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An overview on treatment strategies targeting on cutaneous dysbiosis in patients with Atopic Dermatitis

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ABSTRACT

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by immune dysregulation, skin barrier dysfunction, microbial imbalance, and environmental triggers. Increasing evidence highlights the central role of the skin microbiome, and particularly the overgrowth of *Staphylococcus aureus*, in disease onset and exacerbation. The holobiont theory supports the concept that interactions between host genetics and microbial communities contribute to AD pathogenesis.

Conventional therapies can positively influence cutaneous dysbiosis and promote microbial balance. "Emollients plus," containing prebiotics and bacterial lysates such as *Vitreoscilla filiformis* and *Aquaphilus dolomiae*, may increase microbial diversity and reduce AD flares. Topical corticosteroids, calcineurin inhibitors, biologics such as dupilumab and tralokinumab, AHR agonists, and phototherapy have also demonstrated beneficial effects on microbiota composition, particularly through reduction of *S. aureus* colonization.

Innovative microbiome-targeted therapies are emerging, including probiotics, bacteriotherapy, phage therapy, antimicrobial peptides, quorum-sensing inhibitors, and topical ozone therapy. Preliminary studies suggest these approaches may restore microbial diversity and reduce inflammation, although evidence remains limited. Overall, modulation of the skin microbiome represents a promising complementary strategy for improving AD management and preventing disease exacerbation

KEYWORDS: Atopic dermatitis, skin microbiome modulation, holobiome

INTRODUCTION

Atopic dermatitis (AD) is a chronic skin disease with complex and multifactorial pathogenesis. It is well known that in AD there is an alteration of the cutaneous immune response, the integrity of the skin barrier, and the composition of the skin microbiota, and that several environmental factors can trigger or worsen skin lesions [1]. Which of these conditions represents the primary trigger of the disease is still under debate.

Human skin is colonized by millions of microorganisms, such as bacteria, fungi, mites, and eukaryotic virus [2,3]. Microbial strains can interact with the host ecosystem as pathogenic agents. At the same time, they can also interact as beneficial mutualistic organisms or as commensal organisms [4], resulting in a fragile balance that can be easily disrupted when even a slight alteration occurs in one of its components.

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TABLE I. Skin care interventions and their effects on the cutaneous microbiome in AD.

Intervention	Main Components/Characteristics	Effects on Skin Barrier and Microbiome	Clinical Benefits
Detergents	Acid pH (4.0–6.0), ceramides, soap-free, fragrance-free	Maintain acid pH, preserve ceramide synthesis, reduce microbiome disruption	Reduced irritation and cutaneous inflammation
Conventional Emollients	Ceramides, cholesterol, fatty acids (3:1:1 ratio)	Restore barrier function, lower skin pH, enhance antimicrobial peptide production	Reduced AD severity and flare frequency
Emollients Plus	Glycyrrhetinic acid, niacinamide, sterols, flaxseed oil, xylitol and galacto-oligosaccharides prebiotics, PEA, Avena sativa, bacterial lysates	Promote microbial diversity, support commensal growth, reduce pathogen colonization	Improved SCORAD, reduced flares, decreased corticosteroid use

The microorganisms that colonize the skin influence the physical characteristics of the most superficial skin layers, affect local metabolism [5], and regulate cutaneous immunity [6] as well as the repair of the skin barrier [7].

Increasing evidence has shown that the composition and activities of the microorganisms colonizing the skin are crucial for the onset of AD. In this context, the holobiont theory can be effectively applied to AD. This theory recognizes the importance of the interaction between the host's genetics and that of the microorganisms colonizing the host's mucosae and skin.

In a multiple and diversified genetic cycle, host predispositions combine with environmental triggers to alter the microbiome, resulting in skin inflammation [8].

In this paper, all the possible targeted treatment strategies for cutaneous dysbiosis in patients with AD will be explored, focusing on the effect of skin care and pharmacological therapy in improving the interaction and modulation of the holobiome of the skin. New perspectives and innovative therapies will also be examined, specifically targeted on the microbiome, with the aim of reducing the pathological colonization of skin, which plays a key role in exacerbating inflammation in AD.

DETERGENTS

Cleansing in AD plays a key role in controlling the composition of the cutaneous microbiome. Maintenance of an acidic pH is crucial for the activity of enzymes involved in the formation of epidermal ceramides (β-glucocerebrosidase and acid sphingomyelinase) and for preserving the lamellar bilayer structure of the stratum corneum [9]. Cleansers with an acidic pH between 4.0 and 6.0, containing ceramides and free of soap, are less irritating than alkaline soaps and can reduce cutaneous inflammation [10,11].

It is important to ensure that cleansers are free of fragrances, allergens, haptens, and sodium lauryl sulphate, which reduces the expression of natural moisturizing factor (NMF), alters microbiota composition, and leads to downregulation of profilaggrin [12] (Tab. I).

EMOLLIENTS

The beneficial effects of emollients on the cutaneous microbiota are mediated through their action on the skin barrier [13,14]: they reduce skin pH [15], promote the production of antimicrobial peptides [16], and maintain the lipid composition of the skin.

Moisturizers containing ceramides have demonstrated good efficacy in reducing disease severity [17,18], as well as the number and frequency of AD flares [19].

Normal restoration of the skin barrier can be achieved through the application of lipids containing ceramides, cholesterol, and fatty acids in an equimolar ratio of 3:1:1 (Tab. I).

EMOLLIENTS PLUS

In European guidelines, newer-generation emollients are referred to as "emollients plus" [20]. They contain multiple active ingredients and non-pharmacological substances capable of interfering with the pathophysiological mechanisms of AD, such as glycyrrhetinic acid, niacinamide, sterols, glycosphingolipids, flaxseed oil, xylitol and galacto-oligosaccharides, which exert selective antibacterial and prebiotic activity.

Another ingredient, acting as a skin barrier–repairing agent, is palmitoylethanolamide (PEA). PEA is an endogenous fatty acid amide that is deficient in atopic skin and has been shown to reduce itching through modulation of the cannabinoid receptors CB1, which are primarily expressed in the central nervous system and certain peripheral tissues, and CB2, which are widely distributed throughout the immune system, including mast cells and cutaneous nerve fibres. Furthermore, colloidal oatmeal & oat plantlet extracts (Avena sativa) are useful ingredients. They are known to release anti-inflammatory

cytokines contributing to the hydration of dry skin, alleviating symptoms associated with irritated and inflamed skin [21]. Studies have shown that oat-derived compounds can improve skin hydration by regulating the expression of junctional proteins that are involved in maintaining skin barrier integrity [22].

Additional active components include bacterial lysates like *Vitreoscilla filiformis* [20,23], which may directly modulate the cutaneous microbiome by increasing its diversity [24,25], significantly reducing the number and severity of disease flares [26] and decreasing the need for topical corticosteroids [27].

Another emollient plus containing *Aquaphilus dolomiae* has been shown to be effective in reducing the proliferation of Staphylococcus aureus, leading to improvement in SCORAD index, xerosis, and pruritus in children with mild AD [28,29].

The prebiotics contained in emollients plus may promote the growth of commensal bacteria such as *Staphylococcus epidermidis*, thereby preventing colonization by pathogenic bacteria [30] (Tab. I).

TOPICAL AND SYSTEMIC ANTIBIOTICS

A recent Cochrane review concluded that antibiotics may provide only a slight improvement in the severity of AD [31]. Currently, the use of antibiotics in AD is recommended only in the presence of evident clinical infection [32]. The use of antibiotics for *Staphylococcus aureus* decolonization remains controversial due to the risk of inducing antimicrobial resistance and altering the microbiota [33].

Systemic antibiotic therapy should be combined with topical treatment only in cases of extensive superinfection involving more than 2% of the body surface area, poor response to topical therapy, or frequent relapses. Based on current resistance patterns, cephalexin, or another first-generation cephalosporin may be recommended for 7-10 days. In cases of AD with widespread or recurrent impetiginisation, administration of amoxicillin-clavulanate or a fluoroquinolone is recommended [34]. Regarding topical antibiotic treatment, the most suitable molecules are fusidic acid and mupirocin, with 2-3 applications per day for 7-10 days [34].

Recurrent infections in patients with AD are frequently associated with nasal colonization by *S. aureus*; when nasal swab results are positive, intranasal decolonization with mupirocin has been shown to be effective, administered twice daily in both nostrils for 5 days per month over 3 months.

TOPICAL ANTI-INFLAMMATORY AGENTS

Topical corticosteroids (TCS) represent the first-line treatment for the management of AD. In addition to their anti-inflammatory effects, they can also reduce *Staphylococcus aureus* colonization [35].

Topical calcineurin inhibitors are capable of modulating the cutaneous microbiota. In an open-label study involving 9 patients with AD and 12 healthy controls, after 4 weeks of treatment with tacrolimus, the skin microbiota composition of patients with AD was comparable to that of healthy control subjects [36]. In the same study, patients with AD showed a lower prevalence of the phyla *Actinobacteria* and *Proteobacteria* and a higher prevalence of *Firmicutes*; after tacrolimus treatment, a significant increase was observed in several commensal genera, including *Dermacoccus*, *Pseudomonas*, *Corynebacterium*, *Proteus*, *Micrococcus luteus*, and *Lactococcus* [36].

BIOLOGICS

Dupilumab has been shown to be effective in reducing *Staphylococcus aureus* colonization and increasing the abundance of *Cutibacterium* and *Corynebacterium* species, proportionally to the level of stratum corneum hydration. A randomized, double-blind study (dupilumab vs placebo; 2:1) enrolling 71 patients with moderate-to-severe AD, demonstrated that 100% of participants, who at baseline were colonized with *S. aureus* showed a significant reduction in *S. aureus* and clinical improvement after treatment that was proportional to the degree of reduction in *S. aureus* colonization [37].

Tralokinumab, a high-affinity fully human monoclonal antibody that specifically neutralizes interleukin-13 (IL-13), has demonstrated a favorable efficacy and safety profile for treatment of adults with moderate-to-severe AD in phase 3 trials [38,39]. After 16 weeks of tralokinumab therapy, an increase in microbial diversity, reduction of *S. aureus*, and increase of coagulase-negative commensal staphylococci have been observed. These findings suggest that IL-13 may represent a key driver of cutaneous dysbiosis in AD [40].

AHR AGONISTS AND DYSBIOSIS

Topical treatment with aryl hydrocarbon receptor (AHR) agonists appears to be effective in reducing the abundance of *Staphylococcus* species in patients with AD [41]. The therapeutic effect of coal tar treatment has been attributed to targeting the cutaneous bacterial composition through AHR-mediated activation in keratinocytes, leading to increased production of antimicrobial peptides (AMPs).

Tapinarof is a new topical therapeutic AHR modulator that exerts its effects in AD through AHR activation, inhibition of IL-4/IL-13-mediated signal transduction, downstream of STAT6 activation, and upregulation of filaggrin (FLG), loricrin (LOR), and involucrin (IVL) [42].

PHOTOTHERAPY

UVB phototherapy is considered a second-line treatment in adults and adolescents with AD. UVB phototherapy seems to produce a significant increase in microbial diversity, a reduction in *Staphylococcus aureus* colonization, and a decrease of relapses in this chronic inflammatory skin disorder [43].

Treatment with narrowband UVB (nb-UVB) for 6–8 weeks in adults with AD induced changes in skin microbiota of lesional areas, which

TABLE II. Emerging microbiome-targeted therapies for AD.

Therapy	Mechanism	Microbiome Effect	Current Evidence
Staphylococcus hominis A9 (ShA9)	Bacteriotherapy with beneficial commensal	Reduces *S. aureus* burden and psmα toxin expression	Limited effect on AD severity
Lactobacillus reuteri DSM 17938	Probiotic bacteriotherapy	Modulates local immune response	Safe and effective in preliminary studies
Phage Therapy (Staphefekt SA.100)	Selective lysis of *S. aureus*	Targets pathogenic bacteria without broad microbiome disruption	Conflicting clinical results
Nitrosomonas eutropha (B244)	Nitric oxide production	Microbiome modulation and immune regulation	Improvement in pruritus reported
Omiganan Pentachloride (CLS-001)	Antimicrobial peptide	Controls excessive *S. aureus* growth	Under clinical development
Oral Microbiome Modulators (EDP1815, STMC-103H, KBL697)	Gut-skin axis modulation	Potential systemic microbiome effects	Phase I clinical trials

became evident after demonstrated clinical remission, but did not affect the microbiota of non-lesional skin [44].

INNOVATIVE APPROACHES TARGETING *S. AUREUS* DYSBIOSIS

Recently, new therapies, specifically targeting the microbiome, are being explored to reduce the pathological colonization of skin, which exacerbate inflammation in AD [45]. These approaches include treatment with probiotics, repopulation of AD lesions with beneficial commensals, phage therapy, small molecules and peptides that inhibit *S. aureus* colonization, humanized monoclonal antibodies targeting bacterial toxins, and quorum-sensing inhibitors that block virulence factors [46].

Bacteriotherapy offers theoretical advantages by enhancing host defence without interfering with the immune system and without inducing resistance, as can occur with antibiotics. Of particular interest is *Staphylococcus hominis* A9 (ShA9), which after one week of application has been shown to reduce *S. aureus* skin burden and decrease expression of the pro-inflammatory toxin psmα, although without significantly reducing AD severity [47].

Several *Lactobacillus* strains have shown direct or indirect antipathogenic effects by interfering with keratinocyte adhesion, producing antimicrobial metabolites, and acidifying the skin surface [46]. Topical application of *Lactobacillus reuteri* DSM 17938 has demonstrated safety and anti-inflammatory efficacy in patients with AD [49]. Development of bacterial strains designed to enhance skin barrier integrity or induce anti-inflammatory responses is also underway (Tab. II).

Topical ozone therapy has also shown efficacy in reducing lesion severity and *S. aureus* colonization in AD, while promoting increased microbial diversity, suggesting a rebalancing effect on the dysbiotic microbiome of AD lesions [50].

Studies conducted to date are limited by small sample sizes and short treatment durations; therefore, further evidence is required before definitive recommendations can be made regarding the use of these products in patients with AD [4,51].

OTHER INVESTIGATIONAL THERAPIES

Several other strategies are currently under investigation to modulate the cutaneous microbiota.

Clinical trials on phage therapy have demonstrated contrasting results. Staphefekt SA.100, a recombinant phage endolysin that binds to *S. aureus* cell walls and cleaves peptidoglycan bonds, resulting in bacterial cell death, is currently under study [52].

Nitrosomonas eutropha (B244), an ammonia-oxidizing bacterium capable of producing nitric oxide, showed good results in inducing significant improvement in pruritus [53].

Cationic antimicrobial defence peptides are also promising candidates for controlling excessive *S. aureus* growth in AD. Among these, Omiganan pentachloride (CLS-001) is under development as a topical agent [54,55]. Several oral microbiome modulators are currently in phase I clinical trials, including EDP1815, STMC-103H, and KBL697 [53] (Tab. II).

Oral probiotics

Probiotics have been investigated as an adjunctive therapeutic approach in AD. Selected strains, particularly *Lactobacillus rhamnosus* and *Bifidobacterium lactis*, seem to contribute to a decrease in disease severity. In clinical practice, commonly used doses range from 5-10 x 10^9 CFU per day in children [56].

The beneficial effects of probiotics are thought to result from multiple mechanisms. They enhance epithelial barrier function by upregulating tight junction proteins, thereby reducing intestinal permeability and limiting microbial translocation. In addition, probiotics promote immune tolerance by increasing the production of anti-inflammatory cytokines, such as interleukin-10 (IL-10), which supports the activity of regulatory T cells and suppresses excessive inflammatory responses. They also help restore microbial homeostasis by increasing the abundance of beneficial bacteria, including Lactobacillus and Bifidobacterium species, while reducing dysbiosis and limiting the overgrowth of pathogenic microorganisms such as *Staphylococcus aureus*.

Lactobacillus plantarum CJLP133 has demonstrated beneficial effects in children with AD, in particular regarding the management of skin inflammation through immunomodulatory mechanisms [57].Clinical studies in pediatric patients with moderate-to-severe AD have shown that those who responded favorably to probiotic supplementation were characterized by elevated total IgE levels, increased expression of transforming growth factor-β (TGF-β), and a higher proportion of $CD4^{+}CD25^{+}Foxp3^{+}$ regulatory T (Treg) cells. Treatment with *L. plantarum* CJLP133 was associated with a significant reduction in disease severity, accompanied by an expansion of the Treg cell population, suggesting enhanced immune tolerance and improved regulation of inflammatory responses [58].

The current evidence is at a preliminary stage, and further studies are needed to standardize probiotic interventions and explore the long-term effects.

CONCLUSIONS

Cutaneous dysbiosis caused by an altered function of the holobiont and its specific components can be managed with conventional AD therapies, although these approaches must consider factors such as skin barrier characteristics, and in particular physiological pH. Multiple studies are evaluating the efficacy and safety of bacteriotherapy to implement a truly comprehensive approach to moderate-to-severe AD that engages all relevant pathophysiologic components.

Despite growing interest in microbiome modulation and correction of dysbiosis, it remains unclear whether high *S. aureus* colonization independently affects immune responses and inflammation, irrespective of other factors such as patient age, disease course, and duration. Recent studies highlight early childhood as a critical period for developing an appropriate immune response to microbes, suggesting that this may represent a key window for microbiome-targeted interventions. Optimizing the skin microbiome nevertheless represents a promising complementary strategy in the management of AD.

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Conflicts of interest statement

The authors declare that they have no competing interests.

Author's contributions

NM conceived the manuscript. FC, BG, PC, GM, EG wrote the first draft and finalized it.

All authors revised the manuscript and approved the final version.

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