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USE OF PROBIOTICS IN CHILDREN AS PROPHYLAXIS FOR THE DEVELOPMENT OF ATOPIC DERMATITIS: SYSTEMATIC REVIEW

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Abstract: (1) Introduction: Atopic dermatitis (AD) is a disease with a low mortality rate, but which has a relevant impact on patients' health and quality of life. The use of probiotics, due to their possible immunomodulatory effect, has been studied as an alternative, both therapeutic and prophylactic, for AD. (2) Objectives: To synthesize the evidence regarding the effect of the use of probiotics by children up to 5 years of age, in relation to the incidence of atopic dermatitis in this population. (3) Methods: The systematic search for evidence was carried out on the PubMed, EMBASE and Cochrane Library platforms. The inclusion criteria for study selection were children up to 5 years of age with usual or high risk of developing AD. The intervention evaluated was the use of probiotics by this population, in the determined age group. (4) Results: 19 studies were selected, totaling 23,983 children who received probiotic supplementation as an intervention. Among the selected studies, six showed a protective effect. An RCT (Schmidt 2019) with 285 children found a lower incidence of AD in the intervention group (4.2%) when compared to the control group (11.5%). In contrast, the other 13 selected studies did not show a protective effect for AD. (5) Conclusions: In this systematic review, probiotic supplementation in the postnatal period for children up to 5 years old did not prove to be an intervention with a protective effect on the incidence of AD. Future studies are needed to evaluate both the subtypes of probiotics used and their use in periods different from those evaluated.

Keywords: Atopic Dermatitis. Probiotics. Prophylaxis. Systematic review.

LIST OF ACRONYMS AND ABBREVIATIONS

B. Bifidobacterium; C. Control; CASP: Critical Appraisal Skills Programme; AD: Atopic Dermatitis; RCT: Randomized Clinical Trial; USA: United States of America; FLG: Filaggrin; GALT: Gut-Associated Lymphatic Tissue; HR Hazard Ratio; I.: Intervention; CI: Confidence Interval; IgE: Immunoglobulin E; L.: Lactobacillus; LGG: Lactobacillus GG; WHO: World Health Organization; OR: Odds Ratio; mRNA: Messenger Ribonucleic Acid; RR: Relative Risk; SCORAD: Scoring Atopic Dermatitis; TLR: Toll Like Receptors; UFC: Colony Forming Units.

INTRODUCTION

DESCRIPTION OF THE DISEASE

Atopic dermatitis is a chronic itchy inflammatory skin disease, the prevalence of which varies between 5 and 20%. The majority of cases begin before the age of 5 and there is a slightly higher incidence of females (1.3:1). The incidence of AD has increased and can affect any race or geographic location, although there appears to be a higher incidence in urban areas and developed countries, especially in Western societies [1].

Family and personal history of atopy (atopic dermatitis, wheezing and allergic rhinitis) are the main risk factors. Approximately 70% of patients who present the condition have a positive family history of atopic diseases. For children with at least one atopic parent, the risk of developing the condition is two to three times greater than that of the general population [2].

In the acute setting, the characteristic clinical presentation is intense itching, associated with erythematous papules and vesicles with exudates and crusts. In subacute or chronic conditions, dry, scaly lesions or excoriated erythematous papules are noted.

Thickening of the skin due to chronic injury (lichenification) and fissures can develop over time. The distribution of these lesions is determined, among other factors, by the age at which symptoms present. Individuals under two years of age, in general, have greater involvement of the extensor surfaces of the limbs, scalp and malar region. However, children over 2 years of age develop injuries to the flexor face (such as antecubital and popliteal fossae), in addition to ankles, wrists and neck [4].

Currently, the diagnosis of the disease is established by the criteria established by "The United Kingdom Working Group". A mandatory criterion added to three or more major criteria confirms the disease [5,6]:

a) Mandatory criterion:
   i) Evidence of itchy skin, including reports from parents or guardians of children scratching themselves.
b) Greater criteria:
   i) i) History of injuries in flexural regions, including antecubital fossa, popliteal fossa, neck, periorbital region and anterior surface of the ankles;
   ii) History of asthma or allergic rhinitis (or history of atopic disease in a first-degree relative for children under 4 years of age);
   iii) History of dry skin in the last year;
   iv) Visible dermatitis on flexor surfaces. For children under 4 years of age, this criterion is replaced by visible dermatitis on the malar regions, forehead and extensor surface of the limbs;
   v) Onset of symptoms before 2 years of age. This criterion is not used for diagnosis in children under 4 years of age.

Classifying the severity of the disease is also an important part of the management of these patients, as it is a determining factor in the choice of treatment. This classification is best established through scores, with SCORAD (Scoring Atopic Dermatitis) being the most widespread currently. It is a score based on the analysis of the extent of the lesions (A), their characteristics (B) and subjective symptoms (C). The extent of the lesions is determined through the percentage of body area affected by the disease. The characteristics considered include erythema, excoriation, lichenification, papules, exudation or crusts and xerosis, for each of which a score of 0 to 3 is established, depending on the degree of intensity. Finally, symptoms (C) correspond to itching and nocturnal awakenings, both classified subjectively, on a scale of 0 to 10 by the patient himself. The scores are included in the formula (A/5 + 7B/2 + C), with a result of less than 25 points being classified as mild disease, 25 to 50 as moderate and a result greater than 50 as severe [6].

Although still unknown, the etiology of the disease is multifactorial and appears to involve environmental factors (such as diet, exposure to tobacco and pollutants), genetic and immunological factors. Among the genetic factors, mutation of the filaggrin gene (FLG) is the most associated with AD. FLG is one of the proteins responsible for maintaining the integrity of the skin by ensuring the union of keratin molecules in the stratum corneum of the epidermis. Deficiency in the production of this agent, therefore, leads to dysfunction in the epidermal barrier, and, ultimately, local dehydration and greater penetration of allergens.

As for immunological mechanisms, exposure to allergens is responsible for triggering an immune response, which in individuals with AD occurs anomalously. The innate immune response must rely on the action of Toll Like receptors (TLR), which in turn, would act to reinforce the intercellular junction, reducing the penetration of these agents. However, in atopic patients specifically, TLR dysfunction is observed. Furthermore,

in AD, even in areas of healthy skin, local infiltration by T lymphocytes is noted, demonstrating an exacerbated inflammatory response, also responsible for part of the disease's symptoms. Among other findings, patients also present a predominance of T-helper 2 (Th2) cells in relation to T-helper 1 (Th1) and high levels of immunoglobulin E (IgE) [4,6].

Part of the immunological imbalance seems to be justified by the inappropriate development of the intestinal microbiota. Both the innate and acquired responses require early microbial exposure for their complete maturation. Allergic diseases, including AD, appear to be associated with late microbial exposure. Therefore, the use of probiotics, by restoring the intestinal microbiota, has been the subject of studies due to its therapeutic and prophylactic potential for AD [7].

DESCRIPTION OF THE INTERVENTION

Probiotics, as defined by the World Health Organization, comprise "live microorganisms that, when administered in adequate quantities, confer benefits to the patient's health" [8]. In studies carried out with rodents, for example, late colonization of the intestinal microbiota was associated, among other outcomes, with impaired development of gut-associated lymphatic tissue (GALT) [7]. The early consumption of probiotics, therefore, correlates with the correct maturation of the immune system, with the suppression of the Th2-mediated response being one of its possible effects.

This finding is especially relevant in the context of AD, which results, among other factors, from an imbalance in the immunological response, with a predominance of Th2 cells in relation to Th1 cells.

Therefore, in view of this scenario, several studies have been developed in order to clarify the immunomodulatory effects of probiotics, especially in patients with AD.

In a double-blind trial, 230 infants diagnosed with AD associated with suspected cow's milk allergy were separated into groups in which they received, for four weeks, in a randomized manner, Lactobacillus GG (LGG), a mixture of 4 strains of probiotics or placebo. The results suggest that IgE-sensitized individuals may be more likely to benefit from probiotic use. A reduction of 38.4 points in SCORAD was observed in patients with moderate to severe AD (SCORAD >= 30) who received LGG, compared to those who received placebo (reduction of 28.5 points; p=0.008) [9].

A systematic review with meta-analysis, which included 25 randomized clinical trials (RCTs), showed that there was a significant difference in the reduction of SCORAD values, (mean reduction of 4.51 points; CI = [-6.78;-2.24]) for patients who received probiotic treatment when compared to the placebo group. It is worth mentioning that, when evaluating the age groups separately, it is noted that the effect of treatment on SCORAD was statistically significant in the group of children between 1 and 18 years old (-5.74; CI [-7.27; -4. 20]; p < 0.00001). On the other hand, there was no difference between the use of probiotics and placebo among children under 1 year old (0.52; CI [-1.59;2.63]) [10].

Regarding the primary prevention of AD, despite controversial results in the literature, some studies reveal a reduction in the incidence of the disease with the use of probiotics by pregnant women, especially Lactobacillus GG (LGG), in the prenatal period, associated only with use in the postnatal period, by the patient himself [11]. A systematic review published in 2013 by the University of California, which mostly included randomized clinical trials,

showed a protective effect of the use of LGG in the pre- and postnatal periods, with a relative risk (RR) of 0.51 (CI 95% [0.32-0.84]) on the incidence of the disease [12]. At the same time, another systematic review with meta-analysis that analyzed fifteen RCTs, totaling 3,495 individuals, also revealed a reduction in AD rates among those who received probiotics in the pre- and postnatal periods (OR = 0.54, CI [0.5–0. 59], p = 0.0001), [13]. In contrast, a randomized clinical trial, whose intervention included the administration of a probiotic formulation in pregnant women from the 36th gestational week until delivery, and then, in newborns up to 6 months of age, did not demonstrate a reduction in the frequency of atopic dermatitis in children, up to 2 years of age (OR 1.07, 95% CI [0.72 - 1.6]; p =0.71) [14].

The evidence is even more controversial and scarce when it comes to the use of probiotics only after birth. The same systematic review that showed a reduction in the incidence of AD with pre- and post-natal use of the formulation, did not demonstrate the same result with its use only in the post-natal period (OR = 0.89; 95% CI [0.59–1.35]; p = 0.59) [13]. Likewise, another double-blind RCT that proposed the administration of LGG up to 6 months of age in children at high risk for atopy did not show a protective effect of the probiotic after 2 years of follow-up (HR = 0.95; 95% CI [0.59 - 1.53]; p = 0.83) [15].

However, a Danish randomized clinical trial showed that among all the children who developed atopic dermatitis during the study, around 74% of them were in the placebo group. The remaining 26% of the intervention group received a mixture of LGG +*Bifidobacterium animalis subsp lacti* daily, during the first 6 months of life, configuring a relative risk (RR) for developing the disease of 0.37 (95% CI [0.14-0.98]; P=0.036) [16].

WHY IS THIS REVIEW IMPORTANT?

Currently, AD treatment consists of a range of pharmacological and non-pharmacological measures, whose indications vary according to the severity of the disease. However, universally, its management is based on protecting and hydrating the skin, controlling symptoms and reducing recurrence rates. Therefore, the daily use of moisturizers and emollients, cessation of exposure to agents that trigger exacerbations, education of the patient and their family, in addition to the use of topical corticosteroids are measures used for patients at all levels of the disease. [17,18].

For those with symptoms of moderate to severe intensity, topical calcineurin inhibitors (such as tacrolimus) as well as phototherapy are alternatives. In patients with more severe conditions or those refractory to initial treatments, it may be necessary to resort to systemic therapies such as corticosteroids, cyclosporine, methotrexate, azathioprine and some monoclonal antibodies (among them, dupilumab) [17].

Despite being a disease that predominantly affects children and adolescents, only around 40 to 60% of patients experience remission of AD after puberty, and even among these cases, some may still experience exacerbations during adulthood [19,20]. AD is not a disease associated with high mortality rates, but itching, pain, visible skin lesions and side effects of pharmacological treatments are responsible for the extensive impact on the quality of life of these individuals [21]. Low self-esteem, shame, stress and insecurity are feelings frequently reported by patients, having a negative impact on their social life and academic and professional performance[20,21].

Furthermore, the presence of the disease is associated, both in the adult and pediatric populations, with a higher incidence of major depressive disorder and anxiety disorders[22-26]. Suicidal ideation and suicide attempts are also

more prevalent in these patients, and some studies reveal that the occurrence of all these outcomes is proportionally greater depending on the severity of AD [25-27].

In addition to the social and psychological consequences, the impact of atopic dermatitis also extends to the organic sphere. Skin infections, herpetic atopic dermatitis, anemia and eye diseases (such as keratoconjunctivitis, for example) are among the possible complications of the disease. At the same time, drug treatment is responsible for a large part of the morbidity of this population, and can lead, depending on the drug, to immunosuppression, liver, kidney and adrenal dysfunction, skin atrophy, hypertension, nausea, and even, despite still controversial evidence, the majority lymphoma risk.

Considering this complex scenario involving a patient diagnosed with atopic dermatitis, added to the still inconclusive and scarce evidence regarding prevention measures for the disease, the study regarding primary prophylaxis of this pathology becomes essential.

OBJECTIVES

The objective of this study is to summarize the evidence regarding the effect of the use of probiotics by children up to 5 years of age on the incidence of atopic dermatitis in this population.

METHOD

CRITERIA FOR SELECTING STUDIES

This systematic review was prepared in accordance with the specifications of Cochrane Review Manager 5.4.1. The selected articles comprise those with level I to III evidence design, therefore including systematic review, randomized clinical trial and cohort. Articles from any language and all publication dates present on the analyzed platforms were considered, until the year 2023.

The inclusion criteria for selecting the studies were:

(1) Age group: intervention/exposure and outcome evaluated in children up to 5 years of age - age group which comprises the highest incidence of disease diagnosis;

(2) Risk for developing AD: intervention/exposure evaluated in children both at high risk for developing the disease and with habitual risk. High risk defined as presence of first-degree family members with a history or current diagnosis of allergic rhinitis, asthma, AD or food allergy.

The intervention evaluated was probiotic supplementation, according to the WHO definition [8], for children in the determined age group. The articles must evaluate as one of their outcomes the incidence of atopic dermatitis in this population after the intervention, with the diagnosis of the disease being established according to the criteria required by "The United Kingdom Working Party"[5].

SEARCH FOR STUDIES IN DATABASES

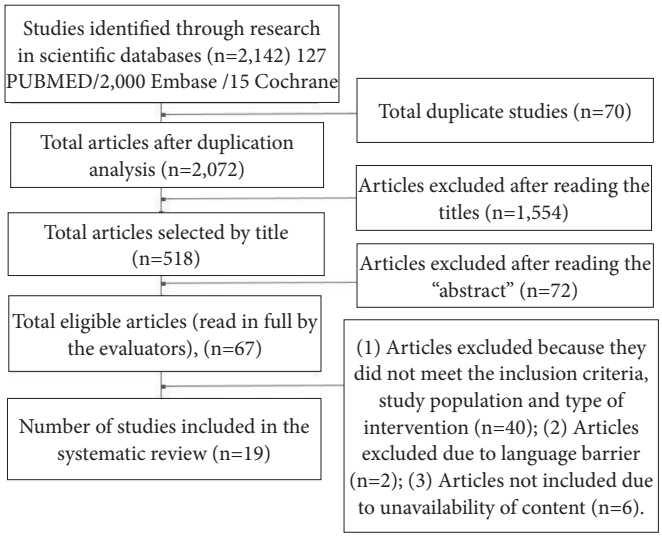
The PubMed, Embase and Cochrane Library platforms were used. For PubMed, the search strategy included the terms: ("Eczema" [Mesh] OR "Dermatitis, Atopic" [Mesh]) AND "Probiotics" [Mesh], in addition to ("Eczema" [Mesh] OR "Dermatitis" [Mesh]) AND "Probiotics" [Mesh], associated with the design and population filters, according to the eligibility criteria explained above. There were 127 and 95 articles, respectively. Titles were compared and duplications were excluded, ultimately resulting in 127 articles.

For searches on the Embase and Cochrane Library platforms, the following terms were used: "dermatitis", "atopic dermatitis" or "atopic dermatitis" and "probiotics", totaling 2,000 and 15 articles, respectively. All titles found were also reviewed and compared to

those previously selected on the PubMed platform, leading to the exclusion of 70 duplications. At the end of the search, on the three platforms, 2,142 articles were selected.

All titles and abstracts were analyzed individually by the authors (L.C, N.M. and B.F), choosing only those that met the eligibility criteria. Subsequently, the studies were compared and differences were discussed together, resulting in 66 articles. These were assessed again by reading the texts in full. Forty-eight were excluded, 40 of these because they did not fit the inclusion criteria, study population and type of intervention; 6 of these were due to the non-availability of the full articles; and 2 of these due to the language barrier. Finally, for the preparation of this systematic review, 19 studies were considered eligible (Flowchart 1).

Some of the main reasons for exclusion included: (1) intervention carried out in the prenatal period (by the pregnant woman), (2) SCORAD classification as the primary outcome analyzed and (3) intervention only with the use of prebiotics and/or synbiotics.



ASSESSMENT OF THE QUALITY OF STUDIES

The quality of the studies and the risk of bias were assessed by the authors (L.C, N.M. and B.F) using the "Critical Appraisal Skills Program" (CASP) tool and were summarized in the following tables.

In **Table 1**, the CASP tool for Randomized Clinical Trials was used. A score of 0-4 classifies the study as low quality, 5-8 as medium quality and 9-11 as high quality. In **Table 2**, the CASP for Systematic Reviews was used. A score of 0-3 constitutes a low-quality study; 4-6 medium quality and 7-9 high quality. Finally, **Table 3** summarizes the evaluation of cohort studies. Scores of 0-4, 5-7 and 8-10 classify studies as low, medium and high quality, respectively.

RESULTS

Data from the selected articles are compiled in **Table 4**. The results presented refer to the incidence of atopic dermatitis after the use of probiotics in childhood. Other information such as study methodology, number of participants and type of intervention are also highlighted.

Among the nineteen studies analyzed, thirteen showed no effect of the use of probiotics on the incidence of atopic dermatitis in children. The "Sun,2021" study, a systematic review with meta-analysis that included nine RCTs, totaling 2,093 children, showed a relative risk of 0.63 for the development of the disease in patients using probiotics in the postnatal period, but did not present any findings statistically significant (p=0.29). Another meta-analysis ("Jiang, 2020"), when analyzing 25 RCTs (3,049 children), obtained a relative risk of 0.88, however with a 95%CI (0.59-.133) and p=0.56 (p>0.05). The RCT "Soh, 2009", containing 253 patients, demonstrated a similar incidence of AD between the intervention group, composed

ECR	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	*Score*	Study quality	Yes (S)
Schimdt, 2019	S	S	S	S	S	S	S	S	N	S	NE	9	High	Not (N)
Cabana, 2017	S	S	S	S	S	S	S	S	S	N	S	10	High	Not Specified (NE)
West, 2009	S	S	S	S	S	S	S	S	S	S	NE	10	High	
Soh, 2009	S	S	S	S	S	S	S	N	N	S	NE	8	Medium	
Taylor, 2007	S	S	S	NE	S	S	S	S	S	S	NE	9	High	

Table 1. P1 –Were the inclusion criteria clear; P2 –There was randomization of the groups analyzed; P3 –Was the exposure measured appropriately? P4 –What was the outcome?; P5 –Were the groups treated equally?; Q6 –Were all patients who entered the study properly accounted for at the end of the study? P7 –Was the result of the proposed treatment for the primary outcome important; P8 –Are the results statistically significant? P9 –Can the results be applied to the local population? P10-Were all important outcomes considered? Q11-Do the benefits outweigh the harms and costs?

SYSTEMATIC REVIEW	P1'	P2'	P3'	P4'	P5'	P6'	P7'	P8'	P9'	*Score*	Study quality	Yes (S)
Sun, 2021	S	S	S	S	S	S	S	N	S	8	High	Not (N)
Li, 2018	S	S	S	S	N	S	S	S	S	8	High	Not Specified (NE)
Cuello-Garcia, 2015	S	S	N	S	S	S	NE	S	NE	6	Medium	
Mansfield, 2014	S	S	S	S	N	S	S	S	S	8	High	
Panduru, 2014	S	S	S	S	S	S	S	N	S	8	High	
Pelucchi, 2012	S	S	S	S	S	NE	NE	N	S	6	Medium	
Osborn, 2007	S	S	S	S	S	S	S	S	NE	8	High	
More, 2021	S	S	NE	S	NE	NE	N	S	NE	4	Medium	
D'Elios, 2020	N	S	S	NE	NE	NE	NE	S	NE	3	Low	
Jiang, 2020	S	S	S	NE	N	S	NE	S	NE	5	Medium	
Sun, 2021	S	S	S	S	S	S	S	S	S	9	High	
Reynolds, 2019	S	S	S	S	N	S	S	S	S	8	High	
Cao, 2015	S	S	S	S	S	S	S	N	S	8	High	

Table 2. P1-Are the inclusion criteria clear?; P2-Was the selection of studies done appropriately?; Q3-Were all relevant studies included?; Q4-Did the author carry out a good evaluation of the studies included? Q5-Combining the results of the review, was it reasonable to do them? Q6-Are the results accurate? P7 –Can the results be applied to the population? P8 –Were all important outcomes considered? P9 –Do the benefits outweigh the harms and costs?

COORTE	P1	P2	P3	P4	P5 (A)	P5 (B)	P6 (A)	P6 (B)	P7	P8	P9	P10	*Score*	Study quality	Yes (S)
Loo, 2023	S	S	S	NE	N	S	S	NE	N	N	S	S	7	Medium	Not (N)
															Not Specified (NE)

Table 3. P1-Is the objective of the study clear?; P2 –Was there randomization of the observed groups?; P3 –Was the exposure measured in a way to minimize bias?; P4 -Was the outcome measured in a way to minimize bias?; P5(A) –Did the authors identify all confounding factors?; P5(B) –Were confounding factors taken into account in the study analysis?; P6(A) –Were all patients who entered the study properly accounted for at the end of the study? P6(B) –Was the patient follow-up time adequate? P7 –Are the results statistically significant? P8 –Were all important outcomes considered? P9 –Can the results be applied to the local population? Q10 –Were the results of this study similar to previous studies?

Study (author/ year/country)	Methodology	Participants (I: intervention/ C: control)	Intervention	Primary outcome	Result
Sun, 2021 (China)	Meta-analysis: includes 9 RCTs	2093 patients (1051 I/ 1042 C)	Mixture of lactobacilli + *bifidobacterium (Lactobacillus GG + B. longum and L. paracasei) + B. longum*	Incidence of AD.	The intervention was carried out only in the postnatal period and had no protective effect (RR 0.63; I^2 63% and p = 0.29).
Schmidt, 2019 (Denmark)	ECR	285 children. (13 I/12 C)	Daily supplementation for 6 months of 1.0g maltodextrin sachets associated with LGG and BB-12, each with a dose of 10^9 colony forming units (CFU)	Incidence of allergic diseases during the intervention period, incidence of sensitization, for example: ImmunoCAP® Phadiatop® test with specific IgE ≥0.35 PAU/L at the end of the intervention, and the incidence of food reactions during the intervention period.	A total of 19 children developed atopic dermatitis during the intervention period; 5 (4.2%) in the intervention group and 14 (11.5%) in the control group (p = 0.036), corresponding to a relative risk of 0.37 (95% CI 0.14–0.98).
Li, 2018 (China)	Systematic review with meta-analysis: 27 RCTs and 1 controlled cohort	6,907 children (3,595 I/ 3,312 C)	Lactobacillus, Bifidobacterium, and Propionibacterium were used as interventions in 15, 16, and 3 studies, respectively. Probiotics used: (1) Lactobacillus, L. rhamnosus, L. reuteri, L. paracasei, L. acidophilus; (2) Bifidobacterium, B. lactis; (3) B. lactis; (4) B. longum; (5) B. bifidum; (6) B. brief; (7) Propionibacterium.	Incidence of AD	The use of probiotics during the prenatal and postnatal period reduced the incidence of AD (OR 0.67; 95% CI 0.54–0.82); however, studies with only postnatal intervention (OR 0.77; 95% CI 0.59–1.01) and studies with prenatal intervention (OR 0.66; 95% CI 0.37–1. 15) did not show a statistically significant decrease in the risk of AD.
Cabana, 2017 (EUA)	ECR	184 children (92 I/ 92 C)	Supplementation with 10 billion colony forming units (CFU) of LGG and 225 mg of inulin in the first 6 months of life. The supplement must be dissolved in 2 ml of expressed breast milk, infant formula or water.	Incidence of AD up to 2 years of age.	At 2 years of age, the estimated cumulative incidence of atopic dermatitis was 30.9% (95% CI, 21.4% – 40.4%) for the control group and 28.7% (95% CI, 19.4 – 38.0%) for the intervention group. For the group that received LGG, HR of 0.95 (95% CI, 0.59 - 1.53) (log-rank p = 0.83).

Cuello-Garcia, 2015 (EUA)	Systematic Review with Meta-Analysis: 29 RCTs, 7 of which evaluated only intervention in childhood.	1,217 children	Probiotic supplementation without limitation of species, formulation, composition or dose. Administered to pregnant and/or lactating women and/or infants.	Allergy prevention: eczema, asthma and/or wheezing, food allergy, allergic rhinitis, adverse effects and serious adverse effects.	Evaluating the studies in which the intervention was carried out only in the postnatal period, an RR of 1.67 was obtained; 95% CI [0.98 - 2.92] in preventing AD.
Mansfield, 2014 (EUA)	Systematic review with Meta-Analysis: 27 articles (16 RCTs)	2,797 children	Probiotic supplementation during pregnancy and childhood. Use of individual probiotics and probiotic mixtures (including 2 or more probiotics in a supplement) was analyzed.	Development of AD.	Supplementation in children reduces the risk of developing atopic dermatitis: RR 0.74 (95% CI 0.67-0.82). *The number of studies with only postnatal supplementation was small, limiting the statistical power of the comparison.
Panduru, 2014 (Romania)	Systematic Review with Meta-Analysis: 16 studies	Not mentioned	Probiotics administered in the pre- and/or post-natal periods (to breastfeeding mothers or directly to newborns)	Development of AD (diagnosed by a doctor).	In the intervention only in the postnatal period, in relation to the incidence of AD compared with placebo, an OR = 0.89 was obtained; [95% CI = 0.59–1.35]; p = 0.59.
Loo, 2013 (Singapore)	Coorte	220 children completed the study.	Administration of cow's milk supplemented with probiotics, from the first day of life to the 6th month.	Long-term effects on allergic outcomes in children aged 5 years.	Probiotic supplementation did not lead to the prevention of allergic diseases: RR 0.8 95% CI (0.5-1.3), between 1 and 2 years of age; RR 0.9 95% CI (0.6-1.4), for 3 years of age; RR 0.8 95% CI (0.6–1.3), for 4 years; and RR 0.8 95% CI (0.5–1.2), at 5 years of age.
Pelucchi, 2012 (Italy)	Systematic Review with meta-analysis: 18 studies (4 with postnatal intervention only)	663 children (328 I/ 335 C)	Supplementation with probiotics compared to the use of placebo (control group).	Incidence of AD and IgE-associated AD.	In the intervention only in the postnatal period, in relation to the incidence of AD, a RR of 0.85 CI95% (0.61–1.19) was obtained; I^2 32%; P= 0.38.

West, 2009 (Swede)	ECR	171 children (84 I/ 87 C)	Daily consumption of cereals supplemented with probiotics (10^8 CFU of LF19).	Cumulative incidence of AD at 13 months of age. Incidence of asthma, allergic rhinoconjunctivitis, IgE concentration and cytokine mRNA expression level were secondary outcomes.	The incidence of AD was 9/84 ([11%] CI95% [4–17%]) in the intervention group and 19/87 ([22%] [CI95% 13–31%]) in the placebo group (p = 0.049). NNT = 9 (95%CI 6.5–11.5). In a patient at high risk for developing atopy, the incidence was 6/55, ([11%] [95%CI 2–19%]) in the intervention group and 14/53, ([26%] [95%CI 14–39%]) in the placebo group (p = 0.038).
Soh, 2009 (Singapore)	ECR	253 children (with a family history of allergic diseases)	Consumption of 60 mL/day of cow's milk supplemented with probiotics (Bifidobacterium longum 107 UFC + Lactobacillus rhamnosus 2 x 108 UFC).	Incidence of AD.	OR: 0.8 [95%CI: 0.4–1.5], with similar incidence of eczema in the intervention (22%) and placebo (25%) groups.
Taylor, 2007 (Australia)	ECR	178 children (89 I/ 89 C)	Maltodextrin supplemented with 3 x 10^9 *L. acidophilus LAVRI-A1,* administered from birth to 6 months of age.	Incidence of AD, food allergy and/or sensitization to allergens.	At 6 months of age, incidences of AD were similar between the intervention group (23/89; 25.8%) and placebo (20/88; 22. %); p = 5.629. At 12 months, there was also no statistically significant difference between incidence rates (p = 5.581)
More, 2021 (EUA)	Systematic Review: 37 RCTs and 1 open trial	Not mentioned.	Lactobacillus rhamnosus (GG, HN001, LPR, LC705) (n=17); L. acidophilus (La-5, LAVRI-A1, AD031), L. paracasei (ST11, ssp. paracasei F19) (n=4); L. reuteri ATCC 55730 (n=2); Lactococcus lactis W58 (n=1), B. animalis (ssp. lactis Bb-12, ssp. lactis HN019) (n=5); B. lactis (HN019, Bb-12, AD011, W52) (n=4); B. longum (BL999, BB536) (n=5); B. breve (Bb99, M16-V) (n=2); B. bifidum (BGN4, W23) (n=2), and Propionibacterium freudenreichii spp. shemani JS (n=1). The duration of the intervention varied between 6 months (n=5), 12 months (n=2) and 24 months (n=1).	Cumulative incidence of AD, asthma and/or allergic rhinitis, severity of AD (SCORAD) and rate of sensitization to allergens.	In general, postnatal use alone did not show a protective effect. Only 3 of 7 studies (43%) that addressed postnatal use of probiotics showed any benefit of the intervention in reducing AD rates.

D'Elios, 2020 (Italy)	Systematic review	Not mentioned.	*Lactobacillus GG* (10^{10} CFU/day) from birth to 6 months of age; or *LGG + B animalis subsp lactis BB-12* (both at a dose of 10^9 CFU).	Incidence of AD; AD severity (SCORAD).	The use of *Lactobacillus* GG did not show a protective effect on the incidence of AD. Using LGG + B animalis subsp lactis BB-12, a significantly low incidence of atopic dermatitis was observed in the intervention group (4.2%).
Jiang, 2020 (China)	Systematic Review with Meta-Analysis: 25 studies (RCT), 14 of which were on prevention	3,049 children	*L. acidophilus LAVRI-A1; Bifdobacterium longum (BL999) + L. rhamnosus (LPR); or Lactobacillus GG.*	Incidence of AD; AD severity (SCORAD).	In the intervention only in the postnatal period, in relation to the incidence of AD, a RR of 0.88 was obtained; 95%CI (0.59–1.33); P =0.56; I^2 =74%.
Osborn, 2007 (Austráaia)	Systematic review	Not mentioned	Probiotics (L. acidophillus; L. johnsonii; L. reuteri; L. rhamnosus; mix of Bifidobacteria infantis, Streptococcus thermophilus, and Bifidobacteria bifidus) associated with human milk or infant formula, added in the manufacturing process or supplied separately, compared to the control (placebo or no treatment).	Prevalence of allergic diseases, including AD, asthma, rhinitis and food allergies.	The use of Lactobacillus rhamnosus GG showed a reduction in the incidence of AD (RR 0.82; 95% CI 0.70-0.95). But with significant heterogeneity (p = 0.03) and (I^2 = 63.6%).
Sun, 2021 (China)	Systematic review with meta-analysis: 19 studies.	4,011 children (2014 I/ 1997C)	It included articles that compared the use of just one probiotic and articles that compared the use of a mixture of probiotics.	Incidence of AD, asthma, allergic disease, rhinitis and wheezing. (17 studies dealt with AD)	OR = 0.73 [95% CI 0.41–1.3], p = 0.28) regarding the incidence of AD after the use of probiotics compared to placebo.
Reynolds, 2019 (EUA)	Systematic review	Not mentioned.	Use of probiotics, polyunsaturated fatty acids, omegas -3, -6 or -7, selenium, zinc, vitamin D or vitamin E.	Incidence of AD and severity of AD (SCORAD)	In an evaluated meta-analysis, which included 10 RCTs, postnatal probiotic supplementation was effective in preventing AD with effect sizes between 0.69 (0.57 and 0.83) and 0.66 (0.49 and 0.89).
Cao, 2015 (China)	Systematic Review with Meta-Analysis: 6 studies	1,955 patients	Use of LAVRI-A1 up to 6 months of age; LF19 from 4 to 13 months of age; or BL999 + LPR up to 6 months of age	Incidence of AD.	RR = 0.98 (95% CI 0.73-1.31), p = 0.89).

TABLE 4

of children who consumed cow's milk (22%), and the placebo group (25%)

Another six studies, however, showed a protective effect of th Studies identified through research in scientific databases (n=2,142) 127 PUBMED/2,000 Embase /15 Cochrane e intervention. (Schmidt 2019, West 2009, Mansfield 2014, D'Elios, 2020, Osborn 2007, Reynolds 2019). In the RCT "Schmidt, 2019", which included 285 participating children, daily supplementation of LGG and BB-12 for 6 months resulted in a RR of 0.37 for the development of AD (95%CI 0.14-0.98; p=0.036). In the intervention group, an incidence of 4.2% was observed, while in the control group the rate of AD was higher (11,5%).

In the systematic review "D'Elios, 2020", the administration of two types of probiotics (*LGG + Animalis subsp lactis BB-12*) from birth to 6 months of age showed a protective effect compared to the isolated use of LGG. In "West, 2009", the use of Lactobacillus F19 during the fourth and 13th month of life reduced the incidence of AD from 22% to 11% (p< 0.05).

DISCUSSION

Despite still controversial evidence regarding the prophylactic and therapeutic potential of probiotics in AD, their immunomodulatory action added to the influence of the intestinal microbiota in the regulation of allergic diseases seemed to guarantee biological plausibility for many of the results found in the medical literature.

In addition to some studies demonstrating the possibility of controlling AD symptoms through the consumption of probiotics (assessed by the reduction in SCORAD) [10], many studies on preventive measures also showed a reduction in the incidence of AD in patients who used the component in the prenatal period (by the pregnant woman) followed by use in the postnatal period, by the patient himself [11-13].

However, in the present study, the use of probiotics only during early childhood did not demonstrate a preventive effect on AD. Among the 19 articles analyzed, only six of them showed a reduction in the incidence of the disease, while the other studies did not show a statistically significant difference for this outcome.

Furthermore, even among the studies that corroborate the protective effect of the intervention, as is the case of "Mansfield 2014" and "Osborn 2007", a restricted sample size and high heterogeneity are observed, compromising its external validity, which is not observed in other studies that corroborate the null hypothesis. The systematic review "Li, 2018", for example, which contains the largest sample number among the included studies (6,907 patients) showed that the intervention carried out only in the postnatal period did not show a statistically significant decrease in the risk of AD (OR 0. 77; 95% CI 0.59–1.01).

It is also worth mentioning that the present study aimed to evaluate the effect of the class of probiotics on the risk of developing AD. Therefore, the analysis of the different subtypes of this element was not part of the inclusion criteria. As evidenced in Table 4, each study included a different species or combination of species as an intervention.

On the other hand, the study provided an update on the methods available for AD prophylaxis, based on robust data research on different platforms. The studies included, analyzed using the CASP ("Critical Appraisal Skills Program") tools, generally presented a low risk of bias, which favors the findings found in this review.

SUGGESTION FOR FUTURE STUDIES

In view of the above, there is a need for new studies that evaluate the effect of different subtypes of probiotics in preventing the development of atopic dermatitis in children. In addition, possible future studies to define more targeted approaches for the different moments in which the intervention is applied, including the pre- and post-natal period, which proved to be a promising proposal for the primary prophylaxis of AD in children.

CONCLUSION

Based on this systematic review, probiotic supplementation for children from birth to 5 years of age did not prove to be an intervention with a protective effect on the incidence of atopic dermatitis.

Therefore, it is not possible to say with certainty about the effectiveness of its use and the external validity of this intervention. Future studies are needed to address this question and corroborate new prophylaxis and treatments for this pathology.

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