Review article

Exploring the skin microbiome in atopic dermatitis pathogenesis and disease modification

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Inflammatory skin diseases such as atopic eczema (atopic dermatitis [AD]) affect children and adults globally. In AD, the skin barrier is impaired on multiple levels. Underlying factors include genetic, chemical, immunologic, and microbial components. Increased skin pH in AD is part of the altered microbial microenvironment that promotes overgrowth of the skin microbiome with *Staphylococcus aureus*. The secretion of virulence factors, such as toxins and proteases, by *S aureus* further aggravates the skin barrier deficiency and additionally disrupts the balance of an already skewed immune response. Skin commensal bacteria, however, can inhibit the growth and pathogenicity of *S aureus* through quorum sensing. Therefore, restoring a healthy skin microbiome could contribute to remission induction in AD. This review discusses direct and indirect approaches to targeting the skin microbiome through modulation of the skin pH; UV treatment; and use of prebiotics, probiotics, and postbiotics. Furthermore, exploratory techniques such as skin microbiome transplantation, ozone therapy, and phage therapy are discussed. Finally, we summarize the latest findings on disease and microbiome modification through targeted immunomodulatory systemic treatments and biologics. We believe that targeting the skin microbiome should be considered a crucial component of successful AD treatment in the future. (J Allergy Clin Immunol 2024;154:31-41.)

Key words: *Atopic eczema, atopic dermatitis, skin microbiome, skin barrier, microbiome, therapy, microbiota, inflammation*

Abbreviations used

AD:	Atopic dermatitis
AGR:	Accessory gene regulator
AIP:	Autoinducer peptide
AMP:	Antimicrobial peptide
CoNS:	Coagulase-negative *Staphylococcus*
DBB:	Diluted bleach bath
FLG:	Filaggrin
QS:	Quorum sensing
RB:	Rose Bengal
SCFA:	Short-chain fatty acid

AD: A SUMMARY

Atopic dermatitis (AD) is a chronically relapsing, inflammatory skin disorder affecting 5.5% of the adult population in Europe. Chronic itch, sleep deprivation, and stigmatization in AD can cause heavy psychological strain on patients and their families.[1,2] Clinical features of the diverse disease entity include dry skin, reoccurring eczema, and severe pruritus. The complex pathophysiologic network in AD comprises genetic (eg, filaggrin [*FLG*] mutations), chemical (increase in pH), and immunologic (shift toward T_H2 cell response) factors in addition to microbial dysbiosis (eg, high *Staphylococcus aureus* abundance) that negatively affect the skins barrier properties.[3-6] Skin barrier dysfunction and microbial dysbiosis are interrelated and interdependent (Fig 1[7]). The development of new therapies has been greatly stimulated by extensive research into the pathophysiologic mechanisms, leading to a new era of treatment for moderate-to-severe atopic eczema through targeted therapies.[8-10] Rather than focusing on symptom control, modern therapeutic approaches address the underlying disease mechanisms.[11,12] As an integral part of the healthy skin barrier, the skin microbiome constitutes a promising therapeutic target relevant to the pathophysiology of AD and barrier integrity.

THE SKIN MICROBIOME IN HEALTH

The ecosystem human skin

The purpose of the human skin barrier reaches beyond being a physical boundary layer between an individual and its environment. It is home to an ecosystem inhabited by bacteria, archaea, fungi, and viruses. This ecosystem has been summarized under the term *microbiome*. To date, novel genomic approaches continue to unravel the full diversity of the skin's microbiome.[13] Typical microbes

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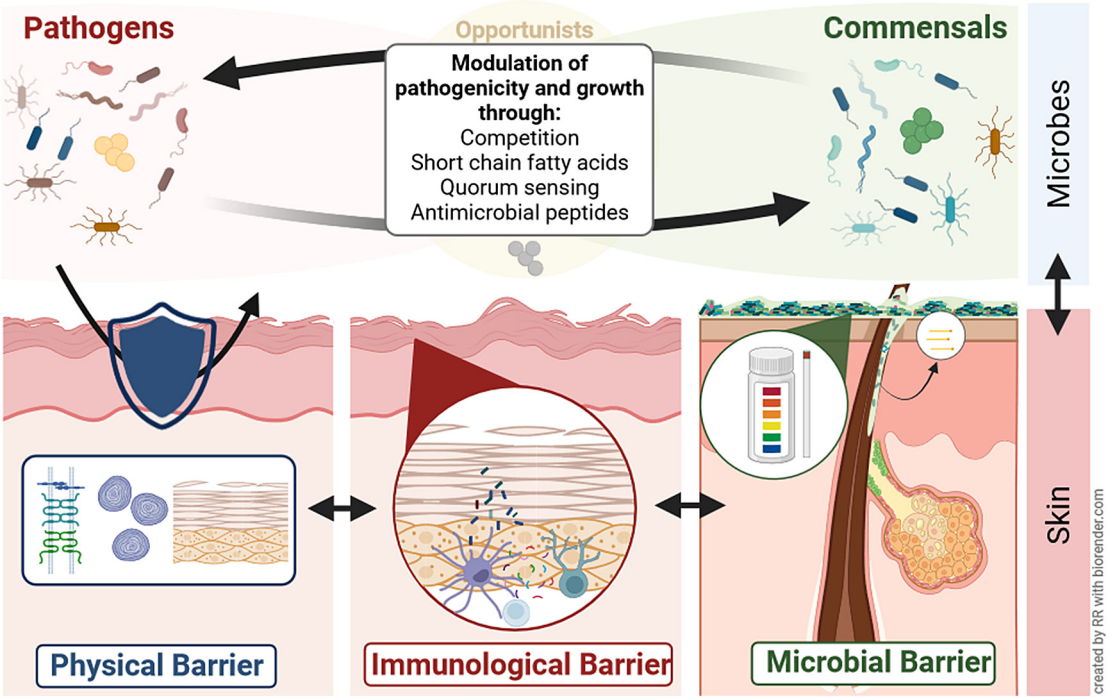

FIG 1. Simplified, schematic overview of the interactions within the "holobiome"[7] of the skin.

found on the skin include yeasts such as *Malassezia* and commensal bacteria such as Corynebacteriaceae, Cutibacteriaceae, Streptococcaceae, and coagulase-negative staphylococci (CoNSs), including *Staphylococcus epidermidis*, *Staphylococcus hominis,* and *Staphylococcus lugdunensis.*[13-19] These symbiotic microbes, which are also known as commensals, break down natural products, support the skin barrier's formation and repair mechanisms, and aid in inducing immunologic tolerance.[14,20,21]

Diversity

One key aspect associated with a healthy skin microbiome is microbial diversity. Diversity can be measured by quantifying the number of species present (*richness*). How evenly these species are distributed within a single sample is described by the term *evenness*. Both measures are combined through the indices Shannon diversity and Simpson diversity and thus consider the number and distribution of species within a single sample.[22,23] Investigations have found that humans less exposed to a "Western lifestyle" show higher microbial diversity.[24] Also, higher diversity has been associated with healthier skin.[25] A recent placebo-controlled study compared children playing in sandpits in day care establishments. Its authors demonstrated that exposure to diversely microbially enriched sand increased the relative abundance of more than 30 bacterial genera. However, no shifts occurred in the placebo group. This demonstrates the significance of the environment in shaping a diverse skin microbiome. The observed changes were associated with plasma cytokine levels and regulatory T-cell levels, supporting the hypothesis that environmental microbiota can contribute to immune modulation and health.[26,27] However, microbial diversity and composition are distinct between and within individuals.[16]

The microbiome in different body locations and age groups

The skin microbiome is established at birth and adapts alongside the developments that come with aging and changes in skin physiology (eg, pubertal seborrhea, elderly xerosis).[28-30] However, within a given stage of life, the skin microbiome remains relatively stable in healthy individuals.[28,31-33] The skin is made up of different microenvironments with different levels of sebum, moisture, and differences in pH. These factors strongly influence the ecologic niche and microbial composition.[14,25,34] Sebaceous areas are highly colonized by sebum-utilizing cutibacteria and *Malassezia* yeasts. Dry and moist areas are inhabited by proteobacteria, corynebacteria, and staphylococci.[16,35] Furthermore, dry skin regions seem more even, rich, and functionally distinct than sebaceous and moist areas.[16] However, the exact microbiome composition is highly individual and believed to be influenced by intrinsic (age, genetics, sex, ethnicity) and extrinsic (lifestyle, skin care routine, environment) factors.[36-39]

Of commensals and competition (host-microbe and microbe-microbe interaction)

Rather than being an isolated system, the skin microbiome is a complex network with environment-microbe, microbe-host, and microbe-microbe interactions.[40] Although the skin provides an ecosystem for skin microbes, it limits bacterial growth through high salt concentration, low pH, and constant production of antimicrobial peptides (AMPs) by the skin keratinocytes and sebocytes.[41-43] This process is also modulated by the resident skin microbes.[44] As all skin bacteria compete for nutrients, active competition strategies have emerged, including intraspecies and interspecies, and even interkingdom, signaling.[45,46] Many

commensals can inhibit the growth or expression of virulence factors from pathobionts (pathogenic microbes under only certain environmental conditions) via quorum sensing (QS), a bacterial communication system that is regulated by bacterial cell number and environmental factors.[46-50] In staphylococci, 4 QS accessory gene regulator (*agr*) types with individual phenotypes that can inhibit each other have been identified.[51,52] Apart from the interference with the communication of other bacteria,[50] some bacteria can, directly and indirectly, inhibit the growth of other bacteria by secreting AMPs, hydrogen peroxide, or short-chain fatty acids (SCFAs).[50] SCFAs are microbial metabolites that can control bacterial growth directly or indirectly by modulating the host inflammatory response.[53] For example, *Malassezia* metabolizes sebum to SCFAs, such as azelaic acid, which has antibacterial and antimycotic properties in a pH range between 4.8 and 5.5.[54]

How these competition strategies can be exploited for AD treatment strategies is further discussed later in this review in the section on modulation of the skin microbiome through "biotics."

THE SKIN MICROBIOME IN AD

A key feature of AD is dysbiosis of the skin microbiome, typically toward *S aureus,* in terms of relative abundance and absolute numbers.[55,56] This dysbiosis leads to a decrease in the microbial diversity measure evenness, whereas the measure richness seems less affected.[38]

Non–*S aureus*–related microbial changes in AD

Apart from *S aureus*–dominated dysbiosis, other microbial patterns (dermotypes) seem to be associated with AD. An AD cohort study observed 2 dermotypes with differential bacterial species compositions and diversities. One dermotype exhibited decreased richness, specifically, a depletion of certain species such as *Cutibacterium acnes,* and was associated with a higher AD severity, changes in host metabolic pathways, and a distinct response to corticosteroids.[57,58]

Furthermore, higher abundance of other *Staphylococcus* species, such as *Staphylococcus capitis*, *S lugdunensis*, and *S epidermidis*, was observed in patients with severe AD.[59] *S epidermidis* expresses the QS-regulated cysteine protease EcpA, which is described to cause skin damage and inflammation.[60] An excess of other bacterial species, such as *Corynebacterium tuberculostearicum*, has also been reported to increase in AD flares, encoding a range of potential virulence genes.[61]

Most studies of skin dysbiosis focus on prokaryotes. However, site-specific alterations in the abundance of fungi and viruses also occur on the skin of patients with AD.[62] The abundance of the typical skin-resident *Malassezia* was reduced in patients with severe AD, whereas *Candida* fungi were found to be more abundant.[63] Although *Malassezia* is a common skin inhabitant, it is also known to release allergens that may be increasingly expressed on the skin of patients with AD with increased skin pH.[64,65] *Malassezia* promotes skin inflammation by inducing a type 17 inflammatory response.[66] *Malassezia*-specific IgE has been proposed as a marker for severity in AD.[67] In the head and neck–refractory phenotype of AD, exacerbation by *Malassezia* is regularly observed and has direct therapeutic consequences.[68] Also, antifungal treatment showed promising results in a meta-analysis.[69] In summary, the role of fungi in AD requires investigation to further enhance therapeutic options.

Because of the presence of RNA and DNA viruses, analysis of the virome on the skin is complex. However, bacteriophages are known to substantially modulate the skin microbiome by infection and genetic exchange.[70] Initial studies of patients with AD showed changes in the occurrence of phages specific to *Propionibacterium* and *S epidermidis*.[62] In the gut of patients with AD, differences in the virome were also reported.[71]

The role of *S aureus* in AD

Not all patients with AD are colonized with *S aureus*; however, a high abundance of *S aureus* is associated with more severe disease and greater type 2 immune deviation, allergen sensitization, barrier disruption, and elevation of lactate dehydrogenase level than in noncolonized patients with AD.[72] The association of disease severity with absolute and relative abundance of *S aureus* is well validated[55,73,74] and appears to be partly associated with host factors such as ethnicity, sex, and age.[38]

The pathogenicity of the pathobiont *S aureus* is associated with its capability to express superantigens (eg, staphylococcal enterotoxins, toxic shock syndrome toxin, and cytotoxins such as toxin and leucocidins), enzymatic toxins (β-toxin), adhesins, proteases, and nucleases, all of which further weaken the skin barrier in AD.[75] The expression of these pathogenic factors is often regulated through the QS *agr* system of *S aureus*.[76,77] Furthermore, *S aureus* can form biofilms that protect against the host immune response and other external factors such as antibiotics.[78] The extent of biofilm production by *S aureus* is positively correlated with AD severity.[79-81] Biofilms can occur in either monospecies or mixed species form and can even consist of interkingdom species mixed with fungi of the genus *Alternaria*. These biofilms are resistant to antimicrobial and antifungal treatment.[82]

S aureus strains isolated from AD-patients differ genomically from strains isolated from healthy individuals or patients with other skin diseases. Typically, the *S aureus* populations in patients with AD are dominated by a single lineage.[83] One trait associated with *S aureus* strains isolated from patients with AD is a loss of function mutation in the capsular polysaccharide enzyme *capD*.[83] However, AD-associated strains have revealed high genetic heterogenicity, suggesting that the pathogenicity is associated with differential gene expression rather than particular genetic features.[84,85] In line with this suggestion, stimulation of keratinocytes with *S aureus* supernatants *in vitro* induced a strain-specific proinflammatory response and differential effect on the skin viability and integrity of keratinocytes, including downregulation of *FLG*.[86] This suggests that strain-specific host-microbiome interactions may play a critical role in the modulation of AD.[80,87]

The microenvironment shapes the skin microbiome in AD

In AD, the skin barrier is disrupted on multiple levels, including genetic, immunologic, chemical, and microbial. Commonly reported is an increase in skin pH in patients with AD.[88] Even though skin pH is not directly correlated with AD severity,[89] it is a crucial factor in shaping the microbial microenvironment. Higher skin pH, toward neutral conditions, has been reported to allow the growth of *S aureus* both *in vitro* and *in vivo,* while allowing the growth of commensals such as *S epidermidis*.[73] Furthermore, this increased skin pH hampers the effectiveness of

antimicrobial proteins produced by keratinocytes.[88] The loss of antimicrobial defense from AMPs in combination with CoNSs enables *S aureus* survival on skin.[90]

Both survival and bacterial pathogenicity are influenced by pH via QS.[91] The expression of various toxins and proteases is regulated through this cell number–induced bacterial communication via the *agr* system in *S aureus*.[76,92] Furthermore, the *agr* system is controlled by several environmental and metabolic factors.[93] These factors include nutrient availability, reactive oxygen species, and pH. Therefore, it is hypothesized that the increased skin pH on "atopic skin" increases *S aureus* colonization[73] in terms of relative and absolute numbers,[94] with both factors activating the *agr* system. Consequently, activation of the QS system can lead to an increased pathogenicity of *S aureus* owing to toxin expression. This process further irritates the skin barrier and causes inflammation, adding to the already imbalanced immune response.[75]

Also, biofilm formation is complexly regulated via QS[92]: although deletion of *agr* is associated with increased biofilm production *in vitro*, this did not hold true *in vivo*.[95] Salicylic acid was found to reduce the activity of the staphylococcal *agr* system and stabilize the biofilm.[96]

Other mechanisms have been described as relevant factors in *S aureus* overgrowth in AD; one such mechanism is a stronger adherence of *S aureus* to corneocytes from patients with AD through binding the N-terminal region of corneodesmosin.[97,98] The adhesion of *S aureus* to corneocytes depends on levels of natural moisturizing factor (eg, urea, lactate, and amino acids).[99] Breakdown products of filaggrin lead to decreased *in vitro* growth of *S aureus*,[100] and *S aureus* penetration is enhanced in a mouse *FLG* loss-of-function model of AD, suggesting that *FLG* mutations allow *S aureus* proliferation.[101] Individuals with *FLG*-mutations exhibit a skin microbiome resembling the microbiome of patients with AD compared to that of healthy controls, suggesting that microbial disbalance is a symptom of barrier dysfunction.[102]

MODULATION OF THE SKIN MICROBIOME IN AD THROUGH THERAPEUTIC INTERVENTION

As a pathophysiologic key player in AD, the skin microbiome can be considered a therapeutic target. However, clinical experience has shown that manipulating a given pathophysiologic aspect within AD inevitably affects the entire skin barrier and ecosystem. Traditionally, treatment of AD comprises barrier-restoring emollients, reactive and proactive anti-inflammatory topical substances, and (in moderate-to-severe cases) systemic anti-inflammatory treatment.[10,103] As treatment options for AD have evolved over the past years, questions have emerged regarding their impact on the skin microbiome. The following section discusses current AD treatment options and their effect on modulating the human skin microbiome within the context of AD (Fig 2).

Emollients

Regulation of the skin's physical and antimicrobial barriers is an intertwined process.[104] Therefore, barrier-stabilizing skin care products such as moisturizers and emollients may help sustain skin microbial balance and diversity. The skin barrier–strengthening properties of various emollients have been evaluated in past years. Specifically, multiple randomized controlled trials have evaluated the effect of preventive emollient treatment in young children with atopic skin disease.[105] Some studies suggest a beneficial effect of early emollient use for AD prevention, hypothesizing that improved skin barrier function could ameliorate skin hydration and prevent allergen penetration into the epidermis.[106-108] However, other studies have failed to confirm this protective effect.[109-112] Similar controversy surrounds the debate on microbiome modification through emollients. Although some studies claim that emollients can normalize the skin microbiome and improve barrier dysfunction in patients with AD,[113] others have found no significant effect on skin microbial biodiversity.[73] The latest reports claim changes in the skin microbiome toward increased richness following lotion application for 5 weeks.[114] In a recently published randomized, evaluator-blind, 5-week study (ClinalTrials.gov identifier NCT03457857), a topical emollient lotion combined with a mild cleanser was compared with a cleanser-only regimen, evaluating its effect on the skin microbiome.[115] The authors of that study found that adding lotion to a skin care regimen in children increased microbial richness and ceramide levels on healthy infant skin. This finding further accentuates the interlinked relationship between barrier function and microbial disbalance in the complex cutaneous ecosystem. Explanatory approaches toward the diverging results emphasize crucial differences between studies in emollient composition, formulation, application regimen, and study population characteristics. The effect of emollient formulation has been assessed in a meta-analysis, conjecturing emollient emulsions to be the most effective in preventing atopic disease.[116] Furthermore, significant differences between different emollient formulations and their barrier-stabilizing properties have been demonstrated.[117] Patients with AD are known to be more prone to microbial disbalance and skin infections. This increased vulnerability of individuals with AD has previously been linked to a deficiency in the expression of AMPs.[118] Significant effects on a molecular level have been described for the commonly prescribed moisturizing agent petrolatum when compared with skin occlusion and healthy skin. These include the petrolatum-induced upregulation of critical AMPs, innate immune responses, and the modulation of the epidermal barrier.[119] However, the observed effects were preeminently restricted to healthy skin and much lower in patients with a dysfunctional skin barrier and a T_H2-skewed immune response. The dysfunctional lipid secretion and lamellar body organization in AD present a further therapeutic opportunity for intervention. Therefore, increased efforts have been made to develop specific emollients containing physiologic lipids, substituting natural lipid composition.[120]

pH modulation

The pH of the skin can affect the growth and survival of bacteria. Modulating the skin pH with topical treatments toward an acidic pH may help promote the growth of beneficial bacteria and inhibit the growth of harmful bacteria such as *S aureus*.[121] In AD patients, increased skin pH was associated with higher *S aureus* skin colonization, concurrent with higher *S aureus* abundance in AD lesions with where the highest skin pH is observed.[122] *In vitro*, higher growth rates of *S aureus* were observed at neutral pH under standard conditions.[3,73,121]

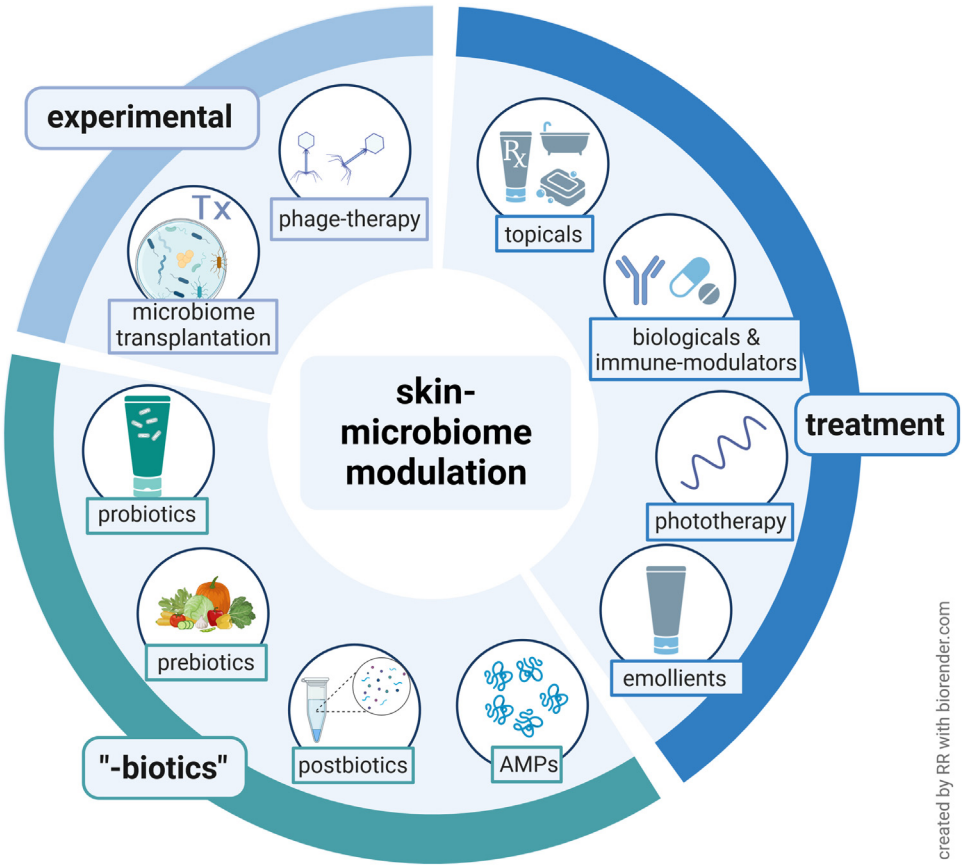

FIG 2. Summary of different approaches toward microbiome modulation.

In addition, the pH influences not only the growth but also the QS-regulated toxin expression of bacteria, with the *S aureus* agr QS system being most active at pH 7.[91,123] In a mouse model, an acidic emollient promoted recovery of the skin microbiome after tape stripping.[124] However, other studies did not find significant differences in the skin microbiome after application of emollients with different pH but a pH-associated increase in *S aureus* growth.[73]

Phototherapy

UV-B light therapy increased microbial diversity and reduced *S aureus* colonization in small numbers of patients.[125] A study found that treatment with narrowband UV-B for 6 to 8 weeks in adults with AD led to changes in the skin microbiota in lesional skin but did not affect the microbiota of nonlesional skin, nose, or throat. These microbial changes in lesional skin occurred after clinical remission, indicating that they are likely secondary rather than primary factors in the development of AD.[125]

Alpine climate therapy, which involves exposure to high-altitude environments, has shown promising results in treating AD and reducing *S aureus*. The therapy's effectiveness may be attributed to increased levels of UV radiation and low pollution in alpine regions. UV radiation has been found to have antimicrobial effects, particularly on *S aureus*. Therefore, the combination of increased UV radiation and reduced air pollution in alpine climates may contribute to the improvement of AD symptoms by modulating the skin microbiome and reducing *S aureus* colonization.[126,127]

Photoinactivation using rose Bengal (RB) and visible light is effective against *S aureus*, regardless of the presence and production of superantigen-encoding genes. RB-based antimicrobial photoinactivation can be a potential treatment option for *S aureus* infections, especially in combination with low-dose antibiotics. Further clinical studies are needed to explore the safety and efficacy of RB-based photodynamic methods.[128]

Systemic anti-inflammatory treatment

Treatment with the IL-4Rα–selective mAb dupilumab does more than restore patients' skin barrier. Recent investigations also observed increased microbial diversity and reduced relative and absolute counts of *S aureus* after treatment with the mAb.[129,130] The effect of selective immune-modulating therapies was recently assessed in a larger cohort, confirming the modulatory effect of dupilumab but not cyclosporin on the skin microbiome.[131] The immediacy of this effect was described as early as 3 days after therapeutic intervention.[132] *S aureus* exposure intrinsically enhances keratinocyte defenses via AMPs.[101] Single-cell analysis of IL-4Rα–deficient mice after *S aureus* exposure recently revealed enhanced AMP production, increased CoNS growth, and reduced *S aureus* colonization, supporting the importance of IL-4Rα–mediated type 2 inflammation for microbial overgrowth.[90]

Importantly, these findings have lasting clinical implications for the patient, as fewer skin infections were observed in children during targeted systemic treatment, with the effect persisting even

after the therapy was discontinued.[133] Different targeted immunomodulatory therapies must be investigated further to elucidate the role of distinct host immune responses and AMPs in the holobiome of patients with AD.[7]

ANTIMICROBIAL APPROACHES

Bleach baths

An opposite approach to acidification of the pH is conducting bleach baths. A recent longitudinal study of AD treatment found that children receiving diluted bleach baths (DBBs) in addition to standard topical treatment exhibited significantly lower skin colonization with *S aureus* skin after 3 months of treatment than did controls, along with reductions in disease severity. These findings suggest that DBB may be a beneficial adjunct therapy for AD, avoiding the adverse effects of antibiotics on the skin microbiome and the risk of bacterial resistance.[134] However, multiple trials investigating the use of DBBs to manage the abundance of *S aureus* in AD did not consistently demonstrate their effectiveness in alleviating the condition. Moreover, the therapeutic effects observed from bleach baths may be due primarily not to their antimicrobial properties[135] but rather to inhibition of the *agr*-regulated toxin expression of *S aureus* via the alkaline pH.[48]

Antibiotics

Systemic antibiotic courses have been shown to decrease microbial diversity and potentially affect skin microbial health and resilience toward developing disease.[136] Therefore, systemic antibiotics are not considered standard treatment in AD, as antibiotics and antiseptic compounds have been shown to increase the selective pressure on *S aureus* isolates in AD and influence the development and persistence of specific resistances.[137,138]

AMPs

AMPs are naturally occurring molecules that can kill or inhibit the growth of bacteria and are often produced by bacteria, as further discussed in the section on modulation of the skin microbiome through biotics.[139,140] In addition, various synthetic AMPs are tested for their activity in modifying microbial composition and biofilm production.[141] In general, small molecules that can interact with host tissue and microbes are promising microbiome therapeutics.[142]

Coal tar

A study examining patients with AD who were undergoing coal tar treatment revealed decreased *Staphylococcus* abundance and increased *Propionibacterium* abundance, resembling a healthier skin microbiota. Additionally, coal tar was found to activate the aryl hydrocarbon receptor, inducing AMPs in keratinocytes and suggesting a therapeutic mechanism for AD treatment by regulating the antimicrobial milieu.[143]

Ozone therapy

Ozone therapy, which is available in various forms, is used as a complementary treatment for various skin conditions and has shown potential for improving the skin and gut microbiomes and having antineoplastic and antiaging effects. The therapy acts through multiple mechanisms, including antioxidant effects, immunomodulation, and modulation of local microcirculation, thus making it a promising strategy for treating cutaneous diseases.[144]

Topical ozone therapy effectively reduced the severity of AD lesions and decreased the proportion of *S aureus*. The therapy also increased microbiologic diversity and the proportion of *Acinetobacter*, suggesting its potential to restore the microbiome balance in AD lesions.[145]

MODULATION OF THE SKIN MICROBIOME THROUGH BIOTICS

Commensal bacterial strains are part of the natural human skin barrier and have the potential to indirectly or directly combat pathobionts such as *S aureus,* with positive outcomes for patients with AD, as was recently summarized in Ito et al.[146] There is evidence that prebiotics, probiotics, and postbiotics can positively affect AD.

Topical probiotics

Probiotics are living, nonpathogenic microorganisms that are used to promote a healthy microbial ecosystem.[147] There is ongoing debate regarding the impact of probiotics on the prevention and progression of AD, as well as their potential therapeutic value. However, the significance of probiotics in topic application and food supplementation as an alternative treatment approach in the emerging "postantibiotic" era is gaining considerable attention and significance.[148-150]

The more we learn about interaction of the skin microbiome and single microbes with cutaneous processes, the more possible interventions can be discovered.[151] Topical application of probiotics is a promising strategy to restore the balance of the skin microbiome by introducing beneficial bacteria. Nakatsuji et al studied *S hominis* A9, a bacterium isolated from healthy human skin, as a topical therapy for AD. Their double-blind, placebo-controlled trial found that *S hominis* could reduce *S aureus* growth.[152] In an open-label phase I-II safety and activity clinical trial, treatment with *Roseomonas mucosa* caused significant improvements in measures of disease severity, reduced topical steroid requirement, and lowered *S aureus* burden.[153] The recently published results of a double-blinded phase IIb clinical using live topical biotherapeutic treatment with B244 (therapeutic ammonia-oxidizing bacteria) indicated reduced itch in treated patients.[154] Furthermore, Lebeer et al showed reduced inflammation after treatment with selected lactobacilli in patients with acne.[155] Overall, probiotic intervention is a promising approach toward reducing inflammation and microbial dysbiosis in inflammatory skin disease.

Many commensals can inhibit the growth or expression of pathogenic factors of pathobionts, such *as S aureus*.[49,50] *S lugdunensis* supports the host defenses by secreting the AMP lugdunin and stimulating the innate immune responses.[19] Other CoNSs, such as *S epidermidis* and *S hominis,* synergize with host AMPs such as LL-37 to selectively inhibit growth of the pathobiont *S aureus*.[140] *S hominis* expresses an AIP, which inhibits *agr*-regulated toxin expression of *S aureus*, preventing epithelial damage in a mouse model.[49,156] On the basis of these experiments, a

synthetic AIP has been shown to successfully prevent epidermal damage in a double-blinded study by inhibiting all *agr* types of *S aureus* and *S epidermidis*.[49] Also, a *Staphylococcus caprae* AIP reduced the *S aureus* burden and infections.[52] These properties are not unique to staphylococci but are instead present in other bacterial species.[139]

However, the treatment with living bacteria remains challenging. First, the microenvironment of the skin must be suitable for the bacteria to survive and thrive to their potential. Second, the risk of adverse effects has to be minimized.[149] Therefore, prebiotics and postbiotics are an exciting alternative.

Postbiotics

Postbiotics include bacteriocins, SCFAs, organic acids, tryptophan, and inactivated microbes and their extracts. They share similar mechanisms of action with probiotics, influencing host cells directly or indirectly to promote beneficial microorganisms and inhibit pathogens.[157]

Although postbiotic effects have been studied mainly in the gut, their impact on epithelial cells and the skin microbiome, particularly in AD, requires further investigation. Postbiotics also provide advantages over probiotics in terms of stability, defined composition, lack of antibiotic resistance transfer, and suitability for immunosuppressed individuals. These characteristics make them promising for cosmetic formulations. Topical application of *Vitreoscilla filiformis* extract or heat-treated *Lactobacillus johnsonii* has been shown to strengthen the skin barrier function, maintain good homeostasis of skin defenses, as well as to stimulate biochemical and cellular immune defenses.[158,159]

Multiple SCFAs, including acetic, butyric, and propionic acid, are produced by *S epidermidis* and are highly effective in inhibiting *S aureus* growth *in vivo* and *in vitro*.[160,161] Hydrogels containing *S epidermidis* and polyethylene glycol dimethacrylate, which following application are metabolized to SCFAs, successfully decolonized wound infections with *S aureus* in a mouse model.[161] Sebum and its microbial-derived metabolite propionic acid might be associated with the initiation of AD-like inflammation.[162] SCFAs also seem to be involved in the skin-gut axis signaling: reduced abundance of bacterial SCFA producers, and hence SCFAs, were observed in the gut of patients with AD and were correlated with skin inflammation and disease severity in AD.[163-165] Furthermore, an increase in SCFAs could provide part of a solution to reduce the development of allergic diseases.[166] However, additional research is needed to explore and identify new postbiotics from various microbial strains.[167]

Prebiotics

Prebiotics are nondigestible food ingredients (dietary fibers) that selectively promote the growth of beneficial bacteria in the gut and skin. Oral supplementation with prebiotics such as fructooligosaccharides has been claimed to improve skin barrier function and have preventive effects through growth stimulation of certain beneficial microbes.[168-170] However, the effect of prebiotics on skin disease is controversial and needs further investigation. Prebiotics are often combined with probiotic microbes as synbiotics, improving the survival and colonization of live beneficial microorganisms and affecting health status.[149,171] The evidence available for the regulatory influence of the gut microbiota on related immune responses in AD is considerable. This paves the way for the therapeutic modulatory use of this gut-skin axis, which has been nicely summarized by Alam et al.[172]

MODULATION OF THE SKIN MICROBIOME THROUGH EXPERIMENTAL APPROACHES

Microbiome transplantation

Transferring the entire microbiome in its natural environment has the advantage of maintaining its integrity and is already being performed to successfully treat gastrointestinal disease with fecal transplants.[173] However, transplantation of the entire microbiome without prior knowledge of its detailed composition is fraught with the risk of transmitting potential pathogenic taxa alongside beneficial microbes,[174] which could lead to severe health side effects.[175] Skin "microbiome transplantation" has additional limitations, including the low yield of bacteria harvested from the skin, the need for culturing to obtain sufficient amounts, and a bias owing to limitations in methodology. Scalability and industry applicability also remain challenges. Furthermore, the recipient environment must be prepared to accept the transferred mixture and should allow donor bacterial strain engraftment.[176] Instead of transferring the whole microbiome from a donor who is assumed to be healthy without knowing how a healthy microbiome is defined, the better and more feasible option may be to supplement the recipient's microbiota with defined microbes or probiotic mixtures.

Phage therapy

Phage therapy using bacteriophages is a potential new therapy for AD. By targeting specific bacterial strains that contribute to the development and progression of the skin disease, the microbiome can be modulated to a healthier state, which may reduce inflammation and improve skin barrier function.[177]

Thanks to their low bacterial resistance, endolysins derived from bacteriophages are considered promising alternatives to combat multidrug-resistant gram-positive bacteria, such as methicillin-resistant *Staphylococcus aureus*; in addition, they are safer, more efficient, and easier to produce than active bacteriophages.[178] However, a therapeutic effect of endolysin treatment in AD has not yet been clinically proved.[179]

The phage SaGU1 effectively suppresses *S aureus* growth *in vitro*, especially when combined with the beneficial bacterium *S epidermidis*. In an *in vivo* experiment using atopic mouse models, individual treatments with *S epidermidis* and SaGU1, each alone and in combination, significantly reduced *S aureus* growth on the skin. These findings suggest that the potential of phage therapy, either alone or in combination with beneficial bacteria, is a promising approach for treating AD.[177]

Topical application of bacteriophages is already being used in wound infection therapy, but administration has to be optimized.[180]

CONCLUSION

Analysis of the skin microbiota has revealed remarkable differences in the skin microbiome composition in many patients with atopic skin disease versus in individuals with healthy skin.

This divergence positions the skin microbiome as a powerful predictor of disease severity and treatment response in AD. Recent advances in sequencing technologies and targeted immunomodulatory therapies have provided new insights into the intricate interactions between microbes and with other microbes and their human hosts. These revelations have in turn paved the way for innovative approaches to manipulate the microbiome as a potential therapeutic target in AD. Our review has aimed to summarize the latest knowledge and research on microbial interactions and their relationship with the host in AD while providing an overview of current approaches to microbiome modulation.

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