Probiotics in Children with Asthma

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A type-2 immune response usually sustains wheezing and asthma in children. In addition, dysbiosis of digestive and respiratory tracts is detectable in patients with wheezing and asthma. Probiotics may rebalance immune response, repair dysbiosis, and mitigate airway inflammation. As a result, probiotics may prevent asthma and wheezing relapse. There is evidence that some probiotic strains may improve asthma outcomes in children.

Keywords: oral probiotics ; asthma ; wheezing ; asthma exacerbation ; add-on therapy

1. Introduction

Asthma is an important issue for healthcare because of its high prevalence; consequently, asthma represents a relevant burden for the healthcare system [1]. In particular, asthma is the most frequent chronic disease in children and adolescents, affecting, for instance, ten percent of Italian school-aged subjects [2].

Asthma is a heterogeneous disease sustained by chronic inflammation of the respiratory tract, reversible airflow limitation, and bronchial hyperreactivity [3]. In addition, symptoms and bronchial obstruction may vary over time and in intensity.

Clinical, functional, and pathological features define asthma phenotypes and endotypes [3]. In this context, the type-2 phenotype is the most frequent in childhood; mostly, allergic asthma is predominant in this context [4].

Managing asthma, therefore, constitutes a remarkable commitment for pediatricians [5]. The asthma workup is based on demonstrating bronchial obstruction reversibility (or, if absent, bronchial hyperresponsiveness to stimuli), and measuring lung function, inflammation intensity, and symptom severity [6]. Asthma treatment has, as its goal, the achievement of asthma control by using relievers, such as symptomatic medications, mainly bronchodilator agents, and controllers, such as anti-inflammatory drugs, especially inhaled corticosteroids. In addition, biologics, such as blocking mediators of inflammation, are indicated for severe asthma [1][3].

However, diagnosis of asthma can be difficult in younger children, especially because of the difficulty of performing reliable spirometry, including any bronchodilator or bronchial stimulation test. As a result, the diagnosis of asthma is made on a clinical basis. In this context, the wheezing symptom is given due consideration.

Wheezing can be defined as a continuous whistling sound released by the airway during exhalation that results from a narrowing of caliber of the lower airway [7]. Infants suffering from wheezing constitute a diagnostic task for the pediatrician, also considering the high prevalence and lack tools available for objective testing in children with persistent wheezing [8]. The most common causes of wheezing in infants and preschoolers are asthma, gastric reflux, bronchiolitis, obstructive sleep apnea, and foreign body aspiration [9]. Less common causes are cardiac disease, pneumonia, and tracheobronchomalacia; rare causes are cystic fibrosis, vascular ring, immunodeficiency, ciliary dyskinesia, congenital bronchial atresia, and epiglottitis [10].

Wheezing in children five years or younger is a common problem. About 1/3 of European and American children aged 1–6 years present wheezing in the preceding six months, and almost half of children have at least one episode in the first six years of life [11]. Much effort has been expended to phenotype wheezing. Phenotyping considers the symptoms' onset and duration. A common classification encompasses three main groups: transient early wheezing, non-atopic wheezing, and atopic wheezing/asthma [12]. In other words, such wheezing could be included in the diagnosis of asthma [1].

However, the resolution of bronchial obstruction remains crucial in treating an acute asthma attack using short-acting β2-adrenergic molecules. In addition, children with recurrent wheezing episodes usually benefit from daily low-dose inhaled corticosteroids [11].

2. The Rationale for Probiotics in Pediatric Asthma

The prevalence of allergic diseases has shown a dramatic increase worldwide, so much so that the term allergy epidemics was coined [13]. Strachan proposed an intriguing hypothesis to explain this epidemiological problem in 1989 [14]. He associated a high prevalence of allergic diseases with the optimal hygiene status of affluent families. In contrast, people living in poor hygienic settings rarely were allergic, so he coined the term "hygiene hypothesis". This hygiene hypothesis presupposed an imbalance of human microbiota. Gut microbiota represent the most relevant source for the development of the immune system in infants. Furthermore, a reduced antigenic "pressure" (as occurs in hygienic situation) promotes the maintenance of the type-2 response, characteristic of the fetus, to avoid maternal rejection. In this regard, it has been demonstrated that microbiota biodiversity may have an essential role in allergy rise [15]. Namely, a decline in biodiversity causes microbial deprivation, consequently disturbed immune response, and microbial imbalance. Biodiversity has been defined as "the variability among living organisms from all sources, including, among other things, terrestrial, marine, and other aquatic ecosystems and the ecological complexes of which they are part. It includes diversity within species, between species and ecosystems" [16].

Consequently, the Biodiversity Hypothesis assumes that contact with natural environments enriches the human microbiome, promotes immune balance, and protects from allergy and inflammatory disorders [16]. Consistently, asthmatic children may present dysbiosis of the intestinal and respiratory microbiome [17]. Dysbiosis may promote the start of inflammatory pathways and pitch in bronchial obstruction and airway hyperreactivity. However, exogenous factors can favorably modify the physiological airway microbiota composition (farming environment) or negatively (allergens, air pollutants), as demonstrated by several studies [18]. Moreover, intestinal dysbiosis significantly affects asthma pathogenesis [19]. Antibiotics, gastroprotective medications (mainly proton pump inhibitors), and other drugs may imbalance gut and lung microbiota. The consequent dysbiosis and reduced microbial diversity dysregulate the gut–lung axis, contributing to hypersensitivity and hyperreactivity against inhalant and food allergens. In this regard, the gut–lung axis is crucial in explaining the close relationship between enteric dysbiosis and allergic disorders. Therefore, it is enlightening to understand how dietary supplements may improve respiratory disorders [20]. These concepts are the basis to manipulate the immunity using natural remedies. Therefore, it has been envisaged that oral probiotics might restore the microbiota and immune balance.

The World Health Organization states that probiotics are defined as "live microorganisms which confer a beneficial effect on the host" [21]. Several studies evaluated probiotics in preventing allergic diseases and infections [22]. In addition, probiotics have been investigated as an add-on treatment in allergic disorders [23].

The benefits associated with probiotic supplementation depend on the multifaceted mechanisms of action. Maldonado Galeano and colleagues recently reviewed the beneficial effects of probiotics in humans [24]. After administration, oral probiotics interact with the intestinal epithelial cells (IECs) and immunocompetent cells through Toll-like receptors. This interaction stimulates the synthesis of mediators, cytokines, and chemokines. In particular, macrophage chemoattractant protein 1, released by IECs, induces the activation of the mucosal immunity, sustained by increasing immunoglobulin A-secreting cells of mucosal tissues. Probiotics also activate T cells. In addition, probiotics stimulate regulatory T cells to release IL-10, the main regulatory and anti-inflammatory cytokine [25]. Additionally, probiotics consolidate the intestinal barrier by increasing mucins, tight junction molecules, and goblet and Paneth cells. Finally, probiotics modulate gut microbiota by ensuring homeostasis and inhibiting the growth of pathogens [26].

In addition, the viability of probiotics is crucial to ensure their activity on innate immunity [27].

Therefore, probiotics could represent an exciting natural prevention and treatment strategy. They could expand type-1 response, downregulating IgE production, and reinforcing immune response to fight infections [22][23].

3. Systematic Reviews and Meta-Analyses of Probiotics in Asthma and Allergic Diseases

The hygiene hypothesis was based on the premise that a reduced pressure of "good" bacteria in the gut maintains the type-2 polarization in infants. The fetus grows in a type-2 environment to avoid maternal rejection, as it would be recognized as a non-self by the immune system. The external exposure, by diet and respiration, of microbes is the primary stimulus for maturing immunity; it occurs mainly in the gut [28]. As a result, several clinical trials investigated probiotics in allergy during the last decades. Different meta-analyses and systematic reviews evaluated the available studies.

Das and colleagues performed a systematic review of the additional use of probiotics in respiratory allergy [29]. These authors included 12 studies in the review, with 995 participants (547 for treatment and 488 as controls). The analysis revealed that probiotic supplementation significantly ameliorated the quality-of-life (QoL) scores in subjects suffering from allergic rhinitis. In addition, probiotic use prolonged the period free from asthma attacks and reduced the yearly rhinitis exacerbations. However, there was a high heterogeneity among the trials.

Lin and colleagues provided a systematic review and meta-analysis of probiotic supplementation in children with asthma [30]. This review selected 11 studies, including 910 children.

Children experiencing less asthma attacks belonged to the probiotics group (risk ratio 1.3, 95% confidence interval 1.06–1.59). Probiotic supplementation also reduced IL-4 (mean differences −2.34, 95% CI −3.38, −1.29) and increased interferon-γ (mean differences 2.5, 95% CI 1.23–3.76). However, the childhood asthma control test (cACT), asthmatic symptoms during the day and night, the number of symptom-free days, forced expiratory volume in the first second (FEV_1) predicted, and peak expiratory flow (PEF) were unchanged after probiotic use. Therefore, the authors concluded that the outcomes could not recommend or advise against probiotic use in asthmatic children.

Du and colleagues conducted a meta-analysis of randomized controlled trials (RCT) to evaluate probiotic supplementary therapy for asthma, wheezing, and allergic rhinitis in children [31]. The study considered 17 RCTs, including 5264 children analyzed. The pooled data for the risk of developing asthma after probiotic supplementation showed no significant reduction compared with controls (risk ratio 0.86, 95% CI 0.73–1.01). However, *Lactobacillus rhamnosus* GG supplementation only reduced the occurrence of asthma (RR 0.75, 95% CI 0.57–0.99). The supplement in the postnatal group had a similar result.

Meanwhile, it failed to identify that probiotic supplementary therapy has a clear benefit to wheezing. Therefore, the authors concluded that the beneficial effects were based on the specific probiotic strain. It has to be underlined that this study privileges RCT concerning the prevention of asthma and wheezing.

Wei and coworkers conducted an RCT meta-analysis investigating the possible association between probiotics and incidence of asthma in infants [32]. Globally, 19 RCTs, enrolling 5157 children, fulfilled the inclusion criteria for the analysis. The results showed that probiotics did not affect the risk of asthma onset (RR 0.94, 95% CI 0.82–1.09) or wheezing (RR 0.97, 95% CI 0.88–1.06) compared with placebo. However, a subgroup analysis by asthma risk demonstrated that probiotics diminished wheezing incidence in allergic infants (RR 0.61, 95% CI 0.42–0.90). Therefore, the authors concluded that probiotic supplementation did not diminish the risk of asthma in infants. However, this study focused their attention on preventive studies alone.

Meirlaen and colleagues recently accomplished a narrative review regarding preventing and managing children with asthma and allergic rhinitis using probiotics, prebiotics, and synbiotics [33].

Unfortunately, the analysis of studies showed little evidence to recommend using this substance to prevent asthma and allergic rhinitis in children. However, this consideration derives from the high heterogeneity of the analyzed studies, the frequent low quality, and the use of a considerable quantity of different probiotic strains.

More recently, Chen and coworkers performed a meta-analysis of probiotics for respiratory allergies in children [34]. They included 15 randomized controlled trials including 1388 patients. The study demonstrated that probiotics enhanced quality of life and reduced symptom severity. However, the authors concluded that further research must thoroughly explain mechanisms of action.

4. Probiotic Supplementation in Children with Asthma or Wheezing: The Most Relevant Studies

Giovannini and coworkers performed an RCT exploring the effects of a long-term (one year) consumption of fermented milk containing *Lactobacillus casei* in 187 preschoolers (2–5 years of age) with allergic asthma and/or rhinitis [35]. The findings showed no effect in asthmatic children. On the contrary, *Lactobacillus casei* supplementation diminished rhinitis episodes and shortened diarrhea episodes.

Rose and colleagues investigated the efficacy of *Lactobacillus rhamnosus* GG in preventing sensitization and asthma in 131 infants (6–24 months old) at risks, such as with at least two wheezing episodes and a first-degree family history of the atopic disease [36]. The supplementation lasted six months. The study design included a placebo arm. *Lactobacillus* *rhamnosus* GG significantly reduced the number of sensitizations both after six months and a further 6-month follow-up. In addition, subjects with pre-existing sensitization experienced more minor asthma complaints.

A Taiwanese RCT evaluated the clinical and immunological effects of an 8-week *Lactobacillus gasseri* A5 supplementation in 105 children (6–12 years old) with asthma and allergic rhinitis [37]. The probiotic use enhanced bronchial function, diminished asthma and rhinitis symptoms, and increased the ACT outcomes. Moreover, *Lactobacillus gasseri* A5 significantly diminished the production of TNF-α, IFN-γ, IL-12, and IL-13 by peripheral blood mononuclear cells.

An Italian double-blind placebo-controlled randomized study evaluated the effect of oral *Lactobacillus reuteri* administration on airway inflammation in 50 children (6–14 years old) with mild persistent asthma and house dust mite allergy [38]. The probiotic treatment lasted two months. *Lactobacillus reuteri* significantly decreased the fractional exhaled nitric oxide (FeNO) values and IL-2 levels; it significantly increased IL-10 levels. Thus, this RCT demonstrated that *Lactobacillus reuteri* dampened type-2 inflammation in asthmatic children.

The PANDA study evaluated the effects of a probiotic mixture containing *Bifidobacterium bifidum*, *Bifididobacterium lactis*, and *Lactococcus lactis*, administered during pregnancy and the first year of life [39]. It was an RCT. The probiotic supplementation reduced the incidence of eczema but not atopic dermatitis, such as eczema with sensitization. Therefore, a successive prospective, single-blind study was performed on 83 participants to investigate the outcomes at six years of age [40]. Unfortunately, the study did not show beneficial effects. This finding was in line with the results provided by the literature [41][42][43][44]. Therefore, pre- and perinatal probiotic supplementation seems to have scarce preventive effects. On the contrary, probiotic administration in asthmatic children appears more effective.

An Italian placebo-controlled, double-blind, randomized study consistently investigated the effects of a Bifidobacteria mixture containing *Bifidobacterium longum* BB536, *Bifidobacterium infantis* M-63, and *Bifidobacterium breve* M-16V in 40 children with seasonal allergic rhinitis and intermittent asthma [45]. The supplementation lasted four weeks. Children treated with probiotics significantly reduced respiratory symptoms and improved QoL, whereas the placebo group experienced worsened symptoms and QoL.

Ahanchian and colleagues evaluated a multi-strain synbiotic containing Lactobacillus casei, Lactobacillus rhamnosus, Streptococcus thermophilus, Bifidobacterium breve, Lactobacillus acidophilus, Bifidobacterium infantis, Lactobacillus bulgaricus, and fructooligosaccharides in 72 children (6–12 years old) with mild persistent asthma [46]. The study was randomized and placebo-controlled and lasted 60 days. Children in the synbiotic group had minor viral respiratory infections than the placebo group, but only during the first month. Consistently, actively-treated children used fewer bronchodilators.

A further Iranian RCT investigated the effects of a synbiotic compound containing *Bifidobacterium infantis* and fructooligosaccharide in school children (12 years of age or younger) with mild to moderate asthma [47]. The treatment lasted six months. The synbiotic supplementation induced a significant reduction in outpatient visits for asthma-related problems.

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