



Revisión

Effect of the use of probiotics in the treatment of children with atopic dermatitis; a literature review

Ingrid Pillar Nascimento da Costa Baptista¹, Elizabeth Accioly² and Patricia de Carvalho Padilha³

¹Nutricionist. Specialist in Clinical Nutrition. Instituto de Nutrição Josué de Castro (INJC). Universidade Federal do Rio de Janeiro (UFRJ-Federal University of Rio de Janeiro). ²Professor of the Department of Nutrition and Dietetics from Instituto de Nutrição Josué de Castro (INJC). Universidade Federal do Rio de Janeiro (UFRJ-Federal University of Rio de Janeiro). Grupo de Pesquisa em Saúde Materna e Infantil (GPSMI-Research group in Maternal and Infant Health). Núcleo de Pesquisa em Micronutrientes (NPqM-Micronutrients Research Center). ³Professor of the Department of Nutrition and Dietetics from Instituto de Nutrição Josué de Castro (INJC)-Universidade Federal do Rio de Janeiro (UFRJ-Federal University of Rio de Janeiro). Grupo de Pesquisa em Saúde Materna e Infantil (GPSMI-Research group in Maternal and Infant Health). Núcleo de Pesquisa em Micronutrientes (NPqM-Micronutrients Research Center).

Abstract

Introduction: Atopic dermatitis (AD) is a disease that mainly affects the pediatric population involving chronic and repetitive inflammatory skin manifestations. Its evolution is known as atopic march, which is characterized by the occurrence of respiratory and food allergies.

Aim: To carry out a classical review of the state-of-the-art scientific literature regarding the effect of probiotics on the treatment of children with AD.

Methods: Searches were conducted in Medline and Lilacs through the portals PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>) and SciELO (<http://www.scielo.br>). There was a selection of the available publications in the period from 2001 to 2011, using the keywords atopic dermatitis and probiotics (in English and in Portuguese).

Results: After applying the inclusion and exclusion criteria, we selected 12 case-control studies which were conducted in four European countries and Australia. The methodological quality of the studies was assessed according to the STROBE recommendations. Assessment of agreement among researchers in classifying the quality of the articles showed excellent agreement ($k = 1.00, 95\%$) with a total of 9 papers at B level. The majority of the studies (75%) indicated a beneficial biological effect of probiotics on AD, including protection against infections, enhancement of the immune response, inflammation reduction and changes in gut the flora. The remaining studies showed no beneficial effects according to the outcomes of interest.

Conclusion: The majority of the studies in the scientific literature in this review showed improvements in some inflammatory parameters and in intestinal microbiota and not exactly, changes in clinical parameters. However, the biological effects observed in most of them suggest the possibility of benefits of the use of probiotics as an adjuvant in the treatment of AD.

(Nutr Hosp. 2013;28:16-26)

DOI:10.3305/nh.2013.28.1.6207

Key words: Atopic dermatitis. Alergy. Probiotics.

Correspondence: Ingrid Pillar Nascimento de Costa Baptista.
Instituto de Nutrição Josué de Castro.
Centro de Ciências da Saúde. Universidade Federal do Rio de Janeiro.
E-mail: ipillar@ig.com.br

Recibido: 2-VIII-2012.
1.ª Revisión: 27-IX-2012.
Aceptado: 23-X-2012.

EFEECTO DEL USO DE LOS PROBIÓTICOS EN EL TRATAMIENTO DE NIÑOS CON DERMATITIS ATÓPICA; REVISIÓN BIBLIOGRÁFICA

Resumen

Introducción: La dermatitis atópica (DA) es una enfermedad que afecta principalmente a la población pediátrica, la participación de crónica y repetitiva inflamatoria de la piel la evolución manifestaciones. Its se conoce como marcha atópica, que se caracteriza por la aparición de alergias respiratorias y la alimentación.

Objetivo: Realizar una revisión sistemática de la literatura del estado de la técnica científica sobre el efecto de los probióticos en el tratamiento de niños con DA.

Métodos: Se realizaron búsquedas en Medline y Lilacs a través del PubMed portales (<http://www.ncbi.nlm.nih.gov/pubmed/>) y SciELO (<http://www.scielo.br>). Había una selección de las publicaciones disponibles en el período comprendido entre 2001 y 2011, con la dermatitis atópica palabras clave y los probióticos (en inglés y en portugués).

Resultados: Después de aplicar los criterios de inclusión y exclusión, se seleccionaron 12 estudios caso-control que se realizaron en cuatro países europeos y Australia. La calidad metodológica de los estudios se evaluó de acuerdo a las recomendaciones STROBE. Evaluación de un acuerdo entre los investigadores en la clasificación de la calidad de los artículos mostraron una excelente concordancia ($k = 1,00, IC del 95\%$) con un total de 9 trabajos en el nivel B. La mayoría de los estudios (75%) indica un efecto beneficioso de los probióticos en DA, incluida la protección contra las infecciones, la mejora de la respuesta inmune, la reducción de la inflamación y cambios en la flora intestinal, la mejora de la condición clínica de la EA. Los estudios restantes no mostraron efectos beneficiosos de acuerdo a los resultados de interés.

Conclusión: La mayoría de los estudios en la literatura científica, en el período estudiado, mostró evidencia de beneficios en el uso de probióticos para controlar las manifestaciones clínicas de la DA, sin embargo el costo/beneficio del tratamiento siempre debe ser evaluada.

(Nutr Hosp. 2013;28:16-26)

DOI:10.3305/nh.2013.28.1.6207

Palabras clave: Dermatitis atópica. Alergia. Probióticos.

Introduction

Atopic Dermatitis (AD) is considered a chronic inflammatory disease that affects the skin, and that can precede asthma and other allergic manifestations, sparking the Atopic March.¹ All age groups are affected, and among infants and children the acute form of the disease is predominant, with the presence of erythema, severe itching and oozing blisters that, in general, appear on the scalp, face and on the extending surfaces of the superior and inferior members.²

The pathogenesis of the disease is not fully understood, but studies indicate that the interaction between genetic and environmental factors leads to the development of the disease.³

It is estimated that the prevalence of the disease among children under four years old is approximately 14%.⁴ There are records indicating an increasing prevalence of the disease in the last three decades.⁵ According to Castro et al.⁶ about 50% of the patients present AD in the first year of life. The diagnosis of the disease is based on clinical criteria, as proposed by Hanifin & Rajka⁷, in 1980, which involves the patient's clinical history and physical examination of the affected regions. There are no specific laboratory tests for the detection of the disease.⁸

AD is classified according to degrees of severity based on the SCORAD index, which punctuates the extent and intensity of the dermatitis, the itching magnitude and the sleeping disturbances.⁹ The basic treatment for AD is to promote proper hydration of the skin and to control the inflammatory process with use of medications.⁶

Recently it was proposed that AD should be classified as intrinsic or extrinsic, according to its etiopathogenesis.¹⁰ Its extrinsic form, also known as allergic, affects 70 to 80% of patients, and is related to environmental, food and inhalant allergens sensitivity or high levels of IgE.¹⁰

Approximately 35% of children with moderate and severe forms of the disease have food allergies.¹¹ Food allergy is defined as an adverse reaction to non-toxic food and is a result of an exacerbated immunological response to protein components of food or preparation ingredients, recognized as food allergens, causing adverse health effects.¹²

The onset of food allergy may be due, among other factors, to the break of oral tolerance to the allergen. This strategy is of extreme importance to the body, because it promotes a balance between an anergic response and an effective response to strange agents.¹³ This is illustrated by the fact that, on a daily basis, we get in contact with a high number of foreign proteins that are absorbed without inflammatory signs of clinical importance and, on the other hand, the body fights pathogens which have the gastrointestinal tract as a gateway. According to Jacob et al.¹³ this process is based on nonspecific mechanisms and adaptive immunity, such as the gastric juice, peristalsis, epithelial

barrier, intestinal microbiota, IgA secretion and action of regulatory T cells, allowing the recognition of antigens, but not the amplification of the response to them.

In the case of AD there is a dysfunction of the skin barrier, which normally acts as an important site of protection against environmental allergens, microorganisms and irritant substances.¹

Clinical evidence suggests that the use of probiotics in the treatment of AD improves the clinical status of patients.^{14,15,16} Probiotics are defined as viable microorganisms that confer health benefits when administered in adequate amounts.¹⁷

The present work aims to conduct a systematic review on the state-of-the-art scientific literature regarding the effect of probiotics on the treatment of children with AD.

Materials and methods

This work was conducted in the form of a classical review with the purpose of gathering and evaluating, judiciously, the main findings of the use of probiotics in the treatment of children aged from zero to five years old with AD.

The following steps were performed:

1. *Identification of the work.* Initially, there was a selection of the available articles in the scientific literature regarding the object under study. We used as bibliographic databases sources *Medline* and *Lilacs* through the portals *PubMed* (<http://www.ncbi.nlm.nih.gov/pubmed/>) and *SciELO* (<http://www.scielo.br>), searching the available publications in the ten-year period of 2001 to 2011.

To perform the search work, the following keywords in English were used, *atopic dermatitis and probiotics* and, in Portuguese, *dermatite atópica and probióticos*.

In order to complement the discussion of the findings, textbooks and review articles about the subject were included in the study.

2. *Preliminary assessment studies.* The review was carried out following the steps of assessment proposed by The Cochrane Collaboration (www.cochrane.org).

Randomized clinical studies that employed probiotics in the treatment of children (interventional studies), from zero to five years old with AD were included in the analysis. Studies characterized as revisions, studies with animal, studies without a well defined methodology, summaries or "abstracts" and studies regarding other age groups, as well as, those using probiotics for prevention of AD were not included.

The results of bibliographic searches were screened, independently, by the main researcher and by other researchers by the titles of full publications and abstracts. After the identification of studies that met the criteria of the Cochrane Library, the complete publications selected were acquired and reviewed indepen-

dently by the authors in order to determine the eligibility to the present study.

3. *Assessment of methodological quality of work.* The methodological quality of the included publications was assessed in accordance with the recommendations of the STROBE system (Strengthening the Reporting of Observational studies in Epidemiology),¹⁸ proposed by an international collaborative group composed of epidemiologists, statisticians, researchers and publishers of scientific journals involved in the dissemination of epidemiological studies (www.strobe-statement.org), with special consideration in the selection and detection of bias and follow up losses.

Three categories for quality assessment were established: A) when the study filled out more than 80% of the criteria set out in STROBE; B) when 50%-80% of the criteria were met; C) when less than 50% of the criteria were met. The correlation of quality evaluation between evaluators was again measured by results obtained with the quality scale, using the kappa coefficient calculation (*k*, IC 95%) and the differences were resolved by consensus.

Evaluation was done taking into account the opinion of two evaluators, reserving the opinion of the third author, for cases of results divergence.

4. *Statistical analysis.* The statistical analyses of the information were carried out using the statistical package SPSS version 17.0 for windows (Statistical Package for the Social Sciences). Assessment of the criteria of selection of studies and quality of studies between reviewers, followed the guidance of literature established for correlation measured by kappa: *kappa* < 0.10-absence of concordance, > 0.10 and < 0.40-weak, >0.40 and < 0.75-good agreement and 0.75 or more, an excellent agreement, being considered significant *p* values < 0.05.

Results

A total of 187 studies were found using the keyword “atopic dermatitis” and “probiotics” in both languages. Studies carried out in Brazil or in Portuguese language were not found. After applying inclusion and exclusion criterias, 12 publications were selected, all as case control, held in 4 European countries and in Australia.

Regarding the analysis of the methodological quality of the work, *Kappa* coefficient (IC 95%) was estimated, considering the opinion of 2 researchers independently. The independent inclusion selection of studies for this review of literature presented an excellent concordance agreement (*k* = 1.00, CI 95%) between the evaluators, not being necessary the intervention of a third one, with a total of 9 papers with B classification (75%), 2 classified as C (16.6%) and 1 categorized as A (8.4%). In view of the reduced number of selected works, we decided to keep all of them in the final analysis (table I). It should be high-

lited that despite evaluating a total of 12 articles, this review covers only 9 case studies, because this same sample was used in three articles and another sample in two articles. Importantly, despite a total of 12 articles reviewed, this review covers only 9 case series, because the same sample was used in three articles^{11,15,22} and another, in two articles.^{23,24}

Only 25% of the articles analyzed (*n* = 3) did not describe follow-up losses. Among the articles that reported losses, variation was among 3.77%²⁶ to 42.6%²⁴ of the studied sample. As methodological limitations of the studies, reduced sample size,^{20,27} flaws in randomization process²⁴ and small number of bacterial groups analyzed were reported.²⁷

The significant majority of the articles included children from zero to two years old and only one of them studied children between two and five years old.⁵ The description of the circumstances and goals of the selected studies, inclusion and exclusion criteria and methods employed are presented in table II and in table III.

The primary outcomes studied included improvement of the clinical signs,^{5,15,20,21,22,26} allergy modulation,¹⁹ impact on the immune system^{17,22,25} and on the intestinal^{17,19,20,27} and skin microbiotas,¹⁷ in addition to the effects on the fecal²³ and plasma²⁴ markers of inflammation.

Studies by Weston et al. 2005²¹ and Prescott et al. 2005²² deal with different outcomes, but refer to the same samples. The same occurs in the studies by Viljanen et al. 2005a¹⁵, Viljanen et al. 2005b²³ and Viljanen et al. c 2005.²⁴

The severity of AD was evaluated through SCORAD in all selected articles. The studies included cases of mild,^{19,20} mild to moderate^{26,27} and moderate to severe severity.^{5,21,22} All degrees of severity were included in 41% of the articles.^{15,17,23,24,25}

The analyzed studies included several strains of probiotics, *Lactobacillus rhamnosus* GG;^{5,15,17,20,23,24,26} *Lactobacillus rhamnosus*;²⁵ *Lactobacillus* GG;²⁵ *Lactobacillus fermentum* VRI-033 PCC;^{21,22} *Lactobacillus acidophilus*-NCFM;²⁷ a mix of probiotics containing *Lactobacillus rhamnosus* GG, *Lactobacillus LC705 rhamnosus*, *Bifidobacterium breve* Bbi99 and *Propionibacterium freudenreichii* SSP JS;^{15,23,24} and also *Bifidobacterium lactis* Bb12 strains¹⁹ and *Bifidobacterium lactis* Bi-07.²⁷

Probiotic supplementation was done through the administration of capsules^{5,15,23,24,26,27} or sachets^{21,22} diluted or mixed into non-specified food,^{15,23,24} milk^{5,26} or water.^{21,22,26} Some articles described studies in which the probiotics were previously added to extensively hydrolyzed casein formula,¹⁷ to extensively hydrolysed milk formula^{19,20,25} or to amino acid based formula.¹⁹

Studies presented the offered dose of probiotics in colony-forming units (CFU). The most used concentration of probiotics in studies employing capsules was of 5 x 10⁹cfu^{5,15,23,24,26}, but concentrations of 2x10⁸cfu^{15,23,24} and 10¹⁰cfu²⁷ were also administrated. Among these studies only the one by Larsen et al.²⁷ did not report the amount of daily doses consumed by

Table II
Overview and goals of selected studies

<i>Study/author/year/local</i>	<i>Type of study</i>	<i>Casuistry</i>	<i>Goals</i>
1. Kirjavainen PV et al., 2002 ¹⁹ , Finland	Double blind placebo controlled randomized case control. (DBPCRCC)	Thirty-five children, exclusive breastfeeding in transition to complementary feeding.	To characterize the relationship between the intestinal microbiota and the extension of sensitivity and also assess the efficacy of Bifidobacteria supplementation as modulators in the treatment of allergy.
2. Kirjavainen PV, Salminen SJ, Isolauri E, 2003 ²⁰ , Finland	DBPCRCC	Forty-three children from 3 to 7 months old - 35 remained in the study.	To evaluate the effectiveness of supplementation with viable and heat inactivated probiotic bacteria in the management of atopic disease and observe their effects on intestinal microbiota composition.
3. Weston S et al., 2005 ²¹ , Australia	DBPCRCC	Fifty-six children from 6 to 18 months old - 53 completed the study.	To investigate the effects of probiotics on young children with moderate to severe degrees of AD.
4. Prescott SL et al., 2005 ²² , Australia	DBPCRCC	Fifty-three children from 6 to 18 months old.	To evaluate the effects of the use of probiotics on the immune system and its relationship with clinical improvement of the symptoms.
5. Viljanen M et al., 2005a ¹⁵ , Finland	DBPCRCC	Two hundred and fifty two children from 1 to 11.9 months old - 230 completed the study.	To investigate the benefits of probiotics on the treatment of AD.
6. Viljanen M et al., 2005b ²³ , Finland	DBPCRCC	Two hundred and fifty two children from 1 to 11.9 months old - 230 completed the study.	To investigate the effects of probiotics on the fecal levels of IgA and intestinal inflammation markers in children with food allergy and AD.
7. Viljanen M et al., 2005c ²⁴ , Finland	DBPCRCC	Two hundred and fifty two children from 1 to 11.9 months old - 132 collected blood samples before and after treatment.	To investigate the effects of probiotics on plasma levels of inflammation markers.
8. Brouwer ML et al., 2006 ²⁵ , Netherlands	DBPCRCC	Sixty children under 5 months old, with a supposed diagnosis of CMA - 50 completed the study.	To study the clinical and immunological effects of two probiotics on the symptoms in children with AD.
9. Fölster-Holst R et al., 2006 ⁵ , Germany	DBPCRCC	Fifty-four children under 5 years old - 42 completed the study.	To re-evaluate the effectiveness of oral probiotic administration on children with AD.
10. Grüber C et al., 2007 ²⁶ , Germany	DBPCRCC	One hundred and six children from 3 to 12 months old.	To investigate the therapeutic effect of probiotics as food supplement on children with mild to moderate forms of AD.
11. Nermes M et al., 2010 ¹⁷ , Finland	DBPCRCC	Thirty-nine babies - 37 completed the study.	To investigate the interaction between probiotic and intestinal microbiotas and skin and also with the humoral immunity in children with AD.
12. Larsen N et al., 2011 ²⁷ , Denmark	DBPCRCC	Fifty children from 7 to 24 months old.	Investigate the effects of probiotics on the composition of the main groups of fecal microbiota of children with AD and determine whether the clinical effects are related to changes in intestinal microbiota.

DBPCRCC: Double blind placebo controlled randomized case control; AD: Atopic Dermatitis; IgA: Immunoglobulin A.

the participants, however the other studies stated an administration of twice a day.^{5,15,23,24,26} The dose mentioned in two studies using sachets^{21,22} was of 1×10^9 cfu, twice a day. The studies in which supplemen-

tation was done through milk formulas containing previously added probiotics, reported a concentration of colony-forming units per gram reaching 1×10^9 cfu/g^{19,20} and 3×10^8 cfu/g.²⁵ Nermes et al. 2010¹⁷ high-

Table III
Criteria for inclusion, exclusion and methodology of selected studies

Study	Inclusion and exclusion criteria	Methodology
1 ¹⁹	Children with early onset, contemplating the diagnostic criteria of Hanifin and/or gastrointestinal symptoms, with a family history of atopy, with high risk of chronic allergic disorders, and with developmental and growth delays. Exclusion of those who did not receive exclusive breastfeeding and those whose fecal samples did not provide enough biomass for microbiological quantification.	Thirty five weaning children were randomly distributed in group treatment (GT) and placebo (GP). The GT group received extensively hydrolyzed milk formula with supplementation of <i>Bifidobacterium lactis</i> Bb12 x 10 ⁹ cfu/g. The GP group received extensively hydrolysed milk formula without supplementation. As 5 children from GP and 10 from GT maintained the initial symptoms of the framework in the course of the study, sub-groups within the initial groups were created: GAS (highly sensitized subgroup) – due to the intolerance to hydrolysed milk formula, these children began receiving formula derived from amino acids; and GS (sensitized subgroup) - corresponding to the original formula-tolerant children. Fecal samples were collected from all groups before weaning (average age of 5.2 months) and afterwards only in the GS Group (average of 9 months). The severity of AD was assessed through SCORAD and the extent by sensitivity to total serum IgE. Fecal microbiota of children was also analyzed. Twenty-one children completed the study.
2 ²⁰	To be included in the study children should be tolerant to extensively hydrolyzed milk formula and diarrhea should not be present at the time of study entry.	The participants presented the weak form of AD. The 3 study groups received extensively hydrolysed milk formula. The first group was supplemented with viable <i>Lactobacillus rhamnosus</i> GG 1 x ⁹ 10 cfu/g, the second group was supplemented with the probiotic inactivated by heat (concentration was not described in the study), and the third group (placebo) received the same formula without supplementation. The fecal samples were collected before and after the intervention. The average duration of formula administration was of 7.5 weeks.
3 ²¹	Children from six to eighteen months old, with moderate to severe forms of AD (SCORAD ≥ 25). Children with a history of previous exposure to probiotics, current use of antibiotics, or the presence of other health problems were excluded from the study.	Blood samples were collected before the intervention for IgE analysis. Both groups were given one gram sachets to be diluted in 5 to 10 mL of water and offered to the child as a suspension. The experimental group received an oral solution of <i>Lactobacillus fermentum</i> VRI-033 PCC, concentration of 1 x 10 ⁹ cfu, twice a day for 8 weeks and the placebo group received maltodextrin without probiotics. Participants were stratified by age, initial SCORAD and use/power of topical corticosteroids, which was monitored by medicine tubes weighing and by a daily report. The groups were evaluated in weeks 0, 2, 4, 8 and 16 of the study.
4 ²²	Children from six to eighteen months old, with moderate to severe forms of AD (SCORAD ≥ 25). Children with a history of previous exposure to probiotics, current use of antibiotics, or the presence of other health problems were excluded from the study.	Blood samples were collected before and after the intervention, and also 8 weeks before the end of the study to analyze peripheral mononuclear cell and check allergens sensitivity through RAST test. The response to cytokines (IL-5, IL-6, IL-10, IL-13, IFN-gamma, TNF-α) and to some microorganisms was also compared. Both groups were given one gram sachets to be diluted in 5 to 10 mL of water and offered to the child as a suspension. The experimental group received an oral solution of <i>Lactobacillus fermentum</i> VRI-033 PCC, concentration of 1 x 10 ⁹ cfu, twice a day for 8 weeks and the placebo group received maltodextrin without probiotics. The use of topical corticosteroids was monitored by medicine tubes weighing and by a daily report. SCORAD was re-evaluated at weeks 8 and 16.
5 ¹⁵	Children under 12 months old, presence of suggestive CMA symptoms, and necessarily presence of AD. Children who had used probiotics for a period greater than a week in the six weeks before the study were excluded. The study covered all degrees of severity.	Three groups were formed. The first group (LGG, n = 80), received <i>Lactobacillus rhamnosus</i> GG in a dosage of 5 x 10 ⁹ cfu, and the second group (MIX) which had 76 children received 5 x 10 ⁹ cfu of <i>Lactobacillus rhamnosus</i> GG, 5 ⁹ cfu of <i>Lactobacillus rhamnosus</i> LC705, 2 x 10 ⁸ cfu of <i>Bifidobacterium breve</i> Bbi99 and 2 x 10 ⁸ cfu of <i>Propionibacterium freudenreichii</i> SSP. JS. The placebo group received only microcrystalline cellulose and contained 74 individuals. Concomitantly with the use of probiotics, milk and dairy products elimination diet was followed, as well as a skin treatment with emollients and hydrocortisone 1%, as required, being controlled and verified at every medical visit. The probiotic administration period was of 4 weeks, and the groups received these products in capsules, having to dilute in food its content. At the first visit SCORAD was assessed. Fecal and blood samples were also collected as well as the conduction of skin tests. On the second visit fecal samples were again collected (52 individuals collected samples in the first two visits) and SCORAD was also reassessed. After completing four more weeks they were re-evaluated by SCORAD and the ones who persisted with CMA symptoms were submitted to TDCPC. The authors considered as IgE sensitized any child who had a positive skin test or IgE specific Antigen concentration above 0.7 kU/L.
6 ²³	Children under 12 months old, presence of suggestive CMA symptoms, and necessarily presence of AD, excluding those who had used probiotics for a period greater than a week in the six weeks previous to the study. The study covered all degrees of severity.	Concomitantly with the use of probiotics, milk and dairy products elimination diet was followed, as well as a skin treatment oriented by a nurse. At the first visit SCORAD was assessed, blood was collected and the skin prick test was done. At the second and third visits SCORAD was re-evaluated and children who remained with CMA symptoms until the last visit were submitted to TDCPC. The participants received capsules to be diluted in food, during 4 weeks. It was offered to group LGG, n = 80, <i>Lactobacillus rhamnosus</i> GG in a dosage of 5 x 10 ⁹ cfu. Group MIX had 76 children and received 5 x 10 ⁹ cfu of <i>Lactobacillus rhamnosus</i> GG, 5 ⁹ cfu of <i>Lactobacillus rhamnosus</i> LC705, 2 x 10 ⁸ cfu of <i>Bifidobacterium breve</i> Bbi99 and 2 x 10 ⁸ cfu of <i>Propionibacterium freudenreichii</i> SSP. JS. The placebo group was composed of 74 individuals and received only microcrystalline cellulose. A hundred and two children were selected at random to have fecal samples collected before the treatment, after 4 weeks of probiotic administration and on the first day of TDCPC. The authors considered any child who had a positive skin test or IgE specific Antigen concentration above 0.7 kU/L and positive CMA test as IgE sensitized associated with CMA. IgA total levels, TNF-α, and ECP were measured, in duplicate, in fecal samples.

Table III (cont.)
Criteria for inclusion, exclusion and methodology of selected studies

Study	Inclusion and exclusion criteria	Methodology
7 ²⁴	Children under 12 months old, presence of suggestive CMA symptoms, and necessarily presence of AD. Children who had used probiotics for a period greater than a week in the six weeks previous to the study were excluded. The study covered all degrees of severity.	Concomitantly with the use of probiotics, milk and dairy products elimination diet was followed, as well as a skin treatment oriented by a nurse. Blood samples of 132 children were collected before and after the treatment aiming the examination of C-reactive protein, interleukins IL-2, IL-4, IL-6, IL-10, TNF- α , IFN- γ , ICAM-1 and soluble selectin, TGF- β 1, β 2 and TGF. At the first visit SCORAD was assessed and the skin prick test was done. At the second and third visits SCORAD was re-evaluated and children who remained with CMA symptoms until the last visit were submitted to TDCPC. The participants received capsules to be diluted in food, during 4 weeks. Group LGG, n = 52, received <i>Lactobacillus rhamnosus</i> GG in a dosage of 5 x 10 ⁹ cfu. Group MIX with 42 children received 5 x 10 ⁹ cfu of <i>Lactobacillus rhamnosus</i> GG, 5 ⁹ cfu of <i>Lactobacillus rhamnosus</i> LC705, 2 x 10 ⁹ cfu of <i>Bifidobacterium breve</i> Bbi99 and 2 x 10 ⁹ cfu of <i>Propionibacterium freudenreichii</i> SSP. JS. Group placebo was composed of 38 individuals and received only microcrystalline cellulose. The authors considered any child who had a positive skin test or specific IgE Antigen concentration greater than or equal to 0.7 kU/L as IgE-sensitized. Children who presented positive TDCPC and positive skin test to CM or concentration of IgE specific Antigen to CM greater than or equal to 0.7 kU/L were identified as IgE-sensitized associated with CMA.
8 ²⁵	To be included in the study children should be under 5 months old, meet the diagnostic Hanifin criteria for AD, be suspected as allergic to cow's milk and be fed exclusively by formulas. Children who used anti histamines, oral corticosteroids, probiotics, antimycotics, or antibiotics in the four weeks preceding the study, as well as those presenting congenital gastrointestinal malformation were excluded from the study. All degrees of severity were included in the study.	Initially, all the children received extensively hydrolysed milk formula for 3-5 weeks, when they were tested for CM allergy. Afterwards they were randomly selected to receive extensively hydrolyzed milk formulas for three months. Group NP-Lrh received <i>Lactobacillus rhamnosus</i> 3 x 10 ⁹ cfu/g, Group NP-LGG received <i>Lactobacillus</i> GG 3 x 10 ⁹ cfu/g, and Group NP-P (placebo) received no supplementation. The severity of AD was evaluated before intervention and at months 1, 2 and 3 through SCORAD. Sensitivity to allergens was measured by means of total serum IgE and IgE for specific foods and the skin test for allergy to CM. As inflammatory parameters it was used the eosinophils plasma dosage, urine eosinophil protein X, fecal AT and production of IL-4, IL-5 and IFN- γ in peripheral blood mononuclear cells, that were assessed prior to CMA testing and at the end of the intervention.
9 ⁵	Children should have been diagnosed with AD according to Hanifin criteria to be included in the study. Exclusion criterias were not reported.	Fifty-four children under five years old, with moderate to severe forms of AD, were randomly allocated into two groups. The intervention group received capsules containing 5 x 10 ⁹ cfu of <i>Lactobacillus rhamnosus</i> GG and the placebo group received capsules containing microcrystalline cellulose to be administered twice a day diluted in milk during 8 weeks. SCORAD was evaluated at weeks 0, 2, 4, 6 and 8 of the study. The use of oral corticosteroids and topical antihistamines were recorded in a diary. Blood and feces samples were collected in weeks 0 and 8 for analysis of total IgE, specific food IgE, household allergens and eosinophils count, as well as ECP and soluble CD30. In the fecal sample it was measured AT, calprotectin and ECP.
10 ²⁶	Mild to moderate AD symptoms for more than four weeks was necessary for the inclusion in the study. Exclusion criterias: previous intake of probiotics, immunodeficiency and previous treatment with corticosteroids.	Patients were randomly selected to receive capsules containing placebo (placebo group), or <i>Lactobacillus rhamnosus</i> LGG > 5 x 10 ⁹ cfu per capsule (intervention group). The administration was done through the reconstitution of the contents of the capsule in a spoon with CM or water twice a day during three months. The complications and the use of hydrocortisone 1% were recorded in a journal. The medicine tube was weighted to evaluate the quantity of medication used. Blood samples were collected to assess levels of IgE against CM and egg yolk, at the beginning and end of the study. The severity of the disease was evaluated based on SCORAD.
11 ¹⁷	Being born at term was the inclusion criteria for this study. The exclusion criterias were the presence of skin infections and serious infections. All degrees of severity of the disease were covered.	Patients received for three months extensively hydrolyzed casein formula. The experimental group received this formula supplemented with 5.0 10 ⁹ cfu/g of <i>Lactobacillus rhamnosus</i> GG (ATCC 53103) to achieve a daily consumption of 3.4 x 10 ⁹ cfu. SCORAD was evaluated at months 0, 1 and 3, when also blood and feces were collected as well as a skin swab. At the beginning of the study a skin test for food allergens was done. There was also an evaluation of peripheral mononuclear cells total number and CD19 and CD27 expression.
12 ²⁷	An AD diagnosis by the child's pediatrician was the inclusion criteria. Exclusion criterias were not reported.	Group A (GA) received <i>Lactobacillus acidophilus</i> NCFM (n = 17) and group B (GB) received <i>Bifidobacterium lactis</i> Bi-07 (n = 17) while group C (GC) received placebo, which was a mixture of lactose and silicon dioxide in proportion 1: 1 (n = 16). The daily dosage of probiotics was approximately 10 ¹⁰ cfu, administered by eight weeks in capsules. It was excluded from the participants diet any other product containing probiotics. Fecal samples were collected before and after intervention for analysis of the microflora present in the gut. The severity of AD was also evaluated before and after intervention through SCORAD.

CMA: Allergy to cow's milk; AD: Atopic Dermatitis; AT: α 1-antitrypsin fecal; *E. coli*: *Escherichia coli*; ECP: Cationic protein eosophilic; GAS: Highly sensitized subgroup; GP: Placebo group; GS: Sensitized subgroup; GTB: Group treatment; ICAM-1: Soluble intercellular adhesion molecule 1; IFN- γ : Interferon gamma; IgA: Immunoglobulin A; IgE: Immunoglobulin E; Immunoglobulin M IgM: *Lactobacillus rhamnosus* GG; LV: Cow's milk; n = number of participants; p = p; SCORAD: Scoring Atopic Dermatitis (atopic dermatitis to score); TDCPC: double-blind placebo controlled test for allergy to cow's milk; TGF β 1: Transformation of growth Factor beta 1; TGF β 2: Transformation of growth Factor beta 2; Th1 helper T Lymphocyte: Type void 1; Th2: Helper T Lymphocyte sub type 2; TNF- α : Tumor necrosis factor; cfu: colony-forming units; cfu/g: colony-forming units per gram.

lighted that to achieve a daily consumption of 3.4×10^9 cfu, it was necessary to supplement 5.0×10^7 cfu/g.

The probiotic administration period was of four,^{15,23,24} eight,^{5,20,21,22,26} and twelve^{17,25,26} weeks, with an average of 7.4 weeks of supplementation. There is no information about the period of use of probiotics in the study by Kirjavainen et al. 2002¹⁹.

Allergy cases have been reported in all analyzed studies in this review and the prevalence ranged from 35.8%¹⁷ to 77%²¹ of the studied samples. Allergy to cow's milk, egg, wheat, peanut, codfish, cereal/gliadin were the types of food allergy studied and identified by allergy skin tests or laboratory tests. Nevertheless, the identification of which specific food item was related to the allergy symptoms occurred only in Kirjavainen et al.²⁰

The main results and conclusions of the studies are presented in table IV.

The majority of the selected studies showed beneficial effects of probiotics supplementation,^{15,17,19,20,21,22,23,24} however some studies found no evidence of a positive impact of supplementation on the outcomes of interest related to AD.^{5,25,26,27}

Discussion

Although there is no available data about the prevalence of AD in Brazil concerning the age group studied, estimates performed in other countries indicate that the occurrence of the problem is not negligible. In addition to the clinical implications that contribute to overload the costs in the health sector (hospitalization and health team support), there are indirect costs (pain, suffering, impact on the quality of life and on the professional and education environment). Mancini et al.²⁸ revised the costs concerning AD in the United States and demonstrated that direct national expenditure ranged from 364 million dollars to 3.8 billions dollars, with an annual spending per patient ranging from \$ 167 to \$ 580.

A study conducted by Verboom et al.²⁹ found variations in the cost of treatment per patient, ranging around \$ 71 dollars in the Netherlands and reaching \$ 2559 dollars in Germany. The authors attributed the discrepancy in the results to the variation of population studied (inpatient versus outpatient) and to the different severity levels of AD observed. The more severe cases require more expensive treatments, due to the need for more expensive medications and special care. It was also pointed out that the household expenses are high, because the health system does not cover all the needs required by these patients.

We must highlight that the selected studies were concentrated in the Nordic countries. This region, with continental temperate climate, reaches extremely cold temperatures during winter. Weiland et al.³⁰ suggested that the weather can interfere in the prevalence of asthma and AD. Data from Weiland's study indicated that the prevalence of AD symptoms are positively associated with latitude (the higher the latitude, i.e.

more distant from the line of Ecuador, the higher the level of symptoms) and negatively associated with the annual average temperature (locations with lower temperatures are associated with higher intensity of symptoms). The authors still claim that such impacts act indirectly, since they promote behavioral changes and also because inhabitants of these regions have a reduced exposure to sunlight. Byremo et al.,³¹ studying Norwegian children, found that exposure to sunlight provides positive results in treating AD due to the immuno suppressor effect of ultra violet radiation. There are also reports of clinical symptoms worsening in regions of intense heat,³² due to heat intolerance, excessive sweating³³ and greater exposure to pollen.³⁴

Other environmental factors considered determinant to AD are related to changes in lifestyle. Industrialized and developed countries, as those of Western Europe and the United States, were regarded as places of greater prevalence of allergic diseases, but it has been demonstrated an increase in developing countries, what may be due to the urbanization process, greater exposure to pollutants,³⁵ as well as changes in the dietary pattern.³⁶

In Brazil only the studies carried out by Camelo-Nunes et al.² and Solé et al.³² assessed the prevalence of AD, but in another age group. Both researches encompassed children and adolescents, from 6 to 7 and 13 to 14 years old, respectively, following the protocols established by ISAAC (International Study of Asthma and Allergies in Childhood).³⁷ The first study, which involved data from a Brazilian city, detected a medical diagnosis prevalence for AD of 13.2% to 13.4% in children and adolescents. The study by Solé et al.,³² as part of the multicenter study previously cited, found variations in prevalence, from 7.9% to 15.4% in children, and 2.2% to 14.2% among young people and found that the South of the country has the highest prevalence of severe cases of the disease.

In this review the significant majority of works included children from zero to two years old. Bieber³⁸ indicated that 60% of AD cases begin in the first year of life and 85% of all cases occur before the age of five. Illi et al.³⁹ showed that 43.2% of children with early onset (less than two years old) reach complete remission of symptoms at the age of three. However, the study points out that 38% of people develop the intermittent form, in which symptoms are recurring. The study also makes reference to cases that persist until adulthood.

It should be highlighted that in the age group of zero to two years old there is an establishment of the intestinal microbiota of the individual, which depends on various internal and external factors of the host, such as type of delivery, breastfeeding and diet, in addition to the medications used. At the age of two the intestinal microbiota of the child reaches the characteristic profile of adults.⁴⁰

Several studies demonstrate that the presence of this set of intestinal microorganisms is an important factor that raises the maturation of the immune system, by providing stimulus to the synthesis of cytokines and antigen-presenting cells.¹³ Works have showed that rats

Table IV
Main findings and conclusions of the selected studies

Study	Main findings	Conclusions
1 ¹⁹	The fecal samples of GAS before weaning presented a lactobacillus/enterococcus count significantly greater than GS (p = 0.002). In all cases the total plasma concentration of IgE was directly related to the concentration of <i>e. coli</i> in feces and the count of bacteroides in GS. After the intervention, the number of bacteroides and <i>e. coli</i> grew in group CP, while in group GTB there was a decrease in the number of these microorganisms (p = 0.07 0.02 and bacteroides respectively and <i>e. coli</i>).	Supplementation with bifidobacteria seems to modify the intestinal microflora. The authors acknowledge the need for further studies to confirm this effect.
2 ²⁰	The group which used LGG inactivated by heat presented gastrointestinal complications. All groups showed improvement in SCORAD, however group LGG had a greater reduction in viable SCORAD compared to placebo (p = 0.02). None of the three study groups presented significant changes in the concentration of intestinal bacteria in fecal samples.	It was demonstrated the effectiveness of using viable <i>Lactobacillus rhamnosus</i> GG in the treatment of AD, rejecting its use when inactivated by heat. There was no evidence that the use of probiotics was able to change the intestinal microbiota. The authors suggest that the sample size was a limitation of the present study.
3 ²¹	Seventy one percent (71%) of children presented high IgE to food antigens. SCORAD reduction in the probiotic group was significant (p = 0.03), which did not occur in the placebo group (p = 0.83). There was no significant difference between the groups in relation to the use of topical corticosteroids.	Oral supplementation with <i>Lactobacillus fermentum</i> VRI-003 can provide improvements in both the extent and severity of moderate to severe cases of AD, which is maintained for weeks after the end of the treatment. It is recognized the need for further studies to understand the immune mechanisms of this process.
4 ²²	The administration of probiotics was associated with maturation of IFN- γ responses from Th1 (p = 0.046), sustained for two months after the end of intervention. The increase of IFN- γ responses was directly proportional to the improvement in initial levels of SCORAD. There were no significant differences in the parameters analyzed in the placebo group.	The improvement in AD clinical status is attributed to better IFN- γ responses by Th1 helper T cells, which is considered as one of the key elements of the immune response.
5 ¹⁵	No significant difference was found in relation to the improvement in SCORAD between study groups, with the exception of the use of isolated LGG to IgE-sensitized, which showed a significant improvement in values of SCORAD compared to the placebo group (p = 0.036).	The use of isolated <i>Lactobacillus rhamnosus</i> GG is beneficial in IgE-sensitized children (allergies).
6 ²³	Results indicate increased levels of IgA in LGG and MIX compared to the placebo group (p = 0.01). There was no significant difference in the levels of TNF- α and ECP. The test for CMA was positive in 120 children. TNF- α levels were lower in IgE-sensitized children associated to CMA in group LGG.	Four weeks treatment with <i>Lactobacillus rhamnosus</i> GG can reduce intestinal inflammation in children with AD and CMA.
7 ²⁴	Higher values of IL-6 were detected in Isolated LGG group when compared to placebo (p = 0.036). It was also evidenced higher levels of IL-10 in Group MIX (p = 0.013) in comparison to the other groups. Among children with CMA IgE-mediated, E-selectin levels were higher in MIX and LGG than in placebo (p = 0.035).	The use of probiotics induces a subclinical inflammation that promotes an improvement in immune response reducing allergic symptoms. The use of isolated <i>Lactobacillus rhamnosus</i> GG for IgE-sensitized patients contributes to the improvement of food allergy clinical symptoms.
8 ²⁵	There was no statistical significant difference between the study groups concerning the parameters analyzed, even when excluding the data of four children diagnosed with CMA.	This type of supplementation with probiotics did not make significant impact on the symptoms of the children from the study. A positive effect on the immune system was also not evidenced.
9 ⁵	There was an improvement in the severity of SCORAD in the two groups analyzed, with no statistical significant difference between them. Similar results were found for all the other analyses performed. The researchers indicate the necessity of conducting studies using Mannitol or lactulose on the intestinal barrier of these children. In addition, they reinforce the need to employ efforts to avoid biases.	It was not confirmed the beneficial effect of the use of <i>Lactobacillus rhamnosus</i> GG in children with AD, but the study indicates that there may be specific sub-groups to which it is directed. The authors understand the need for further studies regarding IgE-sensitized.
10 ²⁶	The therapeutic effect of <i>Lactobacillus rhamnosus</i> GG supplementation in children with mild to moderate AD could not be proved.	All parameters analyzed tend to improve as the child grows older, independent of the system adopted.
11 ¹⁷	The proportion of IgA and IgM-secreting cells decreased significantly in the experimental group when compared to the control group (p = 0.044 for IgA and p = 0.036 for IgM). The proportion of B CD19+ cells and +CD17 increased only in the experimental group.	By accelerating the immune maturation, specific strains of probiotics are able to promote protection against intraluminal antigens and to control infections.
12 ²⁷	The improvement of SCORAD was present in all study groups, however there was no correlation with the administration of probiotics, and was positively correlated with the levels of Bifidobacterium (p = 0.03) and negatively with the levels of <i>Lactobacillus</i> (p = 0.01). There was no significant change in the microflora of the children studied.	The administration of probiotics did not affect the composition and diversity of microbes in the feces of children. The improvement in AD was present in all study groups, and cannot be attributed to the use of probiotics, but to the advancing age of children.

CMA: Allergy to cow's milk; AD: Atopic Dermatitis; AT: α 1-antitrypsin fecal; ECP: Cationic protein eosinofilia; GP: Placebo group; GAS: Highly sensitized subgroup; GS: Sensitized subgroup; GTB: Treatment group; IFN- γ : Interferon gamma; IgA: Immunoglobulin A; IgE: Immunoglobulin E; IgM: Immunoglobulin M; LGG: *Lactobacillus rhamnosus* GG; SCORAD: Scoring Atopic Dermatitis; TGF β 1: Transformation of growth Factor beta 1; TGF β 2: Transformation of growth Factor beta 2; Th1 helper T lymphocyte: Type void 1; TNF- α : Tumor necrosis factor α ; *E. coli*: *Escherichia coli*.

raised in free conditions of germs do not develop oral tolerance and their immune system does not reach maturity, however this can be reverted if they receive *Bifidobacterium* supplementation.⁴¹

Damião et al.⁴⁰ point out that intestinal microbiota promotes a “physiological” inflammation state, delicately controlled, allowing the immune system to respond differently to pathogenic bacteria and to auto-logous agents.

The human gut microbiota is formed by *Bifidobacteria*, *Lactobacillus* and other bacterium, including pathogenic species. The dominant flora keeps the others under its control, but food, environmental changes and the use of antibiotics can distort the balance between them.⁴² Collado et al.⁴³ claim that when there is a disruption in the harmony between host and microbiota, diseases may arise. This event is known as dysbiosis,⁴³ and diseases that may be related to this condition are inflammatory bowel disease, antibiotic associated diarrhea and allergies.⁴²

Bifidobacteria are identified as key components for proper immune system stimulation and homeostasis of gastrointestinal tract mucosa.¹³ Reports state that the intestinal microflora of atopic children is differentiated from those who are not allergic, containing higher levels of *Clostridium* and lower levels of *Bifidobacterium*^{41,45} species. This discrepant composition precedes the development of atopy⁴⁶ and the modulation of the microenvironment can promote clinical improvement of pediatric patients with AD.¹³ It is proposed as positive effects of the use of probiotics in AD, the stabilization of the intestinal barrier, the modulation of the response to antigens via regulatory T cell through the reduction of Th2-type cytokines expression and an increase in the production of IL-10 and TGF- β . In addition, it also increases the production of IgA in the gut.⁵ Such evidence could justify the favourable effects of the use of probiotics in situations in which the integrity and/or functionality of the intestinal barrier is affected, as it occurs in cases of atopy. All selected studies in this review state clinical records of some kind of allergy (food or other types of allergy).

The significant majority of probiotics used were related to microbiota of healthy individuals (species of *Bifidobacteria* and *Lactobacillus*). In this review the strain *Lactobacillus rhamnosus* GG was employed in half of the studies.^{5,15,17,20,23,24,26} This strain is related to the control of infectious diarrhea and diarrhea associated with antibiotics.⁴⁷ Bezirtzoglou & Stavropoulou⁴⁸ point that it is still unknown which would be the most indicated bacterial strain for the promotion of a proper intestinal barrier function, indicating the need for further studies on this subject.⁴⁸

It was observed variations in doses, time and forms of administration of probiotics. Kirjavainen et al.¹⁹ were the only ones to take into consideration as reference dose the concentrations used in studies on the use of probiotics in the treatment of children with diarrhea. However, a recent revision by Cochrane indicated a dosage over five billion

cfu⁴⁹ for diarrhea prevention, which would represent 5 times the dose used in the study. This finding demonstrates that there is still controversy over the optimal dose.

It should also be highlighted that children under two years old have an immature immune system. The positive effects of probiotics supplementation on the immune system of pediatric patients was addressed in this review,^{22,24,25} and only the study carried out by Brower et al.²⁵ did not detect benefits over immunity.

Kirjavainen et al.,¹⁹ Nermes et al.¹⁷ and Larsen et al.²⁷ discoursed on the effect of probiotics supplementation on intestinal microbiota composition and only one of them showed positive impact on microbiota.¹⁹

Some of the studies in this review presented, as a primary outcome, the improvement of the patient’s clinical status. The improvement of the patient’s clinical status was presented, by their authors, as a primary outcome in some of the studies of this review.^{5,15,20,21,26} A reduction in the severity of AD was found,^{20,21} primarily for children with food or environmental sensitivity.¹⁵ However the works of Fölster-Holst et al.⁵ and Grüber et al.²⁶ found no evidence of effectiveness on the use of probiotics with that purpose, but indicate the need for further studies regarding this subject.⁵

Illi et al.³⁹ consider that the prognosis is determined mainly by the severity and by the presence of atopic sensitivity. Approximately 35% of children with moderate and severe forms of the disease have food allergies.¹¹ It was noticeable that cases of allergy were present in all studies. Due to the fact that many researches did not demonstrate the results of food and environmental allergens analyses separately and did not submit results to different isolated types of food, it was not possible to have a basis for comparison. Only in the study conducted by Kirjavainen et al.²⁰ it was observed that 41% of the population had food allergy, identifying cow’s milk, egg and wheat as the causes of allergy.

Regarding cow’s milk allergy, which was identified by double blind placebo controlled tests, indexes varied between 8%²⁵ to 57%.^{15,19,20,24,25}

Nonetheless, Gerasimov et al.¹⁶ noted that children with allergy to cow’s milk (CM) may not have success in supplementation with *Lactobacillus*, because the necessary culture medium for probiotic growth contains milk. As a result, traces of milk can be present in the composition of the preparation containing this specific strain even after being industrially processed. Only Brouwer et al.²⁵ reported that the studied probiotics culture medium consisted of an extensively hydrolysed milk formula.

The basic treatment for allergies is to avoid contact with irritants and allergens.^{5,50} Rance⁵¹ notes the importance of early detection and management of allergies because, frequently, people are subjected to unnecessary food restrictions. Considering the critical moment of growth and development of children, it is imperative that appropriate food guides must be adopted, bearing in mind the appropriate amount of nutrients.^{50,52} It is noteworthy that, in cases of moderate to high severity of AD, the injury in the skin as well as the chronic

inflammatory state, characteristic of the disease, may increase protein and energy requirements.⁵³

Researches indicates that there is risk of nutritional disorders in children, including low weight and malnutrition.⁵⁴ The severity of the nutritional disorder is directly related to the number of food items to which the child presents sensitivity.⁵⁰

The type of newborn feeding greatly influences their exposure to antigens. Verhassel⁵⁵ points out that children fed with cow's milk only receive this type of antigen. Children, who are breastfed, come into contact with a diversity of antigens that have been ingested and processed by the mother's gastrointestinal tract, but with reduced allergenic potential, which contributes to the promotion of oral tolerance. In addition to this, breastfeeding permits a transfer of prebiotics, IgA, IgG, lysozyme, lactoferrin and other protective factors,⁵⁵ as well as non-pathogenic bacteria, collaborating with the newborn gut colonization.⁵⁶

Kull et al.⁵⁷ indicated that exclusive breastfeeding for four months or more, decreases the risk of developing AD in the first four years of life, regardless of the child's family allergy history. The study also demonstrated an inverse relationship between early and transitory forms of AD (before two years old) as well as in early and persistent forms and breastfeeding (OR 0.76, 95% CI 0.58; -0.99; and OR, 0.59; 95% CI 0.45, -0.77, respectively). Laubereau et al.⁵⁸ also pointed out breastfeeding as a protective factor for the development of the disease.

Due to the numerous benefits of breastfeeding, it is highly recommended for children coming from families with a history of atopy.^{35,55,57,58,59}

Bosguniewicz et al.⁶⁰ highlight the importance of a nutritionist in the treatment of children with AD, exercising a fundamental role in the evaluation of diets consumed by them, as well as guidance to parents and guardians about the food that should be offered to these children.

Based on the foregoing it is concluded that the intestinal microbiota of atopic children is different from that found in healthy children. However, there are controversies about the widespread use of this alternative therapy in children with AD. It seems that children who have greater benefit are those with a history of food allergies.

Analyzing the works included in this review, most studies showed improvements in parameters of inflammatory intestinal microbiota and not exactly, changes in clinical parameters, what does not allow us to state that the use of probiotics in AD produces clinical effects, relieving symptoms. However, the biological effects observed in most of them suggest the possibility of benefits of the use of probiotics as an adjunct in the treatment of AD, regarding the immunological aspects and gastrointestinal microenvironment, especially in cases associated with food allergy.

References

1. Boguniewicz M, Leung DY. Atopic dermatitis: a disease of altered skin barrier and immune dysregulation. *Immunol Rev* 2011; 242 (1): 233-46.
2. Camelo-nunes IC, Wandalsen GF, Melo KC, Naspitz CK, Solé D. Prevalência de eczema atópico e sintomas relacionados entre estudantes. *J Pediatr (Rio J)* 2004; 80 (1): 60-4.
3. Finch J, Munhutu MN, Whitaker-Worth DL. Atopic dermatitis and nutrition. *Clin Dermatol* 2010; 28 (6): 605-14.
4. Shaw TE, Currie GP, Koudelka CW, Simpson EL. Eczema prevalence in the United States: data from the 2003 National Survey of Children's Health. *J Invest Dermatol* 2011; 131 (1): 67-73.
5. Fölster-Holst R, Müller F, Schnopp N, Abeck D, Kreiselmaier I, Lenz T et al. Prospective, randomized controlled trial on *Lactobacillus rhamnosus* in infants with moderate to severe atopic dermatitis. *Br J Dermatol* 2006; 155 (6): 1256-61.
6. Castro APM, Solé D, Filho NAR, Jacob CMA, Rizzo MCFV, Fernandes MFM et al. Guia Prático para o Manejo da Dermatite Atópica – opinião conjunta de especialistas em alergologia da Associação Brasileira de Alergia e Imunopatologia e da Sociedade Brasileira de Pediatria. *Rev Bras Alerg Imunopatol* 2006; 29 (6): 268-82.
7. Hanifin J, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol Suppl (Stockh)* 1980; 92: 44-47.
8. Solé D, Silva LR, Filho NAR, Sarni ROS, Sociedade Brasileira de Pediatria e Associação Brasileira de Alergia e Imunopatologia. Consenso Brasileiro sobre alergia alimentar 2007. *Rev Bras Alerg Imunopatol* 2008; 31 (2): 65-89.
9. European task force on atopic dermatitis. Severity scoring of atopic dermatitis: the SCORAD index. Consensus Report of the European Task Force on Atopic Dermatitis. *Dermatology* 1993; 186 (1): 23-31.
10. Schmid-Grendelmeier P, Simon D, Simon HU, Akdis CA, Wüthrich B. Epidemiology, clinical features, and immunology of the "intrinsic" (non-IgE-mediated) type of atopic dermatitis (constitutional dermatitis). *Allergy* 2001; 56 (9): 841-9.
11. Eigenmann PA, Sicherer SH, Borkowski TA, Cohen BA, Sampson HA. Prevalence of IgE-mediated food allergy among children with atopic dermatitis. *Pediatrics* 1998; 101 (3): E8.
12. Boyce JA, Assa' A, Burks AW, Jones SM, Sampson HA, Wood RA et al. Guidelines for the diagnosis and management of food allergy in the United States: Summary of the NIAID-Sponsored Expert Panel Report. *Nutrition* 2011; 27 (2): 253-267.
13. Jacob CMA, Castro APBM, Yonamine GH, de Souza FRF, Brandão AC, Ribeiro LMA. Alergia alimentar. In: Jacob CMA, Pastorino AC, editors. *Alergia e imunologia para o pediatra*. 2ª edição. (Coleção Pediatria. Instituto da criança HC-FMUSP. Editores: Schwartsman BGS, Jr Maluf PT.) Barueri, SP: Manole; 2010, pp. 289-313.
14. Rosenfeldt V, Benfeldt E, Valerius NH, Paerregaard A, Michaelsen KF. Effect of probiotics on gastrointestinal symptoms and small intestinal permeability in children with atopic dermatitis. *J Pediatr* 2004; 145 (5): 612-6.
15. Viljanen M, Savilahti E, Haahtela T, Juntunen-Backman K, Korpela R Poussa T et al. Probiotics in the treatment of atopic eczema/dermatitis syndrome in infants: a double-blind placebo-controlled trial. *Allergy* 2005; 60 (4): 494-500.
16. Gerasimov SV, Vasjuta VV, Myhovich OO, Bondarchuk LI. Probiotic supplement reduces atopic dermatitis in preschool children: a randomized, double-blind, placebo-controlled, clinical trial. *Am J Clin Dermatol* 2010; 11 (5): 351-61.
17. Nermes M, Kantele JM, Atosuo TJ, Salminen S, Isolauri E. Interaction of orally administered *Lactobacillus rhamnosus* GG with skin and gut microbiota and humoral immunity in infants with atopic dermatitis. *Clin Exp Allergy* 2011; 41 (3): 370-71.
18. Malta M, Cardoso LO, Bastos FI, Magnanini MMF, da Silva CMFP. Iniciativa STROBE: subsídios para a comunicação de estudos observacionais. *Rev Saude Publica* 2010; 44 (3): 559-65.
19. Kirjavainen PV, Arvola T, Salminen SJ, Isolauri E. Aberrant composition of gut microbiota of allergic infants: a target of bifidobacterial therapy at weaning? *Gut* 2002; 51 (1): 51-5.
20. Kirjavainen PV, Salminen SJ, Isolauri E. Probiotic bacteria in the management of atopic disease: underscoring the importance of viability. *J Pediatr Gastroenterol Nutr* 2003; 36 (2): 223-7.
21. Weston S, Halbert A, Richmond P, Prescott SL. Effects of probiotics on atopic dermatitis: a randomised controlled trial. *Arch Dis Child* 2005; 90 (9): 892-7.
22. Prescott SL, Dunstan JA, Hale J, Breckler L, Lehmann H, Weston S et al. Clinical effects of probiotics are associated with increased interferon-gamma responses in very young children with atopic dermatitis. *Clin Exp Allergy* 2005; 35 (12): 1557-64.

23. Viljanen M, Kuitunen M, Haahtela T, Juntunen-Backman K, Korpela R, Savilahti E. Probiotic effects on faecal inflammatory markers and on faecal IgA in food allergic atopic eczema/dermatitis syndrome infants. *Pediatr Allergy Immunol* 2005; 16 (1): 65-71.
24. Viljanen M, Kuitunen M, Haahtela T, Juntunen-Backman K, Korpela R, Savilahti E. Induction of inflammation as a possible mechanism of probiotic effect in atopic eczema-dermatitis syndrome. *J Allergy Clin Immunol* 2005; 115 (6): 1254-9.
25. Brouwer ML, Wolt-Plompen SAA, Dubois AEJ, van der Heide S, Jansen DF, Hoijer MA et al. No effects of probiotics on atopic dermatitis in infancy: a randomized placebo-controlled trial. *Clin Exp Allergy* 2006; 36 (7): 899-906.
26. Grüber C, Wendt M, Sulser C, Lau S, Kulig M, Wahn U, et al. Randomized, placebo-controlled trial of Lactobacillus rhamnosus GG as treatment of atopic dermatitis in infancy. *Allergy* 2007; 62 (11): 1270-6.
27. Larsen N, Vogensen FK, Gøbel R, Michaelsen KF, Abu Al-Soud W, Sørensen SJ et al. Predominant genera of fecal microbiota in children with atopic dermatitis are not altered by intake of probiotic bacteria Lactobacillus acidophilus NCFM and Bifidobacterium animalis subsp. lactis Bi-07. *FEMS Microbiol Ecol* 2011; 75 (3): 482-96.
28. Mancini AJ, Kaulback K, Chamlin SL. The socioeconomic impact of atopic dermatitis in the United States: a systematic review. *Pediatr Dermatol* 2008; 25 (1): 1-6.
29. Verboom P, Hakkaart-Van L, Sturkenboom M, De Zeeuw R, Menke H, Rutten F. The cost of atopic dermatitis in the Netherlands: an international comparison. *Br J Dermatol* 2002; 147 (4): 716-24.
30. Weiland SK, Hüsing A, Strachan DP, Rzehak P, Pearce N; ISAAC Phase One Study Group. Climate and the prevalence of symptoms of asthma, allergic rhinitis, and atopic eczema in children. *Occup Environ Med* 2004; 61 (7): 609-15.
31. Byremo G, Rød G, Carlsen KH. Effect of climatic change in children with atopic eczema. *Allergy* 2006; 61 (12): 1403-10.
32. Solé D, Camelo-Nunes IC, Wandalsen GF, Mallozi MC, Naspitz CK; Brazilian ISAAC Group. Prevalence of atopic eczema and related symptoms in Brazilian schoolchildren: results from the International Study of Asthma and Allergies in Childhood (ISAAC) phase 3. *J Invest Allergol Clin Immunol* 2006; 16 (6): 367-76.
33. Nnoruka EN. Current epidemiology of atopic dermatitis in south-eastern Nigeria. *Int J Dermatol* 2004; 43 (10): 739-44.
34. Krämer U, Weidinger S, Darsow U, Möhrenschrager M, Ring J, Behrendt H. Seasonality in symptom severity influenced by temperature or grass pollen: results of a panel study in children with eczema. *J Invest Dermatol* 2005; 124 (3): 514-23.
35. Prescott S, Nowak-Węgrzyn A. Strategies to prevent or reduce allergic disease. *Ann Nutr Metab* 2011; 59 (Suppl. 1): 28-42.
36. Flohr C. Recent perspectives on the global epidemiology of childhood eczema. *Allergol Immunopathol (Madr)* 2011; 39 (3): 174-82.
37. Ellwood P, Asher MI, Beasley R, Clayton TO, Stewart AW; ISAAC Steering Committee; ISAAC Phase Three Study Group. ISAAC phase three manual. Auckland, New Zealand, July 2000. ISBN 0-473-06910-5 Disponível em: <http://isaac.auckland.ac.nz/phases/phase3/phase3manual.pdf>. Acesso em 14/02/2012.
38. Bieber T. Atopic dermatitis. *N Engl J Med* 2008; 358 (14): 1483-94.
39. Illi S, von Mutius E, Lau S, Nickel R, Grüber C, Niggemann B et al. The natural course of atopic dermatitis from birth to age 7 years and the association with asthma. *J Allergy Clin Immunol* 2004; 113 (5): 925-31.
40. Damião AOMC, Leite AZA, Lordello MLL, Sipahi AM. Probióticos. In: Waitzberg DL, editor. Nutrição oral, enteral e parenteral na prática clínica. 4ª edição. São Paulo: Atheneu; 2009, pp. 2115-30.
41. Özdemir O. Various effects of different probiotic strains in allergic disorders: an update from laboratory and clinical data. *Clin Exp Immunol* 2010; 160 (3): 295-304.
42. Vandenplas Y. Probióticos e prebióticos na prevenção e no tratamento de doenças em lactentes e crianças. *J Pediatr (Rio J)* 2011; 87 (4): 292-300.
43. Collado MC, Isolauri E, Salminen S, Sanz Y. The Impact of Probiotic on Gut Health. *Curr Drug Metab* 2009; 10 (1): 68-78.
44. Rowland I, Capurso L, Collins K, Cummings J, Delzenne N, Goulet O, et al. Current level of consensus on probiotic science - report of an expert meeting -London, 23 November 2009. *Gut Microbes* 2010; 1 (6): 436-9.
45. Kirjavainen PV, Apostolou E, Arvola T, Salminen SJ, Gibson GR, Isolauri E. Characterizing the composition of intestinal microflora as a prospective treatment target in infant allergic disease. *FEMS Immunol Med Microbiol* 2001; 32 (1): 1-7.
46. Penders J, Thijs C, van den Brandt PA, Kummeling I, Snijders B, Stelma F et al. Gut microbiota composition and development of atopic manifestations in infancy: the KOALA Birth Cohort Study. *Gut* 2007; 56 (5): 661-7.
47. Szajewska H, Wanke M, Patro B. Meta-analysis: the effects of Lactobacillus rhamnosus GG supplementation for the prevention of healthcare-associated diarrhoea in children. *Aliment Pharmacol Ther* 2011; 34 (9): 1079-87.
48. Bezirtzoglou E, Stavropoulou E. Immunology and probiotic impact of the newborn and young children intestinal microflora. *Anaerobe* 2011; 17 (6): 369-74.
49. Johnston BC, Supina AL, Ospina M, Vohra S. Probiotics in the prevention of pediatric antibiotic-associated diarrhea. Cochrane Database of Systematic Reviews 2007, Issue 2, Art. No.: CD004827. DOI: 10.1002/14651858.CD004827.pub2.
50. Cho HN, Hong S, Lee SH, Yum HY. Nutritional status according to sensitized food allergens in children with atopic dermatitis. *Allergy Asthma Immunol Res* 2011; 3 (1): 53-7.
51. Rancé F. Food allergy in children suffering from atopic eczema. *Pediatr Allergy Immunol* 2008; 19 (3): 279-84.
52. Ministério da Saúde; Secretaria de Atenção à Saúde; Departamento de Atenção Básica (BRASIL). Dez passos para uma alimentação saudável: guia alimentar para crianças menores de dois anos, um guia para o profissional de saúde na atenção básica. 2ª edição. Série A Normas e Manuais Técnicos. Brasília, DF. Ministério da Saúde. 2010, p. 8.
53. Mofidi S. Nutritional management of pediatric food hypersensitivity. *Pediatrics* 2003; 111 (6Pt3): 1645-53.
54. López-Campos X, Castro-Almarales RL, Nicot JM. Evaluación del estado nutricional en niños com dermatitis atópica. *Rev Alerg Mex* 2011; 58 (2): 99-106.
55. Verhasselt V. Oral tolerance in neonates: from basics to potential prevention of allergic disease. *Mucosal Immunology* 2010; 3 (4): 326-33.
56. Perez PF, Doré J, Leclerc M, Levenez F, Benyacoub J, Serrant P et al. Bacterial imprinting of the neonatal immune system: lessons from maternal cells? *Pediatrics* 2007; 119 (3): e724-32.
57. Kull I, Böhme M, Wahlgren CF, Nordvall L, Pershagen G, Wickman M. Breastfeeding reduces the risk for childhood eczema. *J Allergy Clin Immunol* 2005; 116 (3): 657-61.
58. Laubereau B, Brockow I, Zirngibl A, Koletzko S, Gruebl A, et al; GINI Study Group. Effect of breast-feeding on the development of atopic dermatitis during the first 3 years of life -results from the GINI-birth cohort study. *J Pediatr* 2004; 144 (5): 602-7.
59. Thygarajan A, Burks AW. American Academy of Pediatrics recommendations on the effects of early nutritional interventions on the development of atopic disease. *Curr Opin Pediatr* 2008; 20 (6): 698-702.
60. Boguniewicz M, Nicol N, Kelsay K, Leung DY. A multidisciplinary approach to evaluation and treatment of atopic dermatitis. *Semin Cutan Med Surg* 2008; 27 (2): 115-27.
61. Moraes MB, Jacob CMA. O papel dos probióticos e prebióticos na prática pediátrica. *J Pediatr* 2006; 82 (5 Suppl.): S189-97.