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 ORIGINAL ARTICLE

Atopic Dermatitis and the Role of the Skin Microbiome in Choosing Prevention, Treatment, and Maintenance Options

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ABSTRACT

Background: Atopic dermatitis (AD) is a common skin condition characterized by disturbed barrier function, skin inflammation, and cutaneous dysbiosis. Clinically, it manifests as chronic-recurrent xerosis, pruritus, and erythematous lesions. Its pathophysiology is complex, making the selection of appropriate treatment options a task.

Aim: To share insights gained from a literature review and discussions with experts in dermatology on key factors related to the prevention, treatment, and management of AD in relation to the skin microbiome.

Methods: Results from an expert panel were summarized and discussed to provide updated recommendations for the treatment and maintenance of AD.

Results: Evidence supports a strategy for managing inflammatory skin diseases with a selenium-rich post-biotic thermal water and biomass containing moisturizer. The moisturizer helps to restore homeostasis of the skin, re-populate a diverse microbiome, encourage the growth of commensal bacteria, and improve barrier function and symptoms of AD.

Conclusions: Normalization of skin microbiome diversity using a topical moisturizer containing post-biotic aqua and biomass may offer a valuable option for the treatment and maintenance of inflammatory skin diseases. Clinicians should discuss the benefits of this treatment in the context of a full AD management program that covers prevention, active treatment, and maintenance.

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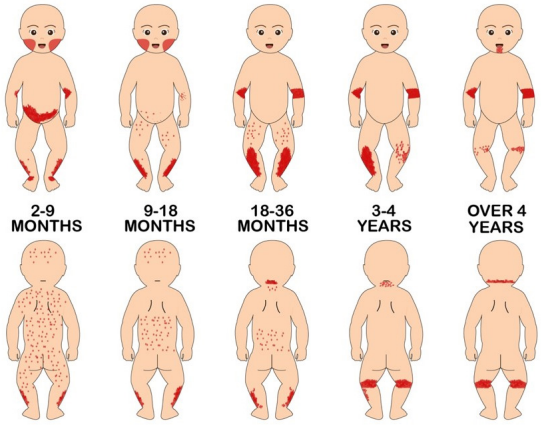
INTRODUCTION

Atopic Dermatitis

Atopic dermatitis (AD) is a common inflammatory skin condition characterized by chronic-recurrent xerosis, pruritus, and erythematous lesions.[1] In industrialized countries, the prevalence of AD has been rising since the 1940s; and it is now one of the most frequent chronic inflammatory skin disorders in the world.[2,3] With a reported prevalence of over 20% in children and up to 8% in adults,[1,4-7] over 92 million people in the United States (U.S.) alone suffer from AD. As there are no objective diagnostic tests for AD,[1] diagnosis is made clinically based on the presence of one or more symptoms, which often include: pruritus, erythema, scaling, xerosis, edema, excoriations, oozing, crusting or lichenification.[2,5] Although AD can affect any area of the body, the typical anatomical locations of flare-ups (defined as acute, clinically significant worsening of the signs and symptoms of AD)[8] depend on age, and patterns change between infancy, childhood, and adulthood.[9] For example, in

FIGURE 1. Common anatomical locations of atopic dermatitis in infancy and childhood, by age range.



infancy, the cheeks are often affected (Figure 1), whereas in adulthood, it preferentially affects the head, neck and flexures eg, antecubital fossae, popliteal fossae.[8,9] AD is associated with substantial disease-related morbidity and disability.[1] Of all skin disorders, AD has the highest disability-adjusted life-years.[10,11] While there are few estimates of the costs of AD, a 2002 study estimated that the direct costs to the payer were USD 3.8 billion, per year.[12]

AD Populations

Children are particularly at risk for developing AD. The onset of AD displays an age-dependent distribution;[6] with symptoms typically appearing between two to six months of age and with 90% of atopic-prone children developing AD by the age of five years.[5] The severity of AD can be classified based on symptomatology, skin lesion characteristics and the size of the affected skin area.[4] Population-based survey data from the U.S. has revealed that the majority (ie, 67%) of childhood AD encompasses a mild disease state, followed by 26% and 7% of moderate and severe disease states, respectively.[4,7,13] There is also evidence to suggest that individual risk factors may predispose specific individuals to AD. Notably, while there is a slight-to-no association between AD and gender,[14,15] there are racial/ethnic disparities, with the severity of AD being higher in African and East Asian populations.[1,16-18] Patients with AD often present with inflammatory diseases, which has led some investigators to believe that systemic immunity may predispose specific individuals.[19] Given the wide variation in prevalence rates worldwide (ie, from 0.9% in India to 24.6% in Columbia), environmental factors are also thought to be involved with the development of AD.[1] While research has investigated many contributing components individually, recent findings indicate that a complex interaction between the environment, host's genetics, skin barrier function, and an immune response are implicated in the development of AD.[2,3]

The Tri-Directional "AD-Skin Barrier-Microbiome Trinity"

AD is a multifactorial disease, with considerable individual variation with regards to the impact and combination of contributing factors.[3] As such, AD has been described as a "heterogenous eczematous disorder".[4] This heterogeneity contributes to the fact that the causes of AD are poorly understood. While its pathogenesis is complex, AD can be characterized by skin barrier dysfunction, aberrant immune response and dysbiosis.[2] As early as the 1990s, investigators have been exploring the hypothesis that a cutaneous barrier abnormality initiates the pathogenesis of AD.[3,20-22] This hypothesis followed the discovery of evidence that suggested a non-immune causative event early in the development of AD. In 2012, Kong and coworkers hypothesized that a decrease in microbial diversity and an increase in the population of staphylococcus precedes the flare of AD (Figure 2). The flared state is characterized by low bacterial diversity, consisting largely of staphylococcus. Only once diversity is increased, and the staphylococcus population normalized does the flare resolve and skin return to its baseline. Since then, the role of barrier function in AD has been investigated in numerous clinical trials.[23-25] Resulting from a disruption in the skin's barrier is an increase in trans-epidermal water loss, and a decrease in skin hydration, a reduction in ceramides, fillagrin, and antimicrobial peptides. Dry and pruritic skin ensues, which prompts scratching, an exacerbation of the barrier dysfunction, and establishment of the itch-scratch cycle. Additionally, barrier dysfunction permits the penetration of external stimuli, such as allergens, toxins, irritants and bacteria which may lead to irritation, inflammation, or infection.[26]

While dysbiosis and barrier disruption are both components of AD, it is unclear which is the chicken and which the egg. Does the disease cause dysbiosis and barrier defect or does the aberrant stratum corneum cause atopic dermatitis? In consideration of these findings, a new concept of the pathogenesis of AD has emerged, which considers the microbiome, barrier function, and AD as an interplaying trinity.

METHODS

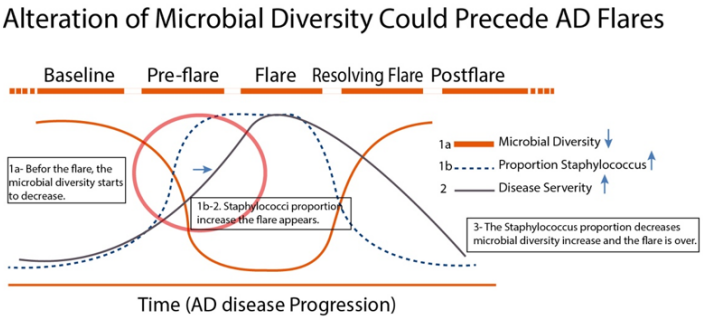
A working group of clinicians, all experienced in managing patient populations with AD, convened for a one-day meeting in New York City on November 2, 2019. To optimize clinical outcomes in AD, the panel reviewed literature surrounding the topic of the skin microbiome in patients with AD and developed and discussed clinical recommendations related to prevention, treatment, and maintenance of AD.

Key Insights

Cutaneous Dysbiosis in AD

Skin microbes play a critical role in maintaining skin health: controlling pathogenic species, priming the immune system, and preventing inflammation and infection. In another bi-

FIGURE 2. The relationship between the skin microbiome and atopic dermatitis. An increase in the proportion of *Staphylococcus aureus* and a reduction in microbial diversity precedes atopic dermatitis exacerbation and the severity of flares-ups. *Figure adapted from Kong et al, 2012.*[34]



directional relationship, dysbiosis leads to barrier dysfunction and barrier dysfunction results in aberrant microbiome.[29] The cutaneous microbiome is an ecosystem that includes a diverse array of microorganisms, including viruses, fungi, mites, and bacteria.[31] The composition of this ecosystem can be altered by many factors, including but not limited to anatomical location,[32] pH, moisture level, and the distribution of hair follicles and sebaceous glands, gender, age, and ethnicity.

A recent review investigated the relationship between the skin microbiota and barrier function and describes how each component can affect the other.[29] Baldwin et al (2017) describe how the skin microbiota can interact with the cutaneous barrier through the release of proteases, lipases, ureases, bactericidal peptides and by quorum sensing and skin nutrition. Conversely, they also describe how the skin barrier interacts with the microbiota through mechanisms such as providing nutrients, controlling the climate, and balancing and regulating bacteria.[29]

In AD and other inflammatory disorders such as psoriasis and acne vulgaris, the importance of maintaining a balanced and diverse microbiota has been demonstrated. In an environment that favors invasive organisms, colonization of pathogenic bacteria may ultimately breakdown the cutaneous barrier. Indeed, over 90% of AD patients have colonization of the pathogenic bacteria *Staphylococcus aureus*, and increasing disease severity has been found to correlate with a reduction in microbial diversity. The temporal shifts in the skin microbiome have long been associated with AD flares. For example, microbial communities at disease sites are dramatically different in AD patients compared to controls.[34] In AD, the proportion of *S. aureus* and commensal *S. epidermidis* are significantly increased during flare-ups; and following therapy, colonies of *Streptococcus, Propionibacterium,* and *Corynebacterium* species are observed.[34] These findings reveal an association between skin microbiome and AD.

Current Topical Treatments for AD

Standard topical therapy in AD includes topical corticosteroids (TCS), calcineurin inhibitors (TCI) and crisaborole, all of which function by inhibition of numerous aspects of the inflammatory response in AD. The use of TCS ultimately reduce the expression of pro-inflammatory genes and effectively reduce inflammation by suppressing the immune reaction mediated by lymphocytes, mast cells, eosinophil, dendritic cells, and macrophages.[9] However, high potency TCS are not suitable for sensitive areas, such as the face, eyelids, genitals, and skin folds; there are local and systemic side effects associated with the extended use of TCS, such as skin atrophy, telangiectasia, striae, dyspigmentation, development of glaucoma, hypothalamic-pituitary-adrenal axis suppression, growth retardation, and Cushing's syndrome.[35,37] Therefore, TCS are not suitable for everyone or in all cases of AD management.

TCIs, such as tacrolimus and pimecrolimus that were approved in 2006, are macrolactams with immunosuppressive characteristics. Like TCS, TCIs decrease the release of pro-inflammatory cytokines. Unlike steroids, they lack many of the unwanted side effects on healthy skin. Also, TCIs have lower transepidermal fluxes, which was thought to increase their safety.[37] However, 5–6 years after release, the FDA issued a black box warning for both drugs regarding the theoretical risk of malignancy. This warning was met with criticism from numerous medical associations regarding the scientific rationale for this decision. Side effects of use are primarily complaints of skin warmth and burning.

Crisaborole ointment (Eucrisa, Pfizer) is a phosphodiesterase type 4 inhibitor with demonstrated efficacy and safety in patients aged two years and older with mild-to-moderate AD.[38] Two multicenter phase III trials demonstrated sustained efficacy when using crisaborole ointment in patients with mild-to-moderate AD, over 28 days.[38] When compared to vehicle, treatment with crisaborole ointment showed reduced pruritus and other signs of AD.[39] Primary side effects of crisaborole are stinging and burning of the skin which generally resolves over time.[39] Furthermore, although TCS and TCIs are effective at reducing the inflammation associated with AD flares, they do not correct abnormalities to the cutaneous barrier, which is a major contributor to the pathogenesis of AD. It is important to remember that although TCS, TCIs and crisaborole are effective at reducing the inflammation associated with AD flares, they do not effectively repair the skin barrier which is a major contributor to the pathogenesis of AD.

The use of quality moisturizers containing occlusives and humectants have been found to improve barrier function, reducing trans-epidermal water loss and improving skin hydration.[35,40] However, partial restoration of the barrier function in AD-affected skin with emollients is not always sufficient as it

does not completely address all aspects of the flawed physiology of the cutaneous barrier. Furthermore, the durability of effect is relatively short lived. As such, they offer only partial and temporary restoration of the skin's barrier function.[36] Utilizing barrier repair creams with physiologic lipids help to address the shortcomings of conventional everyday moisturizers.

Restoring the Diversity of Skin Microbiota in AD Patients

Skin microbes play a critical role in maintaining skin health (eg, suppressing pathogenic species, priming the immune system, preventing inflammation and infection). Microorganisms require water to thrive, and the amount of available water in particular areas partially determines which type of bacteria can inhabit that location. In such a way, water can be viewed as both a culture medium and a prebiotic.[41] Dry environments favor the growth of *S. aureus* and inhibit the growth of beneficial commensal organisms such as coagulase-negative staphylococci.[29] Commensal bacteria thus compete with pathogenic bacteria for the same ecological niche. In unfavorable environmental conditions, (ie, dry skin), this can become problematic as commensal bacterial are an integral part of the healthy innate immune system and provide protection against inflammation and infection.[29] Therefore, maintaining the skin's moist barrier and homeostatic microbiota is necessary to reduce the promotion of pathogenic species and the chronic persistence of AD symptoms.

Through overpopulation of pathogenic organisms comes a loss of the skin's barrier and, subsequently, increased susceptibility to chronic inflammation. This understanding of the critical role of the cutaneous barrier in the pathogenesis of AD has led to recent advances in barrier repair therapies. Many topical treatments have been found to restore the skin's barrier in AD[36,42,43] and some have been found to diversify bacteria preceding the observed improvements in skin barrier function and disease severity.[34] This has led to the hypothesis that the regulation of bacterial populations is necessary to restore skin homeostasis in AD. While emollients can restore barrier function, experts agreed that this is not sufficient to treat AD-affected skin. Instead, they proposed that regulation of bacterial populations to restore homeostasis is required.

The effect of supplementation with probiotics on AD development and severity has been studied in various clinical trials with controversial results.[44-48] Some studies have evaluated the application of prebiotics to "feed" the bacteria, which are part of the healthy epidermis. Following promising preclinical results,[49,50] a treatment formula containing lysates from the Gram-negative bacterium *Vitreoscilla filiformis*, grown in a LRP-Thermal Spring Water (TSW), significantly improved AD severity in a randomized trial.[51]

Post-biotic Aqua Posae Filiformis

The post-biotic Aqua Posae Filiformis (APF), a biomass of *Vitreoscilla filiformis*, a non pathogenic bacteria grown in a medium containing La Roche Posay Themal spring water (LRP-TSW) has been shown to act on the balance of the microfloral balance, without the use of antibiotics.[50] LRP-TSW exhibits both pre- and probiotic properties that enhance the diversity of the skin microbiome.[52] A recent review was undertaken to explore the role of LRP-TSW as a topical pre- and probiotic therapy in improving the diversity of the skin microbiota and reducing dryness and pruritus in inflammatory skin diseases.[52] Investigators concluded that the concentration of minerals (eg, selenium) and nonpathogenic microbes in crude LRP-TSW is thought to explain its therapeutic benefit when used for inflammatory skin diseases at the thermal center of LRP. Clinical studies have shown topical LRP-TSW treatments stimulate the growth of Gram-negative bacteria at the expense of Gram-positive bacteria, which improves skin microbial diversity.[52] This results in an improvement in both non-diseased dry skin and inflammatory skin conditions. These findings support the historical use of thermal spa waters to treat inflammatory disorders. LRP balneotherapy has been shown to effectively treat AD through optimizing microbial diversity to decrease the severity of active lesions.[52]

Recently, it was found that applying an emollient containing LRP-TSW and the biomass of APF (Lipikar Balm AP+, La Roche-Posay Pharmaceutical Laboratories, France), to AD-affected skin was able to return the compositional balance of the microbiome to that of nearby unaffected skin. The composition of this LRP-TSW and APF emollient has been described previously and is summarized in Table 1.[54] In this pivotal study, AD symptoms improved for over 70% of the subjects, with a concurrent increase of bacterial diversity and a decrease in the abundance of Staphylococcus on the affected skin.[54] This trial was significant for confirming the importance of a reduction in the composition of microbial communities in AD flares. For the first time, investigators demonstrated that the topical application of a prebiotic could be used as a therapeutic approach to modulate or balance the immune system and normalize the cutaneous microbiota. Moreover, these results were found to last for at least one month following the discontinuation of the treatment.[55]

DISCUSSION AND CONSENSUS

Guidelines for the topical treatment of AD have not changed significantly over the past ten years with the exception of the introduction of crisaborole.[4,8,34,36] However, treatment of more severe AD has changed dramatically due to the development of agents that target immune responses and inhibit T cells and target Th1, Th2, Th22, phosphodiesterase-4 (PDE4), IL-4, and IL-31.[56] The traditional paradigm of using steroid and antimicrobial strategies to control AD flares is shifting towards a more holistic approach, which encourages optimizing the microbiome through regulatory factors.[30-32] Advisors agreed that the skin microbiota plays a key role in dermatologic health and disease and that skin barrier repair is imperative to AD management.[2,3,21,23] As such,

TABLE 1.

Ingredients of the LRP-TSW Moisturizer[55]		
Component	**Ingredients**	**References**
Emollient A	Shea butter (20%), niaciniamide (4%), mannose	Seite, Zelenkova, Martin (2017)[55]
LRP-TSW	Bicarbonate (387mg/L), calcium (149mg/L), silicate (31.6mg/L), magnesium (4.4mg/L), strontium (0.3mg/L), selenium (0.053mg/L), zinc (<0.005mg/L), copper (<0.005mg/L)	Seite (2013)[53]
Biomass	*Vitreoscilla filiformis*	Seite, Zelenkova, Martin (2017)[55]

they recommend that skincare products targeting AD should be developed with a focus on maintaining the balance of healthy skin microbiome. Overall, board members were in agreement that maintaining microbial homeostasis is a crucial component of AD therapies. Currently, an AD management program that includes reducing pathogenic organisms, optimizing the re-population of the (healthy diversified) microbiome, and restoring the skin barrier is needed. As the microbiome plays a role in the prevention of AD and also in the active phase of the disease,[39,50] a product displaying pre- and post-biotic activity may prove beneficial.

Given the biological properties of LRP-TSW and of the biomass of *Vitreoscilla filiformis*, its use in a LRP-TSW and APF emollient for treating AD warrants consideration as a new strategy for treating inflammatory skin conditions.[52,53] This process combines the beneficial effects of an emollient containing the lysate of nonpathogenic bacteria *Vitreoscilla filiformis*, to target a significant factor in the pathogenesis of AD. LRP-TSW displays anti-free radical, immunomodulatory, anti-inflammatory properties. It also introduces selenium and strontium to reduce the production of inflammatory cytokines.[53] Furthermore, the biomass contained in the LRP-TSW and APF emollient releases lysates that normalize dysbiosis, re-balancing the bacterial content of lesions and nonlesional areas of AD skin.[55] Given these findings, investigators approved of the use of this selenium-rich TSW as an active ingredient in topical, irritant-reducing formulations.[53] Overall, these findings suggest that a new strategy for managing inflammatory skin diseases may be to combine the use of pre- and post-biotics into a moisturizer. Such a treatment may help restore homeostasis of the skin, re-populate the diversity of the microbiome, encourage the growth of commensal bacteria, and improve barrier function and symptoms of AD.

CONCLUSION

Enhancement of skin microbiome richness and diversity with a combination of LRP-TSW and APF in an emollient base may offer a valuable option for the treatment and maintenance of inflammatory skin diseases. Clinicians should discuss the benefits of such a product in the context of a full AD management program that covers prevention, active treatment, and maintenance.

Future Directives

Given that AD progresses through various stages of development, the use of a product that is specially formulated to target a particular phase of the disease may warrant further investigation. For example, future investigations may evaluate a LRP-TSW/APF containing moisturizer during the pre-flare period of AD. The moisturizer is approved for application on children as young as 2 weeks.

DISCLOSURES

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