Probiotics in the prevention and management of human diseases
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10.1 Introduction

Asthma is one of the most common chronic noncommunicable diseases, with around 339 million people affected worldwide (GBD 2016 Disease and Injury and Incidence and Prevalence Collaborators, 2016). The global prevalence of allergic diseases, such as allergic rhinitis, asthma, and atopic dermatitis, is significant and has been increasing over the past few decades (Asher et al., 2006). Allergic rhinitis occurs in 10%—30% of adults and up to 40% in children and its prevalence is increasing (Meltzer, 2016). The global prevalence of doctor-diagnosed asthma in adults is 4.3% [95% confidence interval (CI) 4.2%—4.4%], with a wide variation between countries: the highest prevalence is found in developed countries, such as Australia (21%), and the lowest in developing countries, such as Ethiopia (2%) (To et al., 2012). In children, asthma is more common in boys than in girls due to their smaller airways relative to their lung size, with a switch during puberty, as the prevalence in women is 20% higher than in men (Leynaert et al., 2012). Asthma prevalence is stable or even shrinking in many developed countries, but as lifestyles become more westernized in developing countries there is a fast increase in the prevalence in these parts of the world (Papi et al., 2018). The interaction between the genomic background, changing environmental conditions, such as more pollution (Kuang et al., 2021), increasing obesity, the “hygiene hypothesis”, and less breastfeeding (Enilari & Sinha, 2019), are likely to play a major role. Parental reduction of smoking has proven to reduce asthma (Molero et al., 2018). Important to mention is that in less developed countries the detection rate of allergic disease is likely to be lower, what may result in an underestimation of its prevalence (Arokiasamy et al., 2017). By identifying and characterizing more of these conditions and the involved lifestyle factors, epidemiological studies try to deduce potential strategies for prevention of allergic diseases (von Mutius & Matsui, 2020). Asthma causes impaired quality of life, substantial disability, and avoidable deaths in children and young adults, combined with important health care costs (Papi et al., 2018).

10.1.1 Rationale for using probiotics in atopic diseases

Epidemiological studies have shown that Western living conditions are associated with the rise in allergic diseases. This includes a reduced consumption of fermented food, use of antibiotics and other drugs, and increased hygiene (Kalliomäki et al., 2010). In those who spend their childhood on a farm, allergic diseases are less common (Braun-Fahrländer et al., 1999). The comparison between the composition of microbiota of farm children and the microbiota of children with other lifestyles shows a significant difference (Dicksved et al., 2007). The so-called hygiene hypothesis suggests that a lack of exposure to microbial stimuli early in childhood is a major factor involved in the steep increase in allergy (Kalliomäki et al., 2010). Another important difference in composition of the microbiota was observed between healthy and allergic infants in countries with the high or low prevalence of allergies, pointing to the importance of the gut microbiota in the development of allergic diseases (Kalliomäki et al., 2010).
In the first week of life, the composition of the intestinal microbiota changes rapidly. In contrary to what long time has been believed, an amniotic microbiome has been reported, and as a consequence, the fetal intestine may not be sterile since there is presence of microbial deoxyribonucleic acid in meconium (Valdes et al., 2018). The first altering factor of the neonatal microbiome is the contact with vaginal, fecal, and skin bacteria of the mother. Therefore in cesarean section-born babies, a less diversified microbiome developed. The second altering factor is feeding. Human milk is rich in human milk oligosaccharides, which have prebiotic properties (a substrate that is selectively utilized by host microorganisms conferring a health benefit; Swanson et al., 2020) and promote the growth of selected species of bacteria. Human milk is also a natural bacterial inoculum. The third altering factor are environmental influenced alterations, which may undo the first two beneficial gut alterations: environments, such as neonatal intensive care units, and medication, such as antibiotics or proton pump inhibitors administered perinatal or during early life (Buccigrossi et al., 2013; Goulet, 2015).

Dysbiosis of the young intestinal microbiome can contribute to immune disorders later in childhood because commensal gut bacteria stimulate the development of a balanced immune system, through the gut—lung axis (Elazab et al., 2013). While the microbiota hypothesis may not conclusively explain all observations and does not provide specific guidelines for reducing the allergy epidemic, it does provide a rationale for using probiotics (live microorganisms that, when administered in adequate amounts, confer a health benefit on the host) (Swanson et al., 2020) to modify the gut microbiota to shape the host’s immune response (Kalliomäki et al., 2010). Since a child’s microbiota is not believed to reflect adult patterns until they are 2 years old, the infant microbiota may be more susceptible to manipulation (Sepp et al., 1993).

More knowledge is needed on the mechanisms behind dysbiosis, translocation of microbiota from the gut—lung axis through various mechanisms and for a better evaluation of the therapeutic possibilities to correct this dysbiosis, which in turn can be used to manage various respiratory diseases (Trivedi & Barve, 2020).

The aim of this article is to answer the question if probiotics supplementation can alter the microbiome sufficient to have an efficacious prevention and/or treatment of allergic rhinitis and asthma.

10.2 Prevention of asthma

The increased social and economic burden of asthma makes asthma prevention an important public health goal (Wei et al., 2020).

10.2.1 Animal studies for prevention of asthma through probiotics

The administration of oral probiotic Lactococcus lactis NZ9000 resulted to be beneficial to rats. This probiotic showed to have a preventive effect or relief of inflammatory processes by a decrease of infiltration of pro-inflammatory leukocytes, mainly eosinophils and a decreased lung interleukin (IL)-4 and IL-5 expression in the bronchoalveolar lavage and a reduced level of serum allergen-specific immunoglobulin E (IgE) (Cervantes-García et al., 2020). The probiotic Lactobacillus rhamnosus GR-1 used in another study with mice showed significantly prevented airway hyperreactivity development and prevented microbiome disturbance in the asthmatic animals, supporting the existence of the gut—lung axis (Spacova et al., 2020). An interesting aspect is that most probiotics are given orally; however, a new approached was tested by giving probiotics (Lactobacillus paracasei NCC2461 (Pellaton et al., 2012) and Lactobacillus rhamnosus GG (LGG) (Spacova et al., 2019) in mice through the nasal and showed benefits in reducing inflammation of the lungs (Jamalkandi et al., 2020). One study administered a probiotic Bifidobacterium breve M-16V to pregnant mice and was effective in lowering eosinophils in the bronchoalveolar lavage fluid of neonatal mice and reduced allergic lung inflammation in mice exposed to air pollution (Terada-Ikeda et al., 2020). In another animal study, the intranasal administration of LGG, but not Lactobacillus rhamnosus GR-1, suppressed airway hyperreactivity and reduced the counts of eosinophils, IL-13 and IL-5 in bronchoalveolar fluid (Spacova et al., 2019). In addition to inhibiting inflammatory cell infiltration in lung tissue, LGG was shown to decrease MMP9 expression, a class of enzymes that are involved in the degradation of the extracellular matrix and of which levels were significantly increased in asthma (Mennini et al., 2017). LGG and Bifidobacterium lactis were shown to increase natural regulatory T cells in the lungs of asthmatic mice in another animal study (Feleszko et al., 2007). Furthermore, four Lactobacillus species had markedly different immunomodulatory effects in animal studies (Jeongmin et al., 2013). Lactobacillus salivarius and Lactobacillus fermentum were effective, but there was no effect of Lactobacillus plantarum against allergy demonstrated (Huang et al., 2017). Probiotic strain-specific induction of Foxp3 T regulatory cells was found in mouse allergy models (Lyons et al., 2010).
10.2.2 Human studies for prevention of asthma through probiotics

Preventive agents for respiratory allergies in children compared to animal studies were reported to be low (Wang et al., 2020). A meta-analysis of 2013 showed that the administration of probiotics (Lactobacillus spp. and/or Bifidobacterium spp.) early in life is effective in reducing IgE levels and the risk of atopic sensitization in young children but not the risk of asthma or wheeze (Elazab et al., 2013). There was no difference based on the timing of administration (prenatal to mothers plus postnatal vs. only postnatal) with regard to IgE, but the decrease in the risk of atopy was significant only when probiotics were started during pregnancy and continued after birth (Elazab et al., 2013).

Like in the animal studies, prenatal start of the probiotics might be crucial to colonize mothers so that they transfer them to their offspring during vaginal delivery. Administration of pro- and prebiotics during pregnancy can affect the maternal gut microbiome, potentially resulting in the transmission of tolerogenic mediators, such as regulatory cytokines, antibodies, and growth factors across the placenta, stimulating the development of the fetal immune system (West et al., 2017). This could help to prevent asthma or allergic rhinitis. The findings in pregnant mice are of interest to human since up to now knowledge was restricted to the fact that Bifidobacterium breve M-16V in infants can suppress T helper type 2 immune responses and modulating the systemic type 1 T helper/type 2 T helper balance (Terada-Ikeda et al., 2020). It is well known, that exposure to air pollution during pregnancy increases asthma susceptibility in the offspring. So Bifidobacterium breve M-16V might contribute in reducing asthma in a population living in highly polluted areas (Terada-Ikeda et al., 2020). In 2014, after a long-term follow-up of a randomized placebo-controlled trial (RCT), the Panda study could not demonstrate a beneficial effect on the development of allergic diseases at the age of 6 years from prenatal and 1-year long postnatal use of a probiotic mixture (two Bifidobacterium spp. and Lactococcus lactis) (Gorissen et al., 2014). Unfortunately, after a follow-up of 11 years, the same negative outcome of no association [relative risk (RR) 0.59, 95% CI 0.36–0.96, P = .059], was found (Wickens et al., 2018). This study was a two-center RCT using Lactobacillus rhamnosus HN001 or Bifidobacterium lactis HN019 taken daily from 35-week gestation to 6 months postpartum in mothers while breastfeeding and from birth to age 2 years in infants (Wickens et al., 2018). A more recent meta-analysis including 19 RCT (n = 5157 children) also showed that probiotic supplementation during pregnancy or early life was not significantly associated with a lower incidence of asthma or wheeze in infants (Wei et al., 2020).

Subgroup analysis by asthma risk showed that probiotics significantly reduced wheeze incidence among infants with atopic disease (RR 0.61, 95% CI 0.42–0.90) (Wei et al., 2020). In view of the small sample size in this subgroup analysis, the result should be interpreted with caution. Future powerful trials are needed to confirm if infants with atopic disease could be most likely to benefit from probiotics (Lactobacillus spp. and/or Bifidobacterium spp., Propionibacterium freudenreichii spp. shermanii JS) (Wei et al., 2020).

However, further research is needed to optimize the selection of probiotic species and the configuration of intervention regimens (Wei et al., 2020) because beneficial effects of specific strains might get lost by pooling probiotic strains together since the effects are strain specific. Therefore meta-analysis should be strain specific. Due to the wide heterogeneity of strains, combinations, and doses administered, the efficacy of specific probiotic strains has been difficult to evaluate.

10.3 Probiotics for the treatment of asthma

Unfortunately therapeutic effects of probiotics in asthmatic patients are not well established (Sharma & Im, 2018). A recent study in baby mice showed that Bifidobacterium infantis was able to reduce the infiltration of inflammatory cells by promoting Type 1 T helper and inhibiting Type 2 T helper immune responses (Wang et al., 2020). In a systematic review, the RCTs that studied the effect of probiotic administration on the treatment of asthma showed no positive effects (Vliagoftis et al., 2008). A more recent meta-analysis (including 12 studies) from Das et al. (2013) showed no improvement in quality-of-life scores in asthmatics. However, reduced asthma attacks with probiotics were found. Although some studies suggest some benefit and harm was not reported, the current evidence does not support use of probiotics in treatment of asthma (Sharma & Im, 2018).

10.4 Probiotics for the prevention of allergic rhinitis

The incidences of both perennial allergic rhinitis and seasonal allergic rhinitis have been increasing worldwide and their management is costly (Broek et al., 2010). Currently there is no strong evidence that probiotics are effective in the prevention of allergic rhinitis (Zuccotti et al., 2015), with even some studies suggesting that there may even be an increased prevalence of allergic rhinoconjunctivitis in those taking probiotics in the perinatal period and in childhood.
In a systematic review published in 2014 five RCTs that addressed the preventive role of probiotics in allergic rhinitis were evaluated. The outcome revealed no difference in the incidence of allergic rhinitis between the probiotic and placebo groups [odds ratio (OR) 1.07, 95% CI 0.81–1.42, \( P = .64 \), fixed-effects model], and no significant difference in the prevention of allergic rhinitis (Peng et al., 2015). A 2019 meta-analysis of 17 RCTs including 5264 children, failed to identify that probiotic supplementary therapy during pre- and postnatal periods has a clear benefit in the prevention of allergic rhinitis (Du et al., 2019). However, similar as for the prevention of asthma, the absence of evidence for benefit may be related to shortcomings the study designs and the presence of multiple confounding variables. Research indicates that patients with different chronic rhinosinusitis phenotypes possess distinct nasal microbiota profiles, which influence immune response (Dimitri-Pinheiro et al., 2020). Probiotic intervention may have a promising role in the prevention and adjunctive treatment of allergic rhinitis, although results up to now are disappointing.

## 10.5 Probiotics for the treatment of allergic rhinitis

The treatment of allergic rhinitis continues to be based on allergen avoidance, symptomatic medication, antiinflammatory therapies, and allergy immunotherapy (Juniper et al., 2005). Intranasal corticosteroid sprays are first-line treatment for moderate-to-severe allergic rhinitis and are quite effective (May & Dolen, 2017). However, current medications may have undesirable side effects that may affect quality of life (Juniper et al., 2005). In addition, patient compliance is a main concern. Therefore it is of interest to continue to look for alternatives. It has been proposed that oral administration of probiotics improve the microbial balance in the gut and can modulate immune responses, although this paper discussed symbiotic administration and not probiotic as the title suggests (Jalali et al., 2019). A review from 2010 (seven trials, \( n = 616 \), children and adults mixed) suggested that probiotics (Lactobacillus spp. and Bifidobacterium spp.) can have significant beneficial effects on allergic rhinitis treatment, with the potential to improve the patient’s quality of life and reduce medication use (Das et al., 2010). Similar results were reported in a 2014 meta-analysis including 11 RCTs showing that probiotic intake was associated with a significant overall improvement of the quality-of-life scores and nasal symptom scores of patients with allergic rhinitis [standard mean difference (SMD) \(-2.97, 95\% \text{ CI} -4.77 \text{ to } -1.16\), \( P = .001 \)] (Peng et al., 2015). No improvements of immunologic parameters were noted. However, this meta-analysis was criticized for its methodology (Peng et al., 2015; Turner et al., 2015). The same year, a meta-analysis on the same topic identified 23 studies with 1919 patients, including 21 double-blind RCTs and two crossover RCTs, again including children and adults (Zajac et al., 2015). Seventeen studies showed a significant clinical benefit in at least one outcome measure, whereas six trials showed no benefit (Zajac et al., 2015). Probiotic administration resulted in a significant improvement in quality-of-life scores compared to placebo (SMD \(-2.23, P = .02 \)) (Zajac et al., 2015). Probiotics had no effect on rhinitis total symptom scores (SMD \(-0.36, P = .13 \)) or total IgE levels (SMD 0.01, \( P = .94 \)), although there was a trend toward a reduction in antigen-specific IgE (SMD 0.20, \( P = .06 \)) in the placebo group compared to probiotic (Zajac et al., 2015). A 2016 Meta-analysis of 22 RCTs also came up with evidence of a potential benefit of probiotics in the treatment of allergic rhinitis. Even though probiotics significantly improved the total scores of quality-of-life questionnaires, more high-quality studies are needed to prove the effectiveness of probiotics with validated quality-of-life tools and objective measurements (Güvenç et al., 2016). Among the trials eligible for meta-analysis, the use of probiotics resulted in a significant improvement in Rhinoconjunctivitis Quality of Life Questionnaire scores compared to placebo (SMD \(-2.23, P = .02 \)). Probiotics had no effect on Rhinitis Total Symptom Scores (SMD \(-0.36, P = 0.13 \)) or total IgE levels (SMD 0.01, \( P = 0.94 \)), although there was a trend toward a reduction in antigen-specific IgE (SMD 0.20, \( P = 0.06 \)) in the placebo group compared to probiotic (Güvenç et al., 2016). All meta-analyses report that evidence remains limited due to study heterogeneity and variable outcome measures and that additional high-quality studies are needed to establish appropriate recommendations (May & Dolen, 2017).

In 212 children under 5 years of age from Pakistan, a probiotic product administered as a single dose of a chewable tablet, containing 2 × 109 CFU of Lactobacillus Paracasei (LP-33) was administered daily during 6 weeks while the control group was treated with cetirizine tablet 2.5 mg (≤2 years) or 5 mg (2–5 years) once daily (Ahmed et al., 2019). Significant improvement from baseline symptoms (rhinorhoea, sneezing, nasal blocking, coughing, feeding difficulties, and sleeping difficulties) was reported equally in both groups in almost all children (Ahmed et al., 2019). Although the title of the paper mentions probiotics, the study was in fact performed with postbiotics since they were lyophilized extracts of bifidobacteria, which were shown to suppress allergic rhinitis in mice via inducing IL-10-producing B cells (Xue et al., 2019). Another study showed that Clostridium butyricum extracts so again postbiotics can efficiently inhibit experimental allergic rhinitis by increasing IL-10 expression in the B cells (Zeng et al., 2019).

A pilot study in only 20 adult patients (18–65 years) suggests that probiotics-impregnated bed linen with five different probiotic and natural not genetically modified bacterial strains of Bacillus species (strains of Bacillus subtilis,
Bacillus amyloliquefaciens, and Bacillus pumilus) can improve symptoms and quality of life of patients with dust mite allergic rhinitis (Verheijden et al., 2016). A large-scale study is warranted to further investigate this probiotics-based method (Berings et al., 2017).

10.6 Conclusions

Meta-analyses have shown that marked heterogeneity as well in inclusion criteria, studied products, and primary outcomes between studies makes direct comparison difficult (Papi et al., 2018). Current guidelines from prominent medical societies including the American Academy of Pediatrics, the European Academy of Allergy and Clinical Immunology, the National Institute of Allergy and Infectious Disease, and the European Society for Pediatric Gastroenterology, Hepatology and Nutrition do not recommend the use of probiotics for primary prevention of allergic disease (Kalliomäki et al., 2010). Due to the heterogeneities, the optimal strains, dosages, timing, and duration of probiotic administration remain unknown. However, research in this area is under way and will hopefully give better insights into how probiotics may contribute to the prevention or treatment of atopic diseases (Wang et al., 2020). While data from studies evaluating the role of the gastrointestinal microbiota on allergic disease of the respiratory tract performed in well-controlled conditions suggest a causal relation, data from clinical human studies remain disappointing. Multiple confounding factors influencing the clinical situation are likely to interfere with these outcomes. As an overall conclusion, there is insufficient evidence to recommend administration of probiotics in prevention or treatment of respiratory tract allergies, although there are animal data suggesting benefit and harm have not been demonstrated. It is important to emphasize that future studies require thoughtful prospective considerations in study design and execution with a special focus on clinical phenotyping, sample collection, and processing procedures for microbiome-specific analyses (Huang, Marsland, et al., 2017). There is a need to develop international standards for study designs to ensure uniformity across clinical trials. Future studies are warranted to refine the effector molecules of probiotics and to identify their mode of action in healthy and diseased conditions (Sharma & Im, 2018).

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Conflicts of interest

We have no conflict of interest to declare.

References


