Introduction

Allergic rhinitis is an allergic inflammation of the nasal airways with a rapidly increased prevalence in the past decades.[1] Data show that up to 30% of the general population in the developed countries suffers from one or more atopic disease such as allergic rhinitis, asthma, and atopic dermatitis. Almost 3% of all the general practitioner consultations are for allergic rhinitis in the United Kingdom.[2] While there are still no acceptable treatments for allergic rhinitis, the only remedy is to avoid contacting with the allergen or medications for controlling symptoms.[3] The beneficial effect of probiotics has been demonstrated in the treatment of allergic diseases. One of the most important aspects of the beneficial effect to the host organism is that the probiotics can interact with the host immune system and may modify the natural course of the allergic disease,[4] while how probiotics may influence the immune system remains unclear. Studies indicated that probiotics are a profitable therapeutic treatment of allergic rhinitis.[5] This review highlights the most recent findings regarding the role of probiotics in the treatment of allergic rhinitis. Probiotics are a useful therapeutic remedy in the treatment of allergic rhinitis, but its underlying mechanisms remain to be further investigated.

The types of probiotics using in the treatment of allergic rhinitis

Only a single probiotic strain was intensively involved in the studies of the treatment of most of allergic rhinitis, such as *Lactobacillus acidophilus,[6]* *Lactobacillus paracasei,[6-9]* *Lactobacillus casei,[10-12]* *Lactobacillus rhamnosus,[13,14]* *Bifidobacterium longum,[15-18]* *Lactobacillus johnsonii EM1,[19]* *Lactobacillus gasseri,[20,21]* *Bacillus clausii,[22]* *Escherichia coli Nissle* (EcN) 1917.[23] However, recent studies have been starting to evaluate the treatment effect by using more than one strain of probiotics. For example, *Lactobacillus GG* (LGG) and *L. gasseri* were used in the treatment of allergic rhinitis,[24] and the combined treatment effect of *L. acidophilus* and *Bifidobacterium lactis* were also determined.[25] A probiotic mixture VSL#3 (VSL Pharmaceuticals, Fort Lauderdale, FL), which contains eight different probiotic strains (4 *lactobacilli,*
3 *bifidobacteria*, and 1 *Streptococcus thermophilus*) were used in their study.\(^{[26]}\) Review of literatures revealed that *Lactobacillus* and *Bifidobacterium* were the most popular probiotics studied by researchers. Meijerink *et al.* suggested that the 28 strains of *Lactobacillus* and *Bifidobacterium* are the best choice for research purposes, as they have been isolated from different commercially available products, and being screened for their immunomodulatory properties in a coculture assay with human peripheral blood mononuclear cells.\(^{[27]}\)

**Safety of probiotics in the treatment of allergic rhinitis**

Probiotics means ‘for life’ and is defined by the World Health Organization (WHO) and the Food and Agriculture Organization (FAO) of the United Nations as ‘live microorganisms which, when administered in adequate amounts as part of food, confers a beneficial health effect by producing gut microflora on the host’.\(^{[29]}\) Although, there are no adverse reactions reported in the treatment of allergic rhinitis; however, concerns regarding the safety of probiotics were raised by the outcomes of several clinical trials. For example, a mixture of six probiotic bacteria (*L. acidophilus, L. casei, L. salivarius, L. lactis, B. bifidum*, and *B. infantis*) suppressed the growth of most pathogens that caused pancreatitis complications in the preclinical animal studies,\(^{[29]}\) while this bacterial mixture that was used in the treatment of patients with severe acute pancreatitis could increase the patient’s mortality rate.\(^{[30]}\) In addition, others reported that bacteremia and fungemia would be developed in ill patients and immunodeficient individuals after using probiotic bacteria.\(^{[31]}\) Probiotics might also cause sepsis in immunocompromised populations. Septicaemia in two children with short bowel syndrome was reported who have received LGG supplementation.\(^{[32]}\) Premature infants, children with abnormal immune function, immunocompromised hosts, and autoimmune disorders should avoid using these products.\(^{[33]}\) Other studies reported that *L. reuteri* and *L. plantarum* have been found to carry antibiotic resistance genes, so there is another possible risk of probiotics that it may transfer such genes to the host.\(^{[34]}\) There are also some other side effects of probiotics reported, such as, an increased rate of recurrent wheezing episodes,\(^{[35]}\) an augmented rate of atopic disorders,\(^{[36]}\) increased sensitization to allergens,\(^{[37]}\) adverse gastrointestinal symptoms, diarrhoea, due to heat-inactivated LGG supplementation. Thus, future clinical trials using probiotics should be accompanied by safety monitoring.

**Route of administration in the treatment of allergic rhinitis**

Oral administration of the probiotics is the routine way of treating diseases, for there are several generally accepted characteristics of probiotics: (1) they are microbial organisms; (2) they can survive under gastric, biliary, and pancreatic digestion; and (3) probiotics are able to induce a host response once they enter the intestinal microbial ecosystem and yield a functional or clinical benefit to the host.\(^{[28]}\) A recent study showed that intraperitoneal delivery of *EcN* together with Ovalbumin (OVA)/Alum strongly inhibited the generation of OVA-induced Th2 responses. But applying *EcN* intranasal or orally did not reduce the allergic response.\(^{[35]}\) Other studies reported that the intranasal route with VSL#3 had the capability to prevent the development of an allergic response in inhalant allergy model and oral therapy treatment with VSL#3 was able to significantly reduce both systemic and local anaphylactic symptoms in food allergy model.\(^{[32]}\)

**Mechanism of probiotics in the treatment of allergic rhinitis**

The mechanism of action of probiotics is multi-faceted, and every probiotic may have its own pathways in affecting the host.\(^{[38]}\) Recent data indicated that probiotics could modulate the production of cytokines by monocytes and lymphocytes. In a study that 31 adult volunteers with allergic rhinitis orally received *Lactobacillus* paracasei ST11 for 8 weeks. The results showed that *Lactobacillus* downregulated systemic immune markers interleukin (IL)-5, IL-8, and IL-10 from the peripheral blood mononuclear cells.\(^{[39]}\) Decreased eosinophils and diminished interferon-gamma (IFN-γ) in peripheral blood was reported after the ingestion of *B. longum*, thus also reducing the need for medication in Japanese cedar pollinosis. They suggest that *B. longum* probably works by playing a regulatory effect on Th2 balance in allergic rhinitis.\(^{[38]}\) In a recent study, it was reported that LGG and *L. gasseri* were able to at least partly down-regulate the human Th2 immune response.\(^{[38]}\) With regard to asthmatic children with allergic rhinitis, the use of probiotics resulted in a significant reduction of the TNF-a, IFN-g, IL-12, and IL-13 produced by the peripheral blood mononuclear cells. Therefore, this may suggest that probiotic supplementation has a clinical benefit for children suffering from allergic airway diseases such as asthma and allergic rhinitis.\(^{[38]}\) Another study demonstrates for the first time the ability of *Lactobacillus casei* Shirota to down-regulate both T-helper (Th)-1 and Th2-type cytokines and to beneficially alter the balance of pollen-specific IgG and IgE levels in seasonal allergic rhinitis. These data show that probiotic supplementation modulates immune responses in allergic rhinitis and may have a potential to alleviate the severity of symptoms.\(^{[38]}\) Many studies have shown that allergic rhinitis is characterized by Th2 polarization with an elevated level of Th2-derived cytokines, including IL-4, IL-5, and IL-13.\(^{[38]}\)
It should also be noted that the efficacy might be probiotic specific. Although, probiotics can exert beneficial effects on the host through distinct cellular and molecular pathways, these mechanisms of action may vary from one kind of probiotic to another for the same immune response and may be regulated by a combination of several events. Thus making probiotics’ mechanism of action a challenging, complex, and fertile area for investigation.

**Therapeutic results of allergic rhinitis with probiotics**

Recently, data from several published randomized double-blind, placebo-controlled trials showed that probiotics had a treatment effect on allergic rhinitis.[6-9,13,14,24] Furthermore, other studies figured out that the ingestion of probiotics resulted in a reduction of symptoms in children and adults with allergic rhinitis by reducing the allergic response to house dust mite.[5] Published studies also demonstrated that L. casei reduced the number of rhinitis episodes in 64 preschool children with allergic rhinitis.[10] Nevertheless, these results have been questioned recently by another trial that showed patients treated with LGG during the birch-pollen season that were allergic to birch pollen and apple food had neither reduction of symptom score, nor of sensitization to birch pollen and apple after probiotics supplementation.[14] These indicate that probiotics may be beneficial in the prevention and treatment of allergic rhinitis, but the therapeutic effect remains to be further investigated.

**Novel approaches to improve effectiveness of probiotics in the treatment of allergic rhinitis**

Hitherto, few studies have provided strong evidence showing that probiotics have an exact treatment effect on allergic disease. Many novel approaches to improve the treatment effect of probiotics on allergic rhinitis were done. Some studies focus on finding the exact effective strains, others are trying to use mixed strains to improve efficacy.[6-9] Route of administration was also changed in the treatment of allergic rhinitis in some studies.[23] Recently, LGG, IL-2, and green fluorescent protein (GFP) as a fusion protein (LGG-IL-2-GFP) were used to examine the bacterial uptake and the immune response induced by oral immunization, the result shows that LGG expressing an antigen could produce an effective immune response to the antigen and IL-2 can improve the response by increasing LGG expressing antigen survival in immune cells.[39]

**Conclusion**

Probiotics may have an important role in the prevention and treatment of allergic rhinitis. The clinical benefit of probiotic therapy depends on numerous factors, such as type of bacterium, route of administration, dosing, regimen, and other underlying host factors. Furthermore, selection of the most beneficial probiotic strain and the timing of supplementation still need to be determined. A fusion protein of probiotics may be a novel approach to improve effectiveness in the treatment of allergic rhinitis. Further studies should also clarify the clinical efficacy of probiotics, protocol of selecting, designing of appropriate study populations, and safety of using probiotics. Mechanisms of action of probiotics modulating immune response are also needed to be further elucidated.

**Acknowledgement**

This study was supported by grants from the Canadian Institutes of Health Research (CIHR # 191063, #220058) and Natural Science and Engineering Research Council of Canada (371268). P-CY holds a New Investigator Award from CIHR (#177843).

**References**

1. Asher MI, Montefort S, Bjorksten B, Lai CK, Strachan DP, Weiland SK, et al; ISAAC Phase Three Study Group. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet 2006;368:733-43.

2. Nurmatov U, van Schayck CP, Hurwitz B, Sheikh A. House dust mite avoidance measures for perennial allergic rhinitis: An updated Cochrane systematic review. Allergy 2012;67:158-65.

3. Bousquet J, Lockey R, Malling HJ. Allergen immunotherapy: Therapeutic vaccines for allergic diseases. A WHO position paper. J Allergy Clin Immunol 1998;102:558-62.

4. Yan F, Polk DB. Probiotics and immune health. Curr Opin Gastroenterol 2011;27:496-501.

5. Ishida Y, Nakamura F, Kanzato H, Sawada D, Hirata H, Nishimura A, et al. Clinical effects of Lactobacillus acidophilus strain L-92 on perennial allergic rhinitis: A double-blind, placebo-controlled study. J Dairy Sci 2005;88:527-33.

6. Yonekura S, Okamoto Y, Okawa T, Hisamitsu M, Chazono H, Kobayashi K, et al. Effects of daily intake of Lactobacillus paracasei strain KW3110 on Japanese cedar pollinosis. Allergy Asthma Proc 2009;30:397-405.

7. Wang MF, Lin HC, Wang YY, Hsu CH. Treatment of perennial allergic rhinitis with lactic acid bacteria. Pediatr Allergy Immunol 2004;15:152-8.

8. Peng GC, Hsu CH. The efficacy and safety of heat-killed Lactobacillus paracasei for treatment of perennial allergic rhinitis induced by house-dust mite. Pediatr Allergy Immunol 2005;16:433-8.

9. Wassenberg J, Nutten S, Audran R, Barbier N, Aubert V, Moulin J, et al. Effect of Lactobacillus paracasei ST11 on a nasal provocation test with grass pollen in allergic rhinitis. Clin Exp Allergy 2011;41:565-73.

10. Giovannini M, Agostoni C, Riva E, Salvini F, Ruscitto A, Zuccotti GV, et al; Felicita Study Group. A randomized prospective double blind controlled trial on effects of long-term consumption of fermented milk containing Lactobacillus casei in pre-school children with allergic asthma and/or rhinitis. Pediatr Res 2007;62:215-20.
11. Tamura M, Shikina T, Morihana T, Hayama M, Kajimoto O, Sakamoto A, et al. Effects of probiotics on allergic rhinitis induced by Japanese cedar pollen: Randomized double-blind, placebo-controlled clinical trial. Int Arch Allergy Immunol 2007;143:75-82.
12. Ivory K, Chambers SJ, Pin C, Prieto E, Arques JL, Nicoletti C. Oral delivery of Lactobacillus casei Shirota modifies allergen-induced immune responses in allergic rhinitis. Clin Exp Allergy 2008;38:1289-95.
13. Koyama T, Kirjavainen PV, Fisher C, Anukam K, Summers K, Hekmat S, et al. Development and pilot evaluation of a novel probiotic mixture for the management of seasonal allergic rhinitis. Can J Microbiol 2010;56:790-8.
14. Helin T, Haathela S, Haathela T. No effect of oral treatment with an intestinal bacterial strain, Lactobacillus rhamnosus (ATCC 53103), on birch-pollen allergy: A placebo-controlled double-blind study. Allergy 2002;57:243-6.
15. Xiao JZ, Kondo S, Yanagisawa N, Takahashi N, Odamaki T, Iwabuchi N, et al. Probiotics in the treatment of Japanese cedar pollinosis: A double-blind placebo-controlled trial. Clin Exp Allergy 2006;36:1425-35.
16. Xiao JZ, Kondo S, Yanagisawa N, Takahashi N, Odamaki T, Iwabuchi N, et al. Effect of probiotic Bifidobacterium longum BB536 [corrected] in relieving clinical symptoms and modulating plasma cytokine levels of Japanese cedar pollinosis during the pollen season. A randomized double-blind, placebo-controlled trial. J Investig Allergol Clin Immunol 2006;16:86-93.
17. Xiao JZ, Kondo S, Takahashi N, Odamaki T, Iwabuchi N, Miyaji K, et al. Changes in plasma TARC levels during Japanese cedar pollen season and relationships with symptom development. Int Arch Allergy Immunol 2007;144:123-7.
18. Xiao JZ, Kondo S, Yanagisawa N, Miyaji K, Enomoto K, Sakoda T, et al. Clinical efficacy of probiotic Bifidobacterium longum for the treatment of symptoms of Japanese cedar pollen allergy in subjects evaluated in an environmental exposure unit. Allergol Int 2007;56:67-75.
19. Lue KH, Sun HL, Lu KH, Ku MS, Sheu JN, Chan CH, et al. A trial of adding Lactobacillus johnsonii EM1 to levocetirizine for treatment of perennial allergic rhinitis in children aged 7-12 years. Int J Pediatr Infectionalgyrology 2012;7699-1001.
20. Morita H, He F, Kawase M, Kubota A, Hiramatsu M, Kurisaki J, et al. Preliminary human study for possible alteration of allergen-induced immune responses in allergic rhinitis with fermented milk prepared with two probiotic strains of Lactobacillus gasseri TMC0356. Microbiol Immunol 2006;50:701-6.
21. Chen YS, Jan RL, Lin YL, Chen HH, Wang JY. Randomized placebo-controlled trial of Lactobacillus for the treatment of allergic rhinitis. Pediatri Pulmonol 2010;45:1111-20.
22. Ciprandi G, Vizzaccaro A, Cirillo L, Tosca MA. Baccillus clausii effects in children with allergic rhinitis. Allergy 2005;60:702-3.
23. Bickert T, Trujillo-Vargas CM, Duechs M, Wehlebben G, Polte T, Hansen G, et al. Probiotic Escherichia coli Nissle 1917 suppresses allergen-induced Th2 responses in the airways. Int Arch Allergy Immunol 2009;149:219-30.
24. Kawase M, He F, Kubota A, Hiramatsu M, Saito H, Ishii T, et al. Effect of fermented milk prepared with two probiotic strains on Japanese cedar pollinosis in a double-blind placebo-controlled clinical study. Int J Food Microbiol 2009;128:429-34.
25. Ouwehand AC, Nermes M, Collado MC, Rautonen N, Salminen S, Isolauri E. Specific probiotics alleviate allergic rhinitis during the birch pollen season. World J Gastroenterol 2009;15:3261-8.
26. Di FG, Barletta B, Butteroni C, Corinti S, Tinghino R, Colombo P, et al. Use of probiotic bacteria for prevention and therapy of allergic diseases: Studies in mouse model of allergic sensitization. J Clin Gastroenterol 2008;42 Suppl 3:S130-2.
27. Meijerink M, Wells JM, Taverne N, de Zeeuw Brouwer ML, Hilhorst B, Venema K, et al. Immunomodulatory effects of potential probiotics in a mouse peanut sensitization model. FEMS Immunol Med Microbiol 2012;65:488-96.
28. Ozdemir O. Various effects of different probiotic strains in allergic disorders: An update from laboratory and clinical data. Clin Exp Immunol 2010;160:295-304.
29. Ridwan BU, Koning CJ, Besseling MG, Timmerman HM, Brouwer EC, Verhoef J, et al. Antimicrobial activity of a multispecies probiotic (Ecologic 641) against pathogens isolated from infected pancreatic neccessosis. Lett Appl Microbiol 2008;46:61-7.
30. Besseling MG, van Santvoort HC, Buskens E, Boermeester MA, van Goor H, Timmerman HM, et al. Acute Pancreatitis. Verkogoe Nederland. Probiotic prophylaxis in patients with predicted severe acute pancreatitis: A randomised, double-blind, placebo-controlled trial. Ned Tijdschr Geneeskd 2008;152:685-96.
31. Snyderman DR. The safety of probiotics. Clin Infect Dis 2008;46 Suppl 2:S104-11.
32. Kunz AN, Noel JM, Fairchok MP. Two cases of Lactobacillus bacteremia during probiotic treatment of short gut syndrome. J Pediatr Gastroenterol Nutr 2004;38:457-8.
33. Salminen S, von WA, Morelli L, Marteau P, Brassert D, de Vos WM, et al. Demonstration of safety of probiotics — a review. Int J Food Microbiol 1998;44:93-106.
34. Egermann M, Roos S, Lindmark H. Identification and characterization of antibiotic resistance genes in Lactobacillus reuteri and Lactobacillus plantarum. J Appl Microbiol 2009;107:1658-68.
35. Kopp MV, Hennemuth I, Heinzzmann A, Urbanek R. Randomized, double-blind, placebo-controlled trial of probiotics for primary prevention: No clinical effects of Lactobacillus GG supplementation. Pediatrics 2008;121:e850-6.
36. Kalliomaki M, Kirjavainen P, Eerola E, Kero P, Salminen S, Isolauri E. Distinct patterns of neonatal gut microflora in infants in whom atopy was and was not developing. J Allergy Clin Immunol 2001;107:129-34.
37. Taylor AL, Dunstan JA, Prescott SL. Probiotic supplementation for the first 6 months of life fails to reduce the risk of atopic dermatitis and increases the risk of allergen sensitization in high-risk children: A randomized controlled trial. J Allergy Clin Immunol 2007;119:184-91.
38. Walker WA. Mechanisms of action of probiotics. Clin Infect Dis 2008;46 Suppl 2:S87-91.
39. Kandasamy M, Selvakumari JA, Mooshchala S, Huat BB, Kun LY, Mahendran R. Lactobacillus rhamnosus GG secreting an antigen and Interleukin-2 translocates across the gastrointestinal tract and induces an antigen specific immune response. Microbiol Immunol 2011;55:704-14.

How to cite this article: Yang G, Liu Z, Yang P. Treatment of Allergic Rhinitis with Probiotics: An Alternative Approach. North Am J Med Sci 2013;6:465-8.

Source of Support: This study was supported by grants from the Canadian Institutes of Health Research (CIHR # 191063, #220058) and Natural Science and Engineering Research Council of Canada (#3671286). P-CY holds a New Investigator Award from CIHR (#177643). Conflict of Interest: None declared.