

# Probiotic Use in Allergic Rhinitis Management

Subjects: Allergy

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Allergic rhinitis (AR) is a common medical condition affecting up to 40% of the general population. A type 2 immunity determines eosinophilic inflammation that, in turn, elicits typical nasal symptoms. Type 2 immunity is eminently characterized by polarization of innate and adaptative B and T cells, increased production of type 2 cytokines, including interleukin-4 (IL-4), IL-5, and IL-13, and impaired function of allergen-specific T regulatory cells (Tregs). This immunologic derangement promotes allergic inflammation, characterized by an abundant eosinophilic infiltrate and the presence of mast cells. The mast cells are activated by allergen exposure and release pro-inflammatory mediators, including histamine. These mediators interact with specific receptors and, consequently, are responsible for the appearance of typical AR symptoms: nasal itching, sneezing, rhinorrhea, and nasal congestion.

Keywords: oral probiotics ; allergic rhinitis ; dysbiosis ; inflammation ; immunity

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## 1. The Rationale for Probiotic Use in Allergic Rhinitis Management

There is a well-established awareness that the prevalence of allergic diseases has been impressively raised in the last decades. Consequently, several attempts have been made to explain this important phenomenon. In this context, the hygiene hypothesis has garnered much acclaim and has been mainly studied <sup>[1]</sup>. The observation has sustained the so-called allergy epidemics in which poor hygienic conditions protect from allergies while “clean” settings arrange for allergies. Namely, adequate microbiota biodiversity guarantees a correct maturation of the immune system in infants <sup>[2]</sup>. Contrarily, the impaired composition of microbiota facilitates poor immunity maturation and favors allergy <sup>[3]</sup>. Moreover, newborns display a type 2 immunity as this immune disposition protects the fetus from the potential maternal rejection as recognized non-self.

Allergic subjects present dysbiosis and impaired biodiversity in the gut and target organs <sup>[4]</sup>. Dysbiosis harms AR as it promotes allergic inflammation. However, there is evidence that some environmental factors may contribute to eubiosis <sup>[5]</sup>. In particular, exposure to microbial fragments (e.g., farming settings) promotes balanced microbiota preventing allergy <sup>[6]</sup>.

Moreover, a gut-airways axis permits the crosstalk between the digestive tract and respiratory mucosa. In other words, enteric microbiota significantly affects respiratory microbiota and vice versa <sup>[7]</sup>. Subjects with AR present a dysbiosis associated with inflammatory pathways and symptom severity <sup>[8]</sup>. Therefore, the combination of all this evidence suggests the possibility of manipulating the immune system to return a physiological response in AR. In this regard, probiotics have been proposed as an ideal candidate to counteract dysbiosis in allergic rhinitis <sup>[9]</sup>. Probiotics are “live microorganisms which confer a beneficial effect on the host”, as proposed by the World Health Organization <sup>[10]</sup>.

Probiotic supplementation may exert manifold benefits due to its complex mechanism of action <sup>[11]</sup>. Probiotics represent the current strategy to heal dysbiosis revitalize biodiversity, and balance microbiota. However, the mechanisms of action are complicated and still not completely defined. The detailed description of the probiotics mechanisms of action goes beyond the purpose of the present review. Consequently, a summary of the concept will be presented. Many recent reviews are available <sup>[12][13][14][15][16][17][18][19][20][21][22][23][24]</sup>.

Briefly, probiotics act on innate immunity through the toll-like receptor, switching off the antigen-presenting machinery. The activation of innate immunity displays several positive effects, as schematically represented in **Figure 1**. However, some effects on immune results have to be presumed as the present evidence derives from small studies.

**Figure 1.** Schematic representation of the possible probiotic mechanisms of action in allergic rhinitis.

First, probiotics may down-regulate type 2 immunity by reducing allergen-specific IgE and “pro-allergic” cytokine production; contextually, probiotics stimulate allergen-specific IgG and IgA production. Consistently, probiotics may expand type 1 immunity, increasing the production of “protective” cytokines (IFN- $\gamma$ , IL-6, and TNF- $\alpha$ ). As a result, probiotics make allergic subjects less prone to infections and also promote the synthesis of anti-infective agents, such as bacteriocin and secretory IgA. In addition, probiotics may dampen the inflammatory cascade by stimulating the production of anti-inflammatory mediators, including short-chain fatty acids (mainly  $\omega$ 3), that reduce cellular infiltrate. Finally, probiotics may restore the function of allergen-specific Tregs and consequently increase the production of regulatory cytokines (IL-10 and TGF- $\beta$ ).

Therefore, there is evidence that probiotics could confer some beneficial effects to allergic subjects rebalancing their immunity and reinforcing mucosal defense against pathogens. However, more methodologically robust studies are needed to confirm these possible effects of probiotics.

## **2. New Evidence in the Literature**

Four more studies on the use of probiotics in the treatment of AR have been published in the past year, which were not covered by the meta-analyses mentioned above. Therefore, they will be presented here to provide updated knowledge about this issue.

The first study is to investigate the probiotic prophylactic treatment in children with AR <sup>[25]</sup>.

The tested compound was a probiotic mixture including *Bifidobacterium animalis* subsp. *Lactis* BB12 and *Enterococcus faecium* L3. The outcome measures were nasal symptom scores and the need for rescue medication. The study included 250 children and adolescents. Subjects were stratified into two groups: actively treated (150) or control (100). The probiotic mixture was administered three months before the pollen season. Patients treated with probiotics experienced less severe symptoms than controls. Consistently, probiotic-treated children used less symptomatic drugs than controls. Consequently, the investigators concluded that the mixture containing BB12 and L3 exerted significant preventive effects on the AR course.

The second study explored the effects of a commercial probiotic preparation containing four strains: *Lactobacillus acidophilus* LA02, *Lactobacillus delbrueckii* LDB01, *Lactobacillus rhamnosus* LR04, and *Streptococcus thermophilus* FP04 [26].

Twenty-eight AR patients took the probiotic mixture for 60 days; they were evaluated at baseline, after the treatment, and during a two-month follow-up. The probiotic product significantly reduced rhinitis total symptom scores and visual analog scale. Consistently, probiotics reduced the peripheral eosinophils, the levels of type 2 cytokines IL-4 and IL-5, and increased biodiversity in stool microbiota composition. Interestingly, the microbiota changes correlated with clinical and immunological parameters. Consequently, the study concluded that this probiotic preparation could be envisaged as a helpful add-on strategy in AR patients. The outcomes provided by this study were particularly impressive, mainly concerning the cytological and immunological results. It has to be noted that such positive results were not observed by most other studies exploring these aspects. However, it should be emphasized that this study should be considered a preliminary study conducted on a small sample of patients. Therefore, these results, which are undoubtedly attractive, need confirmation by studies conducted with a more robust and appropriate methodology.

Another study evaluated an intranasally administered probiotic assemblage containing *Lactobacillus rhamnosus* SP1, *Lactobacillus paracasei* 101/37, and *Lactococcus lactis* L1A, compared with placebo [27].

Participants were subdivided into two groups: actively treated (12) and placebo-treated (12). Treatment lasted three weeks. Outcome measures were quality of life scores, total nasal symptom score, peak nasal inspiration flow, fractional exhaled nitric oxide, and cytokines assay. Cultures were also performed to detect the colonization of strains. Unfortunately, the only significant result concerned a slight decrease in IL-17. Therefore, the authors concluded that the topical administration of a probiotic mixture was ineffective in AR patients. Probably, the duration and the topical route were inadequate to observe benefits.

Finally, an Australian study investigated the effects of a probiotic drink ("NC-Seasonal-Biotic") containing four strains: *Lactobacillus reuteri* GL 104, *Lactobacillus plantarum* LPL28, *Lactobacillus rhamnosus* MP108, and *Bifidobacterium lactis* BI04, and a fructooligosaccharide as prebiotic, compared with placebo [28]. Forty patients concluded the 10–12-week intervention period. The active group showed a significant improvement in clinical parameters and consistent quality of life scores. In addition, the probiotic drink restored the Th1/Th2 ratio.

These recent studies, therefore, added new proof evidencing that probiotics could help manage patients suffering from AR. However, two main lessons have to be acknowledged. First, the probiotic supplementation duration should be adequate to allow colonization and completion of the immunological mechanism of action. Second, the effectiveness depends on the specificity of single strains.

Moreover, the outcomes reported in AR were substantially consistent with what has been reported in the asthma model [29][30][31].

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## References

1. Strachan, D.P. Hay fever, hygiene, and household size. *BMJ* 1989, 299, 1259–1260.
2. Haahtela, T. A biodiversity hypothesis. *Allergy* 2019, 74, 1445–1456.
3. Convention on Biological Diversity. 1992. Available online: [www.biodiv.org/convention](http://www.biodiv.org/convention) (accessed on 4 July 2022).
4. Hufnagl, K.; Pali-Schoell, I.; Roth-Walter, F.; Jensen-Jarolim, E. Dysbiosis of the gut and lung microbiome has a role in asthma. *Sem. Immunopathol.* 2020, 42, 75–93.
5. Cukrowska, B.; Bierała, J.B.; Zakrzewska, M.; Klukowski, M.; Maciorkowska, E. The Relationship between the Infant Gut Microbiota and Allergy. The Role of *Bifidobacterium breve* and Prebiotic Oligosaccharides in the Activation of Anti-Allergic Mechanisms in Early Life. *Nutrients* 2020, 12, 946.
6. Kang, Y.B.; Cai, Y.; Zhang, H. Gut microbiota and allergy/asthma: From pathogenesis to new therapeutic strategies. *Allergol. Immunopathol. (Madr)* 2017, 45, 305–309.
7. Dang, A.T.; Marsland, B.J. Microbes, metabolites, and the gut-lung axis. *Mucosal Immunol.* 2019, 12, 843–850.
8. Matsubara, A.; Nomura, A.; Yamaguchi, T. The relationship between allergic rhinitis and gut microbiota. *Aerugi.* 2022, 71, 191–194.

9. Lopez-Santamarina, A.; Gonzalez, E.G.; Lamas, A.; Mondragon, A.D.C.; Regal, P.; Miranda, J.M. Probiotics as a Possible Strategy for the Prevention and Treatment of Allergies. A Narrative Review. *Foods* 2021, 10, 701.
10. FAO/WHO. Expert Consultation Health and Nutrition Properties of Probiotics in Food Including Powder Milk with Live Lactic Acid Bacteria. Available online: <http://isappscience.org/wp-content/uploads/2015/12/FAO-WHO-2001-ProbioticsReport.pdf> (accessed on 4 July 2022).
11. Plaza-Diaz, J.; Ruiz-Ojeda, F.J.; Gil-Campos, M.; Gil, A. Mechanisms of action of probiotics. *Adv. Nutr.* 2019, 10, 549–566.
12. Wang, H.T.; Anvari, S.; Anagnostou, K. The role of probiotics in preventing allergic disease. *Children* 2019, 6, 24.
13. Balta, I.; Butucel, E.; Mohilyuk, V.; Criste, A.; Dezmirean, D.N.; Stef, L.; Pet, I.; Corcionivoschi, N. Novel insights into the role of probiotics in respiratory infections, allergies, cancer, and neurological abnormalities. *Disease* 2021, 9, 60.
14. Maldonado Galdeano, C.; Cazorla, S.I.; Lemme Dumit, J.M.; Velez, E.; Perdigon, G. Beneficial effects of probiotic consumption on the immune system. *Ann. Nutr. Metabol.* 2019, 74, 115–124.
15. Al Nabhani, Z.; Eberl, G. Imprinting of the immune system by the microbiota early in life. *Mucosal Immunol.* 2020, 13, 183–189.
16. Huang, J.; Zhang, J.; Wang, X.; Jin, Z.; Zhang, P.; Su, H.; Sun, X. Effect of probiotics on respiratory tract allergic disease and gut microbiota. *Front. Nutr.* 2022, 9, 821900.
17. Cristofori, F.; Dargenio, V.N.; Dargenio, C.; Miniello, V.L.; Barone, M.; Francavilla, R. Anti-inflammatory and immunomodulatory effects of probiotics in gut inflammation: A door to the body. *Front. Immunol.* 2021, 12, 578386.
18. Lin, C.; Lin, Y.; Zhang, H.; Wang, G.; Zhao, J.; Zhang, H.; Chen, W. Intestinal “Infant-Type” Bifidobacteria mediate immune system development in the first 1000 days of life. *Nutrients* 2022, 14, 1498.
19. Das, R.R.; Naik, S.S.; Singh, M. Probiotics as additives on therapy in allergic airway diseases: A systematic review of benefits and risks. *BioMed Res. Int.* 2013, 2013, 231979.
20. Guvenc, I.A.; Bayar Muluk, N.; Mutlu, F.S.; Eski, E.; Altintoprak, N.; Oktemer, T.; Cingi, C. Do probiotics have a role in the treatment of allergic rhinitis? A comprehensive systematic review and meta-analysis. *Am. J. Rhinol. Allergy.* 2016, 30, 157–175.
21. Lin, J.; Zhang, Y.; He, C.; Dai, J. Probiotics supplementation in children with asthma: A systematic review and meta-analysis. *J. Ped. Child Health* 2018, 54, 953–961.
22. Du, X.; Wang, L.; Wu, S.; Yuan, L.; Tang, S.; Xiang, Y.; Qu, X.; Liu, H.; Qin, X.; Liu, C. Efficacy of probiotic supplementary therapy for asthma, allergic rhinitis, and wheeze: A meta-analysis of randomized controlled trials. *Allergy Asthma Proc.* 2019, 40, 250–260.
23. Wei, X.; Jiang, P.; Liu, J.; Sun, R.; Zhu, L. Association between probiotic supplementation and asthma incidence in infants: A meta-analysis of randomized controlled trials. *J. Asthma* 2020, 57, 167–178.
24. Meirlaen, L.; Levy, E.I.; Vandenplas, Y. Prevention and management with pro-, pre- and synbiotics in children with asthma and allergic rhinitis: A narrative review. *Nutrients* 2021, 13, 934.
25. Anania, C.; Di Marino, V.P.; Olivero, F.; De Canditiis, D.; Brindisi, G.; Iannilli, F.; De Castro, G.; Zicari, A.M.; Duse, M. Treatment with a Probiotic Mixture Containing Bifidobacterium animalis Subsp. Lactis BB12 and Enterococcus faecium L3 for the Prevention of Allergic Rhinitis Symptoms in Children: A Randomized Controlled Trial. *Nutrients* 2021, 13, 1315.
26. Torre, E.; Sola, D.; Caramaschi, A.; Mignone, F.; Bona, E.; Fallarini, S. A Pilot Study on Clinical Scores, Immune Cell Modulation, and Microbiota Composition in Allergic Patients with Rhinitis and Asthma Treated with a Probiotic Preparation. *Int. Arch. Allergy Immunol.* 2022, 183, 186–200.
27. Mårtensson, A.; Nordström, F.U.; Cervin-Hoberg, C.; Lindstedt, M.; Sakellariou, C.; Cervin, A.; Greiff, L. Nasal administration of a probiotic assemblage in allergic rhinitis: A randomised placebo-controlled crossover trial. *Clin. Exp. Allergy.* 2022, 52, 774–783.
28. Ried, K.; Travica, N.; Paye, Y.; Sali, A. Effects of a Probiotic Formulation on Seasonal Allergic Rhinitis in Adults-A Randomized Double-Blind Placebo-Controlled Trial: The Probiotics for Hay Fever Trial. *Front. Nutr.* 2022, 9, 887978.
29. Jakubczyk, D.; Górka, S. Impact of Probiotic Bacteria on Respiratory Allergy Disorders. *Front. Microbiol.* 2021, 12, 688137.
30. Ciprandi, G.; Schiavetti, I.; Cioffi, L.; Pane, M.; Drago, L. The Probiotics in Pediatric Asthma Management (PROPAM) study: A Post Hoc analysis in allergic children. *Ann. Allergy Asthma Immunol.* 2022, in press.
31. Ciprandi, G.; Tosca, M.A. Probiotics in children with asthma. *Children* 2022, 9, 978.

