Probiotics and prebiotics in atopic dermatitis: Pros and cons (Review)

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Abstract. Atopic dermatitis (AD) represents a chronic inflammatory skin condition in which the skin barrier is impaired; thus, the permeability is increased. Hence, there is a greater risk of allergic sensitization, as well as a higher pH and lower protection against resident microbes. Since this condition is currently increasing among children, it requires further study, as little is known regarding the pathogenesis that makes the skin prone to chronic relapsing inflammation. Trying to standardize the data regarding the use of prebiotics and probiotics in AD, we encountered tremendous variability in the literature data. Literature abounds in conflicting data: studies regarding prophylactic and therapeutic applications, different types of strains and dosages, applications in young children up to 5 years of age and above, usage of probiotics alone, prebiotics alone or synbiotics combined. There are also conflicting data regarding the outcome of these studies; some confirming a positive effect of prebiotics, probiotics or synbiotics and some showing no efficacy at all. The articles were divided into those assessing probiotics or prebiotics alone and a combination of the two, with studies showing a positive effect and studies proving no efficacy at all. We tried to critically analyze those articles showing weak and strong points. In summary, the most studied probiotics were the strains of *Lactobacilli* and *Bifidobacteria*. The Severity Scoring of Atopic Dermatitis (SCORAD) index was used to measure the efficacy of the treatment. Most studies compared their results with a placebo group and the efficacy when seen in moderate to severe forms of AD in patients with other allergic diseases present. However, the results are difficult to interpret, as in many studies the authors suggest that the disease may have a tendency to improve in time in some groups of patients.

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1. Introduction

Atopic dermatitis (AD) represents a chronic inflammatory skin condition in which the skin barrier is impaired; thus, the permeability is increased. Hence, there is a greater risk of allergic sensitization, as well as a higher pH and lower protection against resident microbes. Since this condition is currently increasing among children, it requires further study, because little is known regarding the pathogenesis that makes the skin prone to chronic relapsing inflammation (1).

AD is a chronic pruritic, remitting, relapsing inflammatory skin disorder. It is usually related with different symptoms of *immunoglobulin E (*IgE)-associated allergy, such as allergic rhinoconjunctivitis, allergic asthma and IgE-mediated food allergy. Often, it is the first phase in the sequential development

of other different atopic conditions, being called the 'atopic march', which includes urticaria, chronic allergic rhinitis, chronic allergic conjunctivitis and asthma (2-4).

Atopic conditions have been on the rise during the past few decades, particularly in industrialized countries. Thus, it seems that the modern lifestyle represents one of the main contributing factors to this worldwide epidemic (5,6).

Different studies show different data, but there is consensus between epidemiological data that approximately 20% of children are affected by AD, both in developed and developing countries (7).

With roughly 60% of cases occurring between 0 and 6 months, AD generally manifests in the first 5 years of life (8,9).

Environmental factors, genetics and immunologic markers are some of the elements responsible for the development of AD (10).

There is also an agreement regarding the link between digestive allergens and food diversification in the onset of AD in children up to 5 years of age, whereas in children above 5 years of age respiratory allergies predominate (11,12).

The gastrointestinal tract of a newborn is sterile at birth; the developing microflora in the early postnatal period is involved in the activation of innate and adaptive immunity (13). The development of atopy occurs when inadequate microbial stimulus leads to unbalanced gut microflora, favoring the persistence of a neonatal Th2-dominant immune response (14,15).

The consumption of sterile food, proper hygiene, reduced family size, as well as the increased use of antimicrobial medication have resulted in lower rates of infection during childhood; this reducing early contact to microbes (16,17). This may interfere with the development of the child's immune system, which tends to be directed towards a T-helper (Th)2 phenotype in infants, while postnatal maturation is linked with gradual inhibition of Th2 and increasing Th1 affinity (18-20). The hypothesis that early microbial exposure is a key feature for Th1-skewed immune response in healthy children during the postnatal period is strongly supported by epidemiologic and experimental data (21,22).

There is great interest in the role of microbial products such as probiotics in the prevention and treatment of allergic disease, due to the growing concern regarding the adverse immunologic effects of increasingly more hygienic environments (23).

Positive challenges, such as the exposure of infants to daycare environments and pets, various nonpathogenic bacteria, which may enhance protective immunity against allergic disorders, is beneficial (24).

In patients with AD, skin damage is probably caused mainly by aberrant Th2-type immune responses, resulting in overproduction of proinflammatory cytokines against common environmental allergens (25,26).

Imbalances in certain gut bacterial species are associated with atopic disorders, according to the results of decades of research (27). Despite the fact that the importance of dysbiosis in the gut microbiota in patients with AD has been stressed by these studies, the specific microbial dysfunction that adversely affects the regulation of inflammation underlying AD remains unknown (28,29).

Several grading systems have been used to assess AD, the most common being the SCORAD severity score (Severity Scoring of Atopic Dermatitis) (30) and IGA (Iinvestigator Global Assessment).

In preparation of this review, we searched the Web of Science database regarding articles published in the last 10 years, using key words such as probiotics, prebiotics, synbiotics, skin microbiome, and atopic dermatitis. Sponsored articles or articles whose authors had relevant conflict of interest were excluded. A total of 63 relevant original articles and reviews were critically reviewed.

2. Probiotics and prebiotics

Probiotics are living microorganisms, which may provide positive health benefits by boosting the gastrointestinal microbiome and by regulating the Th1 and Th2 immune system response (31,32).

Nonetheless, the definition of a probiotic cannot elucidate what type of potential health benefits it grants. In addition, not all probiotics influence the immune system in the same manner (33).

By inhibiting the T-helper cell type-2 (Th2)-mediated response and by improving the Th1/Th2 ratio, probiotics can reduce the severity of AD (34). When inhibiting the Th2 cell response, cytokines such as interleukin (IL)-4, IL-5, IL-6 and IL-13 are no longer released, interferon (INF)-γ decreases (cytokine released by Th1 cells), phagocytosis is stimulated, and serum IgA is increased (35).

Microorganisms should comply with the majority, if not all, of the following criteria to qualify as a probiotic: identification at genus, species and strain level, being safe for food and clinical use, being able to survive intestinal transit, being able to adhere to mucosal surfaces, being able to colonize the human intestine or vagina (at least temporarily), producing antimicrobial substances, being able to antagonize pathogenic bacteria, possessing clinically documented and validated health effects and being stable during processing and storage (36).

Probiotics belong to the *Lactobacillus* group (*L. rhamnosus* GG, *L. sporogenes*, *L. reuteri* RC-14, *L. plantarum* 299v, *L. acidophilus*, *L. lactis*). *Bifidobacterium group* (*B. bifidum*, *B. longum*, *B. infantis*), *Streptococcus* group (S. *thermophillus, S. lactis, S. fecalis*); in addition, there are non-bacterial organisms (non-pathogenic yeast *Saccharomyces boulardii*). *Bifidobacterium* and *Lactobacillus* are a part of the regular microbial flora. These represent Gram-positive, anaerobic types of bacteria. Some types produce both lactic acid and other antimicrobial substances, such as hydrogen peroxide and bacteriocins (small proteins with potential bactericidal effect) (37).

Prebiotics represent selectively fermented dietary ingredients, which promote particular alterations in the composition and/or activity of the gastrointestinal microbiota, with benefits for the health of the host (38). They are indigestible substances that affect the host in a beneficial manner by selectively stimulating the growth and/or the activity of a limited number of bacterial strains already established in the gut flora (39). Prebiotics are nondigestible oligosaccharides in general and fructooligosaccharides in particular. They seem to stimulate the growth of endogenous bifidobacterial (40).

Prebiotics increase the production of short-chain fatty acids (SCFAs) (acetate, propionate and butyrate) with

anti-inflammatory effects (41), decrease the generation of toxic fermentation products (42) and enhance the Th1/Th2 ratio, increase lymphocyte and/or leukocyte numbers in gut-associated lymphoid tissues and increase intestinal IgA secretion (43).

Consequently, a food ingredient is categorized as prebiotic when it meets three criteria: firstly, it escapes digestion in the upper gastrointestinal tract and reaches the colon intact; secondly, it ferments due to the intestinal microflora. Third, it should stimulate the growth of intestinal bacteria linked to wellbeing and health in a selective manner (44-47).

3. The microbiome

The microbiome represents a set of microorganisms (bacteria, fungi, archaebacteria and protozoa) and viruses, which colonize a specific environment. Physiologically, and sometimes pathologically, they co-exist in a symbiotic relationship with the human body (48).

New scientific findings have demerge from the study of the human microbiome. Currently, there is a wide range of available data: a vast database of bacterial species isolated from many body areas is currently available to scientists. Their task is to pinpoint any dysbiosis potentially responsible for allergic diseases (48).

The gut microbiome represents a key postnatal immune regulator, which promotes the immune maturation of Th1 and Treg lymphocyte functions and suppresses the Th2 response, prevalent during the fetal period. Dysbiosis, intended as a dysregulation of the microbiome, particularly if present in the neonatal period, can be a cofactor in the genesis of allergic disorders, because of its role in the disruption of immune maturation (49).

The absence of antibiotic therapies in the early years of life, vaginal delivery, exclusive breastfeeding for the first 4 months, the presence of pets at home during infancy or pregnancy, the absence of maternal antibiotic therapies during pregnancy are some of the elements that appear to result in the establishment of a protective microbiome against allergic disorders. All of them are actually linked to lower rates of childhood allergies (50).

The research regarding newborns delivered either vaginally or by Caesarean section showed that various areas (mouth, skin, intestines) are colonized by species like *Sneathia* and *Lactobacillus spp*. (bacteria present in the maternal genital tract). Children delivered by Caesarean section display a widespread of *Staphylococcus* and *Streptococcus spp*. These results are in accordance with previous epidemiological studies that show a low risk of developing allergic disorders in newborns delivered vaginally (51).

According to the diet-microbiome hypothesis, changes in the Westernized diet that reflect a lower intake of fiber may result in alterations in the gut microbiome, followed by decreased production of immunomodulatory products, particularly SCFAs, which have anti-inflammatory effects and contribute to the maintenance of epithelial barrier function (52).

There are studies that have reported a lower incidence of asthma in children living in a rural area compared to those living in urban areas. The exposure to animals, in particular, plays a protective role against bronchial hyperreactivity. This does not occur only in children, but also during the fetal period; the children of mothers who spend their pregnancies in rural areas have less chances of developing asthma; this suggests a modulation of the fetal immune system by the microbiome (53).

Studies regarding gut infections caused by *C. difficile* have described the role of the dysregulation of the gut microbiome following antibiotic therapies; the growth of this bacterium and the resulting stage of infection have been effectively inhibited through the use of fecal transplant in order to correct the gut dysbiosis. This therapeutic success supports the finding of microorganisms (also called probiotics) or substances that can be metabolized and contribute to the growth of some bacterial species (prebiotics) used to treat other states of dysbiosis that cause allergic diseases (48).

Children born by vaginal delivery are colonized by bacteria found in the maternal vaginal and gastrointestinal microbiota, while newborn delivered by Caesarean section are colonized by bacteria present on the skin (51).

In order to determine possible differences between the skin of healthy individuals and that of subjects with the disorder, the skin microbiome was studied. The results reported that subjects with AD had a greater concentration of *S. aureus* compared to healthy subjects and that the composition of the skin microbiota underwent drastic changes as a result of corticosteroid therapy. In fact, during exacerbation of an atopic flare, the skin showed reduced bacterial biodiversity that was gradually repopulated as a result of corticosteroid therapy. Conversely, the most prevalent staphylococcal species on the skin of healthy controls belonged to the genus *Epidermidis* that, in association with other coagulase-negative *staphylococci (CoNS)*, can secrete antimicrobials that limit the overgrowth and biofilm formation of *S. aureus* (54).

It appears that not only bacterial species of the microbioma are implicated in the development of AD. Lunjani *et al* showed that fungal *Malassezia* DNA was detected in 90% of AD skin lesions and might contribute to the inflammatory process pathogenesis by secreting immunogenic proteins that induce the production of proinflammatory cytokines on keratinocytes (55).

4. Controversies

Trying to standardize data regarding the use of prebiotics and probiotics in AD, we encountered tremendous variability of data. Literature abounds in conflicting data: studies regarding prophylactic and therapeutic applications, different types of strains and dosages, applications in young children up to 5 years of age and above, usage of probiotics alone, prebiotics alone or synbiotics combined. There are also conflicting data regarding the outcome of these studies, some proving a positive effect of prebiotics, probiotics or synbiotics and some showing no efficacy at all.

We performed a review of the most relevant articles regarding the use of these substances which were divided into those studying probiotics or prebiotics alone and a combination of the two, studies showing a positive effect and studies proving no efficacy at all. We tried to critically analyze those articles showing weak and strong points.

Thus, Passeron *et al* published a double-blind prospective randomized study on the optimal combinations of probiotics and prebiotics (synbiotics), which could have efficacious results in the treatment of AD, moderate and severe forms in children 2 years of age or older. The average age of the patients included in the study was 5.8 years. Initially, they included 48 patients divided into two groups, who received $1.2x10^9$ colony-forming units of *Lactobacillus rhamnosus Lcr35*, plus a prebiotic or an identically prebiotic preparation alone three times a day for 3 months. The SCORAD score was initially calculated and had to be at least 15, and it was again established to evaluate the efficiency of the treatment. The total SCORAD score mean in both groups was statistically significant after 3 months of treatment. The authors did not find any statistical differences between the two groups of treatment using the objective SCORAD score and total SCORAD or the total numbers of flares during the entire study or the mean numbers of flares in the month before the study and at the end of the treatment. Regarding topical treatments, the authors divided patient into three groups, according to what they were administered: topical steroids, calcineurin inhibitor ointments and emollients only. The authors did not find any statistically significant difference between the three groups regarding the total quantities of ointment used. The three groups formed regarding the ointment treatments were unequal; 34 patients in the first group, 11 in the second and only 3 in the third group. The study confirmed that the synbiotic treatment did not have better results than the prebiotics used alone. The small number of patients included in the study and the age of the patients included could also represent a weak point of the study, a higher efficiency having been stressed in children younger than two years of age. The comparison of prebiotics with synbiotics as approaches in the treatment of AD represents a strong aspect of the study, in comparison with studies that focus on probiotics or prebiotics alone (39).

The International Scientific Association for Probiotics and Prebiotics (ISAPP) convoked a board comprised of physiologists, nutritionists and microbiologists in May 2019, with the purpose of revising the 'synbiotics' definition, as well as their scope. They updated the definition to 'a mixture comprising live microorganisms and substrate(s) selectively utilized by host microorganisms that confers a health benefit on the host'. According to the board, by only defining synbiotics as a combination of probiotics and prebiotics would have suppressed the innovation of synbiotics, which are meant to work conjointly. In addition, the requirement that every element should meet the evidence, as well as dose specifications for both prebiotics and probiotics, could result in an impediment. Instead, the board made clear that a complementary synbiotic has not been designed so that its constituent parts work cooperatively while a synergistic synbiotic does not have to. A synbiotic whose substrate is used selectively by the co-administered microorganism constitutes a synergistic symbiotic (56).

According to research, the species belonging to the *Lactobacillus*, *Bifidobacterium* and *Streptococcus* genera represent the most used living microorganisms in the tested formulations. Generally, the substrate constituents are inulin, fructo-oligosaccharides or galacto-oligosaccharides; however, doses differ significantly, from as low as 100 mg to as much as 10-15 g per day. For instance, in a double-blind randomized controlled trial (RCT), the consumption twice per day of a synbiotic composed of *Lactobacillus casei* 10 (10^9 CFU), fructo-oligosaccharides (100 mg), *Lactobacillus rhamnosus* HS111 (10^9 CFU), *Lactobacillus acidophilus* 10 (10^9 CFU), *Bifidobacterium bifidum* (10^9 CFU) 4 days before and 10 days after surgery for periampullary neoplasms led to a reduced number of infections postoperatively. In addition, it resulted in fewer non-infectious complications, a shorter duration of antibiotic therapy, a reduced number of hospitalization days and lower mortality rate than in patients who received a placebo, namely sucrose (57). Even though such low doses would not be expected to be responsible for a prebiotic effect in complementary synbiotics, they could, theoretically, be sufficient to stimulate a cognate microorganism in a synergistic synbiotic formulation. In an RCT on 225 overweight and obese adults, a mixture of polydextrose (12 g per day) and *Bifidobacterium animalis* subsp. *Lactis* 420 led to a certain reduction in the body fat mass of 4.5%, while the individual treatments produced no effects (58). Nonetheless, in this study, the use in a selective manner has not been established. Therefore, by itself, this research does not provide concluding proof that the combination tested was either a complementary or a synergistic synbiotic.

Aldaghi *et al* performed an RCT on 81 subjects with AD. The subjects were assigned to three groups at random. The synbiotic group received a dose of 5 drops/day of a synbiotic, besides the routine treatment. The vitamin D3 group received 1,000 units (IU) of vitamin D3 daily, aside from the routine treatment. According to the results, an effective way to reduce the severity of AD in infants is represented by multistrain synbiotics, alongside vitamin D3 supplements and routine treatments (59).

There are several RCT studies that have shown no efficacy of symbiotics in the outcome of AD. Dissanayake *et al* studied emollients vs. synbiotics in AD and showed that neither had any effect on reducing the progression of AD and food allergy at 1 year of age in a group of 459 children under 1 year of age (60).

In a study published by Isolauri *et al*, children younger than two years old with proven allergy to cow's milk had a better response to probiotics (61).

Different strains of prebiotics have been studied in order to manipulate the gut microbiome.

In a double-blind randomized placebo controlled trial, published by Weston *et al*, 56 children were included and then divided into two groups. In the first group, children received treatment with a probiotic ($1x10^9$ *Lactobacillus fermentum* VRI-033 PCC) two times per day for 8 weeks. In the second group, an equivalent volume of placebo (maltodextran) was administered during the same period of time. The children included in the study were aged between 6 and 18 months, with an average of 11.5 months, with moderate or severe AD. The SCORAD index was established to determine the efficacy of the treatment. An inclusion criterion in the study for the patients was having an SCORAD index ≥25. Patient included were evaluated at week 0 when included, weeks 2 and 4 during the study and week 8 at the end of the study and at a later control, week 16 post-treatment. Topical corticosteroid treatment was continued during the study. Regarding the SCORAD index, the authors highlighted better improvement in the

probiotic group compared to the placebo group at each week of the evaluation, with a reduction in the SCORAD index over time being statistically significant only in the probiotic group. The authors also analyzed the quality of life using the Dermatitis Family Impact Questionnaire (DFIQ), frequency of topical corticosteroid usage and parental impression of the intervention. The results were favorable in both groups regarding the DFIQ after treatment. Concerning the amount of topical corticosteroid applied, no significant difference was observed in any of the groups after treatment (62).

Every patient included in the study (62) was tested for total IgE and underwent an radioallergosorbent test (RAST), showing that total IgE was elevated in most patients, and RAST testing for specific IgE was positive to food mix in most of the patient, but they were less frequently positive to house dust mite allergen-specific IgE. Therefore, data on allergen avoidance regarding house dust mite may not be effective in controlling AD in children, as shown in a review published in 2020 (12). Bumbacea *et al* found a statistically significant difference in lower respiratory tract infections with a lower incidence of infections in the probiotic group, but no difference was seen regarding gastrointestinal symptoms or wheezing. One of the explanations invoked by the authors for the reduction of the SCORAD index in both groups was the fact that the behavior of the patients may have been altered by the inclusion in the study with a better compliance with previously prescribed treatment regimens and that the positive outcome in the placebo group may be explained by the natural evolution of the disease at this age. The follow-up of the patients until week 16 represents a strong aspect of the study, but the total number of patients included in the study was small, with only 56 patients being included (12).

The mechanisms proposed for probiotics consist of modifications in the innate immune system, such as the induction of regulatory T cell development (63) and alterations in Toll-like receptor (TLR) expression (64). Different probiotic strains may have varying effects. The role of *Bifidobacterium* or *Lactobacillus* supplements on TLR expression was assessed by Marlow *et al* in a study that used buccal smears sampled from 331 children. They showed that *Lactobacillus* was associated with 26 polymorphic TLR modifications that lowered the risk of eczema ($P<0.02$), as opposed to only two polymorphisms in those supplemented with *Bifidobacterium* (65).

In vitro, the prebiotics in human milk were found to act as decoy glycan receptors, which resulted in blocking certain parasites, viruses and bacteria from binding to epithelial cells (66-69). It appears that these prebiotics also affect directly the gene expression of epithelial cell surface glycans (70). In theory, the effects of reduced cell surface binding and improved glycan expression would help in the epithelial barrier function, which is proven to play a key role in the prevention of atopy. *In vitro* studies have proven that, alongside these indirect mechanisms, prebiotics seem to directly modulate immune responses to reduce IL-4 production, a known allergy mediator, in the lymphocytes of peanut allergic adults (71). An improved Th1 response, as well as a reduced Th2 (allergic) response to vaccination was found in mice supplemented with prebiotics (72). Moreover, *in vitro*, human milk prebiotics have been shown to reduce leukocyte rolling on TNFα-activated human cells (73), in addition to platelet-neutrophil complex formation and neutrophil activation (74), which could possibly translate to diminished inflammatory responses.

In their review, Zhao *et al* evaluated the treatment efficacy of probiotics in children with AD by seven double-blinded randomized clinical trials, which included gathering 609 patient who received *Lactobacillus*. The outcome was favorable with a significant statistical difference in the SCORAD index. The authors did not include studies using synbiotics or a mixture of prebiotic and probiotics. Children included in the study were not older than 3 years of age. The SCORAD index was used as outcome at the end of the treatment. The authors showed that only preparations containing the *Lactobacillus* species were beneficial and that the duration of 8 weeks of treatment or less showed a statistically significant drop in the SCORAD index. In addition, the authors highlighted the treatment efficacy of the probiotic treatment when used in children of one year or less of age. The review also demonstrated that probiotic treatment in moderate to severe forms of the disorder was more effective than in mild forms. The authors stated that the results of the study may be explained by other studies that have shown lower bifidobacteria strains in the stools of children diagnosed with AD. Regarding the age of the patients, the authors explained that patients younger than 1 year of age might be less exposed to food components that act as allergens at elder ages (75).

A total of 43 patients diagnosed with moderate to severe forms of AD, aged between 0 and 11 years who received 2 doses ($1x10^9$ CFU/sachet of *L. salivarius* LS01)/day during 8 weeks, followed by 1 dose/day during 8 weeks were included in an Italian study published by Niccoli *et al*. Patients continued to use emollients and/or topical steroid treatment if needed. Patients included in the study were evaluated at the beginning of the study and at 4, 8, 12, 16 weeks and 4 weeks after the end of the study at week 20. Objective SCORAD, SCORAD index and itch index were established to evaluate the outcome of the treatment. The authors concluded that after probiotic treatment, patients presented a significant statistical reduction in SCORAD and itch indexes and that effect persisted 1 month after the treatment with probiotic finished. However, the study gathered only a small cohort of patients and the authors pointed that a double-blind study was also required (76).

In a double-blind, placebo-controlled, crossover study published by Rosenfeldt *et al*, 43 patients aged between 1 to 13 years (mean age 5.2 years), received, during a period of 6 weeks, a mix of two probiotics *Lactobacillus rhamnosus* 19070-2 and *Lactobacillus reuteri* DSM 122460 at a dose of 10^{10} colony-forming units of each strain or an placebo preparation (mix of skimmed milk powder and dextrose anhydrate), two times a day. In the study, patients with moderate and severe AD were included. In order to establish the clinical severity of the eczema, patients were evaluated using the SCORAD score. Skin prick tests were performed for patients included in the study, as well as blood tests for serum IgE, serum eosinophil cationic protein and cytokines, such as IL-2, IL-4, IL-10 and INF-γ. Patients were than divided into two groups: group A received a placebo followed by active treatment; group B received active treatment followed by a placebo. Another repartition of the 43 patients included in the study was allergic and nonallergic patients. Allergic patients had a serum IgE lever higher than normal levels combined with positive skin prick test, elevated serum IgE levels with alimentary food component allergies, asthma, or allergic rhinoconjunctivitis.

The personal evaluation of the patients regarding treatment was in favor of the active probiotic treatment with a statistically significant difference. Regarding the SCORAD index during active probiotic treatment, a lowering in the SCORAD index was seen, but with no statistically significant difference. A statistically significant difference during active probiotic treatment with impact on only one of the items of the SCORAD index (extent of the lesion) was seen only in allergic patients. The authors did not find any significant differences regarding topical corticosteroids use between active probiotic treatment and placebo. Concerning serum eosinophil cationic protein, a statistically significant difference was observed between active probiotic treatment and the placebo in favor of probiotics. No significant change was observed between the two groups regarding the cytokine levels. A possible weak point of the study might be the fact that the authors obtained a statistically significant difference only after splitting the SCORAD index. This study represents one of the few studies to use a mix of probiotics compared to a placebo (77).

5. Conclusions

In order to better understand the management of such a complex disorder as atopic dermatitis (AD), with major impact not only on the patients but also on their family, further studies concerning the use of probiotics and/or prebiotics in the treatment of children diagnosed with AD are still required. The main challenge is represented by the great heterogeneity of studies already published. Among these, some compare probiotic with prebiotics as single therapy or in association, as well as single strain vs. mixtures of strains of probiotics. There are also studies regarding various doses or the duration of treatment, as well as the duration of follow-up post treatment. We also observed a great diversity regarding the age of patients included in the studies, the severity of the disease and the inclusion or exclusion of patients with other allergic disease. A possible key solution would be the use of standard guidelines for study designs already proposed in the literature since 2010 by Shane *et al* (78).

In summary, the most studied probiotics were the strains of *Lactobacilli* and *Bifidobacteria*. The SCORAD index was used to measure the efficacy of the treatment. Most studies compared their results with a placebo group and the efficacy when seen in moderate to severe forms of AD in patients with other allergic diseases present. However, the results are difficult to be interpreted, as in many studies the authors suggest that the disease may have a tendency to improve in time in some groups of patients.

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Availability of data and materials

All information included in this review is documented by relevant references.

Authors' contributions

ISF, DH, PL and SA performed the study of the literature data. DB, LMI, SC and RB critically revised the manuscript in light of the literature findings. All authors read and approved the final manuscript for publication.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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