalaj M, Lindstedt M, et al. Clinical efficacy of a topical lactic acid bacterial microbiome in chronic rhinosinusitis: A randomized controlled trial. *Laryngoscope Investig Otolaryngol*. 2017;2(6):410–416.