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(REVIEW ARTICLE)

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Skin microbiome vs. atopic dermatitis: A review

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Abstract

Introduction: The human skin is home-grown to an abundant colonization of bacteria, fungi and viruses. Atopic dermatitis is a chronic or recurrent and pruritic inflammatory skin disease that affects mainly the flexed areas of the skin, affecting the quality of life of the patient. People. In a situation of normal skin without pathology, the bacteria present in greater quantity are Actinobacteria and Firmicutes, and the fungi most easily found are *Malassezia* and *Candida.*

Aim: This review aims to observe the relationship between the skin microbiome and atopic dermatitis as well as to verify the changes that occur at the microbiome level when faced with this pathology and treatment options.

Materials and Methods: To carry out this literature review, articles were collected from "Pubmed", "NCBI" and "Google schoolar" databases, publications dates between 2005 and 2020.

Results and discussion: There are several treatment options for this disease, the use of topical corticosteroids, emollients and topical moisturizing therapy remains the therapy of choice. When an exacerbation of bacterial proliferation is observed, the use of antibiotics, namely anti-staphylococcal drugs, is advisable since there is a considerable increase in the proliferation of *Staphylococcus aureus (S. aureus)* throughout the course of the disease.

Conclusion: According to the bibliography used, it is concluded that during the disease there is an increase in the *S. aureus* community as well as the loss of bacterial diversity in the skin, and the increase in *S. aureus* colonization is facilitated by changes that occur in it due to the presence of the pathology.

Keywords: Atopic dermatitis; Skin microbiome; Human skin; Treatment options

1. Introduction

The skin is part of the integumentary system, which also includes other types of structures, such as hair, nails and glands. This organ has two main tissue layers (dermis and epidermis) and rests on the hypodermis, or subcutaneous tissue, which consists of a stretched connective tissue with collagen and elastin fibers. The dermis provides structural resistance to the skin and is a connective tissue with fibroblasts, some fat cells and macrophages, divided into two layers: the deepest reticular layer and the most superficial papillary layer. The most superficial layer of the skin is the epidermis and is separated from the papillary layer of the dermis by a basement membrane. The epidermis has no blood vessels and is nourished by diffusion from capillaries in the papillary layer. These consist of a stratified squamous epithelial

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layer, with most cells being keratinocytes, which are responsible for the structural strength and permeability characteristic of this layer. In the epidermis, there are also melanocytes (melanin-producing cells, responsible for pigmentation), Langerhans cells (responsible for controlling the skin's immune responses) and Merkel cells (for detection of light touch and surface pressure) [1] .

The skin, is home-grown to the millions of bacteria, fungi and viruses that make up its microbiome. Like those present in the intestine, microorganisms present in the skin play an essential role in protecting against invading pathogens. - the skin is colonized by beneficial microorganisms and serves as a physical barrier to prevent the invasion of pathogens, providing a home for the commensal microbiota. In circumstances where the barrier is broken or when the balance between commensal and pathogenic populations is disturbed, skin disease or even systemic disease can occur [2] .

Acne vulgaris is a chronic skin condition that involves hair follicles and sebaceous glands. Several factors can contribute to the condition, including the skin microbiome. The skin microbiome in the follicle is composed of a diverse group of microorganisms, including *Propionibacterium acnes* and *Malassezia spp*. which have been suggested in the development of acne through the influence of sebum secretion, comedone formation and inflammatory response [3] .

The durability of skin, especially in a dehydrated, acidic and nutrient-poor environment, also contributes to the adversity that pathogens face when colonizing human skin. Despite this, the skin is colonized by a diverse microbiota [2] .

In the future, topical therapeutic innovations are expected involving formulations of microorganisms for the control of skin conditions, seeking a balance between the host ecosystem and the microorganism. For this to be possible, greater knowledge will be needed about the microbiome of different parts of the body, its variations over time and seasonal changes, as well as the effect of factors such as hygiene, lifestyle, geographic locations, among others.

Human skin can be a harsh environment with an acidic pH and constant peeling. Even so, it shows an abundant colonization of bacteria, fungi and viruses and the composition of these microorganisms is subject to ecological and individual variations. The literature remains inconsistent when it comes to the density of skin bacteria, and a possible explanation for this is the variation in the methods used to quantify these microorganisms. At least 19 bacterial phyla (major lineages in the bacteria domain) belong to the skin microbiome. The main ones are Actinobacteria (51.8%), Firmicutes (24.4%), Proteobacteria (16.5%) and Bacteroidetes (6.3%). Most of the identified genera consist of Corynebacteria, Propionibacteria and *Staphylococcus*. Commonly found fungi include those of the *Malassezia* and *Candida* genera. Contrary to what occurs with some members of the bacterial microbiome, there is no strong evidence of a mutualistic or beneficial relationship with the fungal microbiome. However, it is important to consider the still low number of studies carried out focusing on the cutaneous fungal microbiome and its possible effects on the host. In general, more diversity seems to have greater advantages, as it is believed that the more diverse the ecosystem, the more resilient it becomes. In a study carried out by Grice *et al.*, in 2009, representative skin areas affected by microbiological disorders were selected and the relative abundance of the main bacterial groups was compared, taking into account three microenvironments: sebaceous (glabella, alar sulcus, external auditory canal, , occipital, manubrium and dorsum); moist (nostril, axillary vault, antecubital fossa, interdigital space, inguinal fold, gluteal fold, popliteal fossa, plantar heel and umbilicus); and dry (volar forearm, hypothenar palm and buttock). Propionibacteria and *Staphylococcus* species predominated in sebaceous areas, *Corynebacterium* species predominated in humid areas and a mixed population of bacteria resided in dry areas, with a higher prevalence of b-Proteobacteria and Flavobacteriales [4] .

As previously mentioned, the human skin is the organ most exposed to the external environment and, therefore, represents the first line of defense against external chemical and microbial threats.

Recent studies suggest an association between the use of antiperspirants and make-up with the composition of the skin's microbiota [5].

Atopic dermatitis (AD), also known as eczema, according to the World Allergy Organization, refers to the clinical phenotype of the pathology, is a chronic or recurrent pruritic inflammatory skin disease that mainly affects the flexed areas of the skin. It is characterized by dry skin, intense itching, recurrent eczematous lesions and loss of sleep, greatly affecting quality of life; an ill-defined erythema with edema, vesicles and exudation in the acute phase; and skin thickening (lichenification) in the chronic phase (Fig. 1 and 2) [6] [7] .

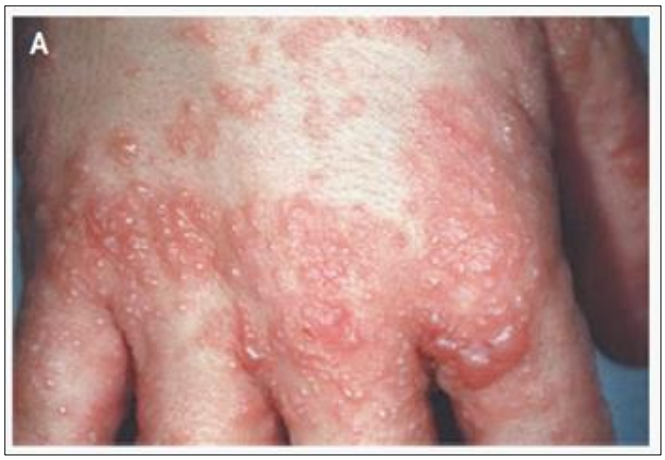

Figure 1 Acute atopic dermatitis with intense erythema and vesicles (7)

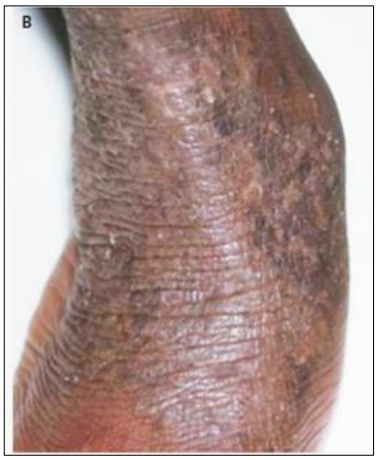

Figure 2 Chronic atopic dermatitis with lichenification (7)

"Atopic dermatitis is a heterogeneous skin pathology associated with variable morphology, distribution and disease course. Its pathogenesis is complex, combining genetic and environmental factors that condition epidermal barrier dysfunction, cutaneous and systemic immune dysregulation and skin microbiome dysbiosis" [8].

AD is thought to be caused by a genetic defect in the filaggrin (a filament-associated protein that binds to keratin fibers in epithelial cells) leading to the breakdown of the epidermis, resulting in contact between immune cells in the dermis and antigen in the environment. external tissue leading to inflammation and itching. Pruritus causes an increase in the breakdown of the epidermis barrier of the skin, thus characterizing a cycle. The pathogenesis of AD is related to lower microbial diversity in areas of predilection for the disease, as well as an increase in the proportion of *Staphylococcus aureus (S. aureus)* during outbreaks [4].

The pathophysiology of this disease can be affected by numerous factors, including race, environment, genetic predisposition, skin barrier dysfunction, immune regulatory abnormalities, and the skin microbiome.(9) Environmental, nutritional, pharmacological and psychological factors may also be involved, which contribute to the aggravation or development of AD [7].

In recent decades, the prevalence of AD has increased rapidly in the world, with values of 1-3% in adults and 10-20% in children, with 60% of cases starting in the first year of life, thus representing a major challenge in Pediatric Medicine. In addition, it appears that AD is higher in urban areas than in rural areas. However, another theory that justifies the prevalence of AD is the "hygiene hypothesis", which implants the colonization pattern and the diversity of the intestinal microbiota. Thus, this theory states that under modern hygienic living conditions, there is a reduction in exposure to microorganisms early in life, which results in inadequate immune priming. Thus, exposure to bacteria and viruses in the child's environment is a crucial factor in the development of allergy [7].

The prevalence and number of diseases associated with AD are substantial. This disease causes significant impairment in quality of life and may also be associated with mental disorders, as well as cardiovascular disease and obesity [9].

Eczema is linked to other hypersensitivity reactions, such as a high risk of allergy, particularly food, asthma, rhinitis, and mental health issues [7].

AD is caused by a complex interaction between immune dysregulation, epidermal gene mutations, and environmental factors that deregulate the epidermis, causing intensely itchy skin lesions. Repeated scratching sets off a self-perpetuating cycle, which can have a significant impact on a person's quality of life [10].

A variety of cell types, including Th2, Th17, Th22, and type 2 innate lymphoid cells contribute to AD. Cytokines in these immune cells cause abnormal epidermal differentiation and skin barrier dysfunction. Furthermore, microbial dysbiosis and antimicrobial peptide deficiency result in *S. aureus* infection [9].

In AD there are two possible causes that explain its existence, such as: extrinsic or mediated by Immunoglobulin E (IgE), with high levels of IgE, and intrinsic or not mediated by IgE, with normal serum levels of IgE. The extrinsic hypothesis is the weakening of the skin barrier and inadequate differentiation of keratinocytes, which allows the penetration of

antigens (Ag). Thus, Ag causes immunological sensitization and consecutively immune activation. In the intrinsic hypothesis, there is a weakening of the skin barrier, which promotes the introduction of allergens. Thus, there is an increase in permeability of the skin barrier and the consequent penetration of allergens and microorganisms.

However, AD is classified as a biphasic disease, with two acute and chronic phases, mainly caused by Th1 and Th2 cell responses. This pathology is more heterogeneous in the acute phase, which consists of Th2 (interleukin (IL) 4, IL5, IL13, IL31 and CCL-18) and Th22 (IL-22 and S-100A proteins) responses. In contrast, the chronic phase comprises the acute phase pathways along with Th1 cells (interferon [IFN] -ʎ, CXCL-9 and CXCL-10). There are other causes that justify the existence of AD, such as inflammation of Th2 cells and imbalance of the epidermal barrier. Thus, there is a decrease in filaggrin (FLG) and claudin 1, causing an imbalance in the barrier. FLG encodes a protein that is responsible for retaining moisture and protecting the skin from environmental allergens. Therefore, FLG is an essential component for the balance of the skin barrier, as its deficiency is associated with an increase in pH, making the colonization of *S. aureus* quite favorable. In addition, there is still some controversy about AD, based on two possible hypotheses: "Inside-Out", due to dysfunction and systemic inflammation of the epidermal barrier, and "Outside-In", with epidermal rupture of the skin barrier, activating an immune imbalance.

In the "Inside-Out" hypothesis, there is an inflammation of the skin, as there is a weakening of the barrier due to the decrease in the production of filaggrin. The rupture of the barrier is due to the transcutaneous penetration of allergens, with an increase in *S. aureus*.

In the "Outside-In" hypothesis, there is an immunological dysregulation, as there is a mutation in the filaggrin gene due to environmental factors, such as temperature and humidity, compromising its production. The breakdown of the cutaneous barrier results from the increase in cutaneous and systemic responses of Th2 cells and IL-4 and IL-a3, with thymic stromal lymphopoietin (TSLP). Thus, they are responsible for generating allergic diseases, such as asthma, and for the progression of AD to other forms of atopy, such as food allergy [7].

The American Academy of Dermatology created simple diagnostic criteria based on symptoms and physical examinations performed [10]. The diagnosis is also based on specific clinical criteria, including personal and family history of atopy, disease course, and clinical manifestations [8].

Maintenance therapy consists of the use of emollients and a daily bath with soap-free cleaning products. The main treatment of AD is based on body moisturizers and the adoption of behaviors that reduce xerosis (symptom of dryness of the skin or eyes.). First-line treatment to control the condition is the use of corticosteroids and second-line topical calcineurin inhibitors that can be used together with topical corticosteroids as first-line treatment, such as pimecrolimus and tacrolimus. Ultraviolet phototherapy is a safe and effective treatment for moderate to severe atopic dermatitis when first-line treatments are not adequate. When there is evidence of secondary infection, the use of antibiotics is recommended, which should present good results for *Staphylococcus* and *Streptococcus* species [4] [10].

Recently, AD treatment has started to progress towards precision medicine. Therefore, several biological agents and small molecules have been developed to block specific cytokines, cytokine receptors or transcription factors. Dupilumab is a monoclonal antibody that reduces type 2 inflammation by antagonizing the action of IL-4 and IL-13 and has been approved by the Food and Drug Administration for patients with moderate to severe AD [9].

In addition to those mentioned above, the treatments that have been mostly used or studied are the following:

- Oral glucocorticoids

They are used in many European countries for the treatment of AD. Its side effects limit its use especially for long-term treatment. Short-term treatment (up to 1 week) may be an option to treat an acute attack in exceptional cases of atopic eczema. Its restricted and limited use is recommended for adult patients with severe atopic eczema.

- Cyclosporine A

Inhibits the production of NF-AT (nuclear factor of activated T cells, which has been shown to be important in the immune response, it is expressed in most cells of the immune system.) dependent on pro-inflammatory cytokines in T cells. Cyclosporine can be used in chronic and severe cases of AD in adults, but its side effects (induces structural and organic kidney damage - Nephrotoxicity) limit its use.

- Azathioprine

It has been used for many years in Great Britain and the United States to treat AD in adult patients. Azathioprine can be used in people with AD if cyclosporine is not effective or is contraindicated.

- Mycophenolate Mofetil

An immunosuppressive drug used in many European countries to treat systemic lupus erythematosus and prevent transplant rejection. It can be used (off label) for the treatment of AD in adults at a dose of up to 2 g/day, if cyclosporine is not effective or is not indicated.

- Methotrexate

It is an immunosuppressant often used in psoriasis. Some doctors are using this substance in cases of AD, with good results. Methotrexate can be used to treat AD in adults if cyclosporine is not effective or is not indicated.

- Alitretinoin

A retinoid that binds to retinoid and rexinoid receptors, thus providing an anti-inflammatory and antiproliferative action. This molecule is used in some European countries for the treatment of chronic hand eczema, irrespective of its pathogenesis. Alitretinoin can be used for atopic hand eczema in adult patients, and an improvement in extrapalmar AD lesions is expected.

- Biological therapy

Biological agents present a relatively new group of therapies created using biological processes that include recombinant therapeutic proteins such as antibodies or protein fusion. Biological agents specifically target inflammatory cells and mediators. In AD, biological agents are used to reduce inflammation by modulating the number, activation and function of immune cells or the action of disease-relevant cytokines or antibodies. In patients with severe AD resistant to topical and systemic treatment, therapy with biological agents (omalizumab, rituximab, or alefacept) may be considered [11].

In a study carried out in mice (Oh *et al.*, 2013) the appearance of *Corynebacterium mastitidis* and *Corynebacterium bovis* was observed in the course of the disease and evidence that the use of specific antibiotics for these bacteria (including *S. aureus*) can reverse dysbiosis. The treatment results in the restoration of the skin's microbiome and greater diversity is believed to have greater advantages. The lipophilic yeast *Malassezia spp*. is related to atopic dermatitis contributing to skin inflammation and that antifungal therapy also has beneficial effects in some patients. Despite the current lack of strong scientific data and comparison with conventional steroid treatment, topical application of ketoconazole has shown improvement in eczema cases in clinical routine, adding to its anti-inflammatory properties.

As stated earlier, although this disease is strongly associated with seborrheic areas, no relationship was found between *Malassezia spp*. and its pathogenesis. On the other hand, AD, which commonly affects drier areas of the body, was related to lipophilic fungi. *S. aureus* is a spherical, gram-positive cocci bacteria commonly found on the skin and in the nasal cavities that can cause problems ranging from simple to severe infections. A problem related to *S. aureus* is the development of antibiotic-resistant strains, thus highlighting the need for new alternatives to deal with its overgrowth in AD. Although the treatment of AD with antimicrobials may have some benefits [4].

Currently, the hypothesis of treatment with probiotics has been studied, which, according to the Food and Agriculture Organization (FAO) and the World Health Organization (WHO), are “live microorganisms that confer health benefits on the host when administered in adequate amounts”. Thus, probiotics have the ability to restore intestinal microflora and stimulate intestinal barrier function [7].

AD comprises a set of host factors, with intestinal and cutaneous dysbiosis as one of the possible therapeutic targets. With so many factors associated with the disease, it is unclear whether changes in skin biology lead to changes in microbiome diversity or whether overgrowth of *Staphylococcus* species occurs initially, leading to disease progression. Therefore, a recent study found a relationship between chronic atopic dermatitis and dysbiosis of *Faecalibacterium prausnitzii* (*F. prausnitzii*) in the human intestine. After analyzing the intestine of 132 people, from which 90 had the disease, it was observed that the enrichment of the intestine with *F. prausnitzii* is strongly related. Furthermore, the

possibility of damage to the intestinal epithelium was verified through the observation of anti-inflammatory substances (butyrate and propionate) in the patients' faeces. Thus, it is possible that the development of methods focusing on *F. prausnitzii* will be useful in the diagnosis and treatment of AD. A prospective, double-blind, placebo-controlled study tested a lotion containing 5% non-pathogenic *Vitreoscilla filiformis* lysate. Seventy-five AD volunteers applied the lotion or placebo twice daily for 30 days. Then, the severity of the disease (Scoring Atopic Dermatitis - SCORAD - clinical tool used to assess the extent and severity of eczema), transepidermal water loss, microbiome and patient report of itching and sleep loss were evaluated. Lysate significantly improved DA on all items evaluated, reducing skin colonization by *S. aureus*. The authors concluded that the results are not only due to the reduction in the bacterial load of *S. aureus*, but also to the immunomodulatory effect on the skin. Subsequently, the immunomodulatory action of the lysate was confirmed by analyzing the differentiation of dendritic cells and the effector functions of dendritic cells and helper T cells in vitro and in vivo. Topical treatment with the bacteria significantly reduced inflammation in mice, and the combination of allergen and lysate showed less induced dermatitis, indicating active immunomodulation. It was observed that the innate sensitivity of non-pathogenic bacteria to Toll-Like Receptor 2 (TLR2) induces tolerogenic dendritic cells and Tr1 regulatory cells, suppressing T-effector cells and cutaneous inflammation. Usually commensal bacteria*, Streptococcus epidermidis (e*) showed inhibition of *S. aureus* in the skin, revealing its potential use in antimicrobial defense against skin infections. Undifferentiated exposure of human keratinocytes to sterile, non-toxic small molecules of <10 KDa in *S*. *epidermidis* conditioned medium increased human b-defensins 2 and 3 mRNA expression and the ability of lysates to inhibit *S. aureus*. The effect was also relevant in vivo with intradermal injection of medium conditioned with *S. epidermidis* in mice 24 and 2 hours before a local infectious challenge with group A *Streptococcus*. Treated mice had significantly lower infections when compared to those not exposed to *S. epidermidis*. . The study revealed the bacteria's potential to activate TLR2 signaling and induce the expression of the antimicrobial peptide, increasing the skin's response against the pathogen. It is believed that the serine protease Esp secreted by *S. epidermidis* not only inhibits biofilm formationbut can also destroy preexisting *S. aureus* biofilms and increase the susceptibility of these biofilms to immunological components. However, it is not known whether *S. aureus* and *S. epidermidis* mutually enhance each other's colonization or whether S. epidermidis increases in an antagonistic response to an increase in the population of *S. aureus*. In a double-blind study by Drago *et al.*, adult patients with moderate to severe atopic dermatitis were randomized into two groups: the first group received treatment with the probiotic *Lactobacillus salivarius* (*L. salivarius)* at a dose of 1 x 109 CFU/g in maltodextrin, and the second group received a placebo, made only of maltodextrin. Treatment consisted of consumption of sachets twice a day for 16 weeks. All patients completed the study and initially there was no difference in eczema severity between groups. After 4 months, a significant reduction in SCORAD was observed only in the probiotic-treated group, and no adverse effects were found during the study. Cytokine production by peripheral blood mononuclear cells was evaluated at the beginning and end of treatment. Patients treated with probiotics showed no change in cytokine production, while those treated with placebo showed a significant increase in IL-4 production associated with reduced IFN-c. Gueniche *et al.*, in an ex vivo study, demonstrated the inhibition of inflammation and barrier reconstruction through the use of *L. paracasei*. Another study, performed by Oh *et al.*, also showed potential beneficial effects where the inhibitory effects of *Lactococcus* sp. HY 499 were verified against the in vitro growth of *S. aureus* and *Propionibacterium acnes* (*P. acnes*), among other bacteria tested.

Since atopic AD is an inflammatory condition affected by skin dysbiosis, it can be considered that probiotics with the potential to restore these factors can contribute to the treatment of this pathology. A review by Sikorska and Smoragiewicz (2013) found a a lot of evidence that various strains of *Lactobacillus* and *Bifidobacterium* isolated from a variety of sources inhibit the in vitro growth of *S. aureus*. The most active strains were *Lactobacillus reuteri, Lactobacillus rhamnosus GG, Propionibacterium freudenreichii, P. acnes, L. paracasei, L. acidophilus, L. casei, Lactobacillus plantarum, Lactobacillus bulgaricus, Lactobacillus fermentum* and *Lactococcus lactis*. This review also included evidence that probiotics can also eliminate or reduce *S. aureus* resistant to methicillin. According to the authors, its effects are mediated both by cell competitive exclusion and by the secretion of acids or bacteriocin-like inhibitors. Based on this information, we can conclude that the use of probiotics can not only prevent the development of strains resistant to known antibiotics, making it progressively more difficult to treat infectious diseases, but also be used as an alternative to treat cases of resistant bacteria. Interestingly, the use of probiotics during pregnancy and early life has been linked to preventing this condition. A meta-analysis of clinical trials involving probiotics and pediatric atopic dermatitis analyzed key data from databases between 1997 and 2007 and concluded that current evidence supports a greater effectiveness of probiotics in the prevention than the actual treatment of AD. This information highlights the importance of balancing the microbiome even before the development of the disease. Although many studies indicate the efficacy and benefits of probiotics as an adjunct in the treatment of atopic dermatitis, according to Boyle *et al.*, there is also evidence that treatment with probiotics is not effective and has a small risk of adverse effects involved. In order for there to be a safe and effective use of probiotics, Extensive studies can be carried out to prove the real benefits of its use in dermatological conditions and to ensure that the benefits are outweighed by the adverse effects that may occur. In addition, the search for alternatives to deal with possible side effects is also important. The divergence of information

observed by Boyle *et al.* highlights the importance of highly reliable studies to obtain data that can be applied in the development of treatments for AD. A summary of the main conventional treatments for AD and the relationship between this pathology and the skin microbiome can be seen in Table 1. The divergence of information observed by Boyle *et al.* highlights the importance of highly reliable studies to obtain data that can be applied in the development of treatments for AD. A summary of the main conventional treatments for AD and the relationship between this pathology and the skin microbiome can be seen in Table 1. The divergence of information observed by Boyle *et al.* highlights the importance of highly reliable studies to obtain data that can be applied in the development of treatments for AD. A summary of the main conventional treatments for AD and the relationship between this pathology and the skin microbiome can be seen in Table 1 [4].

Table 1 Relationship between the microbiome and AD

Condition	**Conventional Treatment**	**Relationship with the microbiome**	**Potentially beneficial microorganisms**	**Main mechanism of action**	**Experimental model**
atopic dermatitis	Moisturizers	Low diversity of microorganisms	*Staphylococcus epidermis*	Activation of TLR2 and serine protease secretion	*in vitro*
	Topical corticosteroids	Increase in the proportion of *S. aureus*	*Lactobacillus salivarus*	immunomodulatory effect	*in vitro*
	Topical calcineurin inhibitors		*Lactobacillus paracasei*	Suppression of inflammation	*in vitro*
	Antibiotics		*Lactococcus* sp.	bacteriocin	*in vitro*
			Lactobacillus and *Bifidobacterium* strains	Inhibition of the growth of *S. aureus* populations	*in vitro*

Probiotics are generally considered safe, but they are not without adverse effects. The Food and Drug Administration (FDA) classifies probiotics as foods, cosmetics, dietary supplements, medical blades not yet considered as medicines.

Research into the clinical safety of probiotics before marketing is important to avoid unwanted effects. Therefore, probiotics must receive FDA approval, like any other drug, including filling out the application for investigation of new drugs and clinical trials. However, labeling of probiotics by manufacturers may include unsubstantiated therapeutic claims, such as misidentification of the probiotic and dose, subjecting the consumer to error. Thus, the Health and Quality Research Agency (AHRQ) states that the available literature is insufficient to confidently determine the safety of using probiotics.

Furthermore, the WHO and the FAO (Food and Agriculture Organization) of the United Nations, demonstrate that probiotics have 4 adverse effects: systemic infections, harmful metabolic activities, excessive immune stimulation in susceptible individuals and gene transfer.

Therefore, future research should assess the efficacy and safety of probiotics as there is a need for improved regulations and labeling. If probiotics and bacteriotherapy are approved as biotherapeutic, these investigations will pave the way for more appropriate regulation and standardization in effective clinical use. However, the safest probiotics that dominate commercial formulas are *Lactobacillus* and *Bifidobacterium* [7].

There are three types of prevention for this pathology: primary, secondary and tertiary. Primary prevention refers to intervention before health effects occur. Secondary prevention involves detecting the disease at an early stage in order to prevent its worsening and tertiary prevention is the reduction of symptoms or improvement in the quality of life of those with an already established disease [12].

AD is an inflammatory skin disease associated with changes in the skin microbiome, with a complex pathogenesis that includes imbalance in immune system signaling, impaired skin barrier and increased skin colonization by *Staphylococcus aureus*. Skin bacterial communities are characterized by increased colonization of *S. aureus*, leading to reduced diversity compared to bacterial communities in healthy skin, and increasing disease severity. On the other hand, fungal communities are richer and more diverse in the skin of AD patients [13].

In recent studies, changes in the skin microbiome have been observed in patients with atopic dermatitis along with the course of treatment. A drastic increase in microbial diversity and a decrease in the proportion of *S. aureus* were observed [14].

This literature review work aims to collect information on the topic "Skin microbiome vs. Atopic dermatitis" and its objective is to verify if there is a relationship between the skin microbiome and atopic dermatitis, what are the changes in the microbiome when we are faced with a case of atopic dermatitis and how to treat it, effectiveness and safety. However, the work has secondary objectives, such as, for example, understanding the constitution of the healthy microbiome and what leads the skin to produce the reactions that lead to the appearance of this disease. Thus, by studying these topics separately, one can arrive to the answer to the main question.

2. Material and methods

This study is a literature review, carried out between November 2021 and June 2022 and for its accomplishment, free access articles were collected from "Pubmed", "NCBI" and "Google schoolar" databases. The keywords used in the research were "Atopic dermatits", "Skin microbiome" and "Human skin". This study includes all scientific articles and scientific reviews that are of interest to the topic in question, with their publication dates between 2005 and 2020. In the databases used, a total of 40 articles were found, of which 14 were used in this bibliographic review being: 1 article from the year 2005, 1 article from the year 2012, 1 article from the year 2016, 2 articles from the year 2017, 2 articles from the year 2018, 3 articles from the year 2019 and 4 articles from the year 2020.

3. Results and discussion

Williams H., in 2005, studied pediatric atopic dermatitis in a specific case of a 10-year-old girl and concluded that both patients and family members are sometimes concerned about the use of topical corticosteroids. For these concerns to be alleviated, the course of this disease must be explained to the patient and family, that is, that a single cause and cure are unlikely, although it is possible to control the progression of the pathology. The author also concluded that for the specific case described in the article, he would recommend once-daily application of a potent topical corticosteroid to the limbs and trunk, with a duration of 10 days, before scheduling a second visit to assess progress. Although data to support the use of emollients are limited, the author tried to maintain remission only by liberal use of emollients, using potent or moderate intensity topical corticosteroids for attacks for 5 days. If such a regimen failed to maintain adequate quality of life, the author would introduce "weekend therapy" – that is, the application of a potent corticosteroid to new and previously active sites of atopic dermatitis every Saturday and Sunday at night to reduce itching. Alternatively, intermittent use of topical tacrolimus or pimecrolimus can be used to reduce rashes. If facial dermatitis requires continued use of mild topical corticosteroids, the author recommends using topical tacrolimus, 0.03 percent, twice daily for three weeks and then once daily until AD resolves using potent or moderate-intensity topical corticosteroids for attacks for 5 days. If such a regimen failed to maintain adequate quality of life, the author would introduce "weekend therapy" – that is, the application of a potent corticosteroid to new and previously active sites of atopic dermatitis every Saturday and Sunday at night to reduce itching. Alternatively, intermittent use of topical tacrolimus or pimecrolimus can be used to reduce rashes. If facial dermatitis requires continued use of mild topical corticosteroids, the author recommends using topical tacrolimus, 0.03 percent, twice daily for three weeks and then once daily until AD resolves using potent or moderate-intensity topical corticosteroids for attacks for 5 days. If such a regimen failed to maintain adequate quality of life, the author would introduce "weekend therapy" – that is, the application of a potent corticosteroid to new and previously active sites of atopic dermatitis every Saturday and Sunday at night to reduce itching. Alternatively, intermittent use of topical tacrolimus or pimecrolimus can be used to reduce rashes. If facial dermatitis requires continued use of mild topical corticosteroids, the author recommends using topical tacrolimus, 0.03 percent, twice daily for three weeks and then once daily until AD resolves. If such a regimen failed to maintain adequate quality of life, the author would introduce "weekend therapy" – that is, the application of a potent corticosteroid to new and previously active sites of atopic dermatitis every Saturday and Sunday at night to reduce itching. Alternatively, intermittent use of topical tacrolimus or pimecrolimus can be used to reduce rashes. If facial dermatitis requires continued use of mild topical corticosteroids, the author recommends using topical tacrolimus, 0.03 percent, twice daily for three weeks and then once daily until AD resolves. If such a regimen failed to maintain adequate quality of life, the

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Ring J. *et al.*, in 2012, they studied the different treatment options for AD cases, as well as their effectiveness. The authors found that the control of AD should consider the individual symptomatic variability of the disease. Basic therapy is focused on topical moisturizing treatment and the prevention of specific and non-specific provoking factors. Anti-inflammatory treatment based on topical glucocorticosteroids and topical calcineurin inhibitors (TCI) is used in cases of exacerbations and, more recently, for proactive therapy in selected cases. Topical corticosteroids remain the mainstay of therapy, but TCI tacrolimus and pimecrolimus are distinct in certain locations. Systemic immunosuppressive treatment is an option for severe refractory cases. Microbial colonization and superinfection may induce disease exacerbation and may warrant additional antimicrobial treatment. Adjuvant therapy includes UV irradiation preferably with a UVA or UVB wavelength of 311 nm. Dietary recommendations should be specific and given only in cases of individual diagnosed food allergy. Allergen-specific immunotherapy to aeroallergens may be helpful in selected cases. In cases where exacerbations are stress-induced, psychosomatic counseling is recommended. Pruritus is the target of most recommended therapies, but some patients require additional antipruritic therapy. Dietary recommendations should be specific and given only in cases of individual diagnosed food allergy. Allergen-specific immunotherapy to aeroallergens may be helpful in selected cases. In cases where exacerbations are stress-induced, psychosomatic counseling is recommended. Pruritus is the target of most recommended therapies, but some patients require additional antipruritic therapy. Dietary recommendations should be specific and given only in cases of individual diagnosed food allergy. Allergen-specific immunotherapy to aeroallergens may be helpful in selected cases. In cases where exacerbations are stress-induced, psychosomatic counseling is recommended. Pruritus is the target of most recommended therapies, but some patients require additional antipruritic therapy [11].

Micha R., in 2017, studied the composition and dynamics of the skin microbiome in acne pathology and the effects of antibiotic treatment on skin microbes. They concluded that the use of bactericidal and anti-inflammatory antibiotics continues to be an important strategy for the treatment of acne, being preferable the rational selection of antibiotics according to the classification of *P. acnes* strains and the susceptibility to the corresponding substance. Given the rapid emergence of antibiotic resistance on a global scale and considering the effects of antibiotic use on the human microbiome, alternative clinical practice to prescribing antibiotics in the treatment of microbial related diseases has become urgent. A recently published study suggested a potential acne vaccination approach, targeting the Christie-Atkins-Munch-Petersen (CAMP) factor as an antigen. Meanwhile, other studies have shown promise in microbiome-based therapies, which can alter the balance between microbial members, influence immune cell function, and prevent disease while restoring a healthy microbiome. In one of these studies, Nakatsuji *et al.* showed that reintroduction of coagulase-negative *Staphylococcus* (CoNS) strains, which produce antimicrobial peptides, decreased the colonization of *S. aureus* in the skin in patients with atopic dermatitis. The study demonstrated how commensal skin bacteria can defend against pathogens and suggested that correction of microbiome dysbiosis could potentially be used to treat or improve certain conditions. Other studies have shown promise in microbiome-based therapies, which can alter the balance between microbial members, influence immune cell function, and prevent disease while restoring a healthy microbiome. In one of these studies, Nakatsuji *et al.* showed that reintroduction of coagulase-negative *Staphylococcus* (CoNS) strains, which produce antimicrobial peptides, decreased the colonization of *S. aureus* in the skin in patients with atopic dermatitis. The study demonstrated how commensal skin bacteria can defend against pathogens and suggested that correction of microbiome dysbiosis could potentially be used to treat or improve certain conditions. other studies have shown promise in microbiome-based therapies, which can alter the balance between microbial members, influence immune cell function, and prevent disease while restoring a healthy microbiome. In one of these studies, Nakatsuji *et al.* showed that reintroduction of coagulase-negative *Staphylococcus* (CoNS) strains, which produce antimicrobial peptides, decreased the colonization of *S. aureus* in the skin in patients with atopic dermatitis. The study demonstrated how commensal skin bacteria can defend against pathogens and suggested that correction of microbiome dysbiosis could potentially be used to treat or improve certain conditions. influence immune cell function and prevent disease while restoring a healthy microbiome. In one of these studies, Nakatsuji *et al.* showed that reintroduction of coagulase-negative *Staphylococcus* (CoNS) strains, which produce antimicrobial peptides, decreased the colonization of *S. aureus* in the skin in patients with atopic dermatitis. The study demonstrated how commensal skin bacteria can

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Robert C. *et al.*, in 2017, studied new therapeutic approaches for moderate to severe AD. As AD treatment evolved towards precision medicine, several biologic drugs and small molecular agents were developed to block specific cytokines, cytokine receptors or transcription factors. Dupilumab is a monoclonal antibody and has been approved by the US Food and Drug Administration for the treatment of moderate to severe AD. In a Phase 3, multicentre, randomized, double-blind, placebo-controlled, parallel-group study, adolescents were given subcutaneous injections of dupilumab monotherapy every 2 or 4 weeks, with a significant improvement in EASI 75 (Eczema Area and Severity Index) at week 16 of treatment.

Therapeutic indications in this pathology are increasing in both adults and children and the formulations are increasingly diversified, ranging from injections to topical creams and oral forms. These medications are specific to certain molecules that cause skin inflammation. Most newer biologics and small molecule antagonists have been reported to be effective and well tolerated. In the future, research in large populations of AD will be necessary to improve therapeutic results and ensure the safety of drugs, as well as the study of new therapeutic approaches, the most promising of which are microbial skin transplantation, biological products and small molecular antagonists targeting major immune pathways [9].

Byrd AL. *et al.*, in 2018, describe DNA metagenomic sequencing studies that were used to assess the taxonomic diversity of microorganisms that are associated with the skin. They discussed recent information on skin microbial communities, including their composition in health and disease, dynamics between species, and interactions with the immune system, focusing on *Propionibacterium acnes, Staphylococcus epidermidis,* and *Staphylococcus aureus.* Although the studies the authors describe advance their understanding of the human skin microbiome, many questions remain about the function of the skin microbiota: what is the role of microorganisms in the skin and in maintaining health or promoting disease states [2].

Mottin VHM*. et al.*, in 2018, developed a review of several articles about changes in the skin microbiome, specifically in acne and AD, which aimed to search for potential treatments based on beneficial microorganisms, called probiotics. Some microorganisms have been shown to act not only in prevention, but also in competition for pathogenic microorganisms and beneficially affect the inflammatory process present in these pathologies. Despite the wide variety of bacteria tested, *Vitreoscilla filiformis* (V. filiformis), *Staphylococcus epidermidis (S. epidermidis*), and species of *Lactobacillus* and *Bifidobacterium* are the ones that showed the greatest potential in the treatment of AD [4]

Bouslimani A. *et al.*, in 2019, performed a study in which they evaluated the impact of four beauty products (a face lotion, a moisturizer, a foot powder and a deodorant) on 11 volunteers over 9 weeks. Mass spectrometry and 16S rRNA inventories of the skin revealed decreases in chemical and bacterial levels and archaea diversity in deodorants discontinuation. Specific compounds from beauty products used before the study remain detectable with half-lives of 0.5 to 1.9 weeks. Deodorant and foot powder increased molecular, bacterial, and archaeal diversity, while arm and face lotions had little effect on bacteria and archaea, but increased chemical diversity. [5]

Torres T. *et al.*, in 2019, carried out a non-systematic review based on a literature search directed at the epidemiology, pathophysiology, clinical features, comorbidities and treatment of atopic dermatitis2. It concluded that although there is currently a better understanding and greater knowledge of the disease, future investigations should continue to explore the interaction between genetic (better definition of AD genotypes and clinical phenotypes) and environmental factors and their effects on disease pathophysiology and severity, as well as treatment outcomes [8].

Kwon S. *et al.*, in 2019, evaluated changes in the skin surface microbiome in patients with atopic dermatitis during treatment. A study was done with 18 people with atopic dermatitis. Patients were divided into 2 groups according to the treatment they would receive. Group 1 was treated with ultraviolet B phototherapy and topical corticosteroids and group 2 was treated with topical corticosteroids only. The microbial diversity of skin lesions greatly increased after treatment. The proportion of *Staphylococcus aureus* showed a significant positive correlation with the severity of eczema. Therefore, the authors concluded that a drastic increase in microbial diversity and a decrease in the proportion of *S. aureus* were observed throughout the treatment of eczema [14].

Natália R. *et al.*, in 2020, carried out a systematic review with the objective of determining the effect and safety of probiotics in reducing the incidence of Atopic Dermatitis, from the pre/postnatal period in infants and children or adults, with the most studied and effective probiotics belonging to the *Bifidobacterium* and *Lactobacillus* genera. The results of this study demonstrate efficacy, efficiency and safety in reducing the incidence of atopy [7].

Frazier W. *et al.*, in 2020, surveyed the most used treatments in cases of AD, such as the use of emollients and daily baths with soap-free cleaning products, the use of topical corticosteroids and calcineurin inhibitors such as pimecrolimus and tacrolimus, ultraviolet phototherapy and antistaphylococcal antibiotics, making a brief reference also to the use of dupilumab. The authors also addressed the diagnostic methods most used in this pathology, which are based on the symptoms presented as well as on physical examinations [10].

Williams HC. *et al.*, in 2020, carried out a systematic review of AD prevention strategies such as the promotion of prolonged breastfeeding, or interventions that reduce ingested or airborne allergens during pregnancy and after birth, as well as the intake of maternal/ infantile, as Vitamin D. However, none of these measures demonstrated effectiveness in the prevention of this pathology. The authors also studied the hypothesis that probiotics could reduce the incidence of AD by about 20%. Improving the skin barrier from birth to prevent AD and food allergy were also one of the prevention options addressed throughout the study [12].

Edslev SM. *et al.*, in 2020, performed a systematic review with the aim of providing an overview of recent literature on the skin microbiome in atopic dermatitis. Therefore, they concluded that several studies have shown that the increase in the *S. aureus* community and the loss of bacterial diversity in the skin are associated with disease severity and crises in children and adults with AD. The increased burden of *S. aureus* colonization is likely facilitated by changes in the skin, including reduced levels of filaggrin and NMFs leading to increased skin pH and compromised skin barrier. Furthermore, the deficiency of commensal bacterial strains with *S. aureus* inhibitory properties contributes to the increase in *S. aureus* density in AD cases. Functional assays indicate that *S. aureus* can exacerbate AD by expressing virulence factors that induce skin inflammation and disruption of its barrier. Thus, changes in the composition of the bacterial community of the skin can be an important inducer of the clinical picture in individuals with established disease.

Currently, there are several treatment options for AD, the most common being the use of topical corticosteroids, emollients and topical moisturizing therapy. The anti-inflammatory treatment of this pathology is based on topical glucocorticosteroids and topical calcineurin inhibitors, such as tacrolimus and pimecrolimus. Microbial colonization and superinfection may induce disease exacerbation and may warrant additional antimicrobial treatment. New therapeutic approaches such as microbial skin transplantation, biological products and small molecular antagonists targeting the main immunological pathways as well as treatments based on microorganisms called probiotics have been studied.

In terms of the skin microbiome, it can be concluded that throughout the course of this pathology there is an increase in the *S. aureus* community as well as a loss of bacterial diversity in the skin. These factors are associated with disease severity and the increased burden of *S. aureus* colonization is facilitated by changes in the skin, including reduced levels of filaggrin and NMFs leading to increased skin pH and compromised skin barrier. Furthermore, the deficiency of commensal bacterial strains with *S. aureus* inhibitory properties contributes to the increase in *S. aureus* density in AD cases. Therefore, it is concluded that cutaneous *S. aureus* can exacerbate AD by expressing virulence factors that induce skin inflammation and disruption of its barrier.

4. Conclusion

In this literature review, AD was studied and what changes occur in the skin microbiome when faced with this pathology, concluding that there is an increase in the proportion of *S. aureus* and a loss of microbial diversity.

The most effective and used therapy is based on the use of emollients and a daily bath with soap-free cleaning products, application of body moisturizers and the adoption of behaviors that reduce skin dryness and the use of corticosteroids. Although this therapy is quite effective, topical therapeutic innovations are expected involving formulations of microorganisms to control skin conditions, such as probiotics. For this to be possible, greater knowledge and more clinical studies will be needed on the microbiome of different parts of the body, its variations over time and seasonal changes, as well as the effect of factors such as hygiene, lifestyle, and geographic locations, among others.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that they have no conflict of interesting**.**

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