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Skin microbiota in atopic dermatitis: victim or executioner?

Chiara Maria Teresa Boggio,[1] Federica Veronese,[2] Marta Armari,[1] Elisa Zavattaro,[2] Elia Esposto,[2] Paola Savoia,[2] Barbara Azzimonti[1]

AUTHOR AFFILIATIONS See affiliation list on p. 29.

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Peer Reviewers Eman Adel Elmansoury, Mansoura University, Mansoura, Egypt; Yunhua Tu, First Affiliated Hospital of Kunming Medical University, Kunming, China

Address correspondence to Barbara Azzimonti, barbara.azzimonti@med.uniupo.it.

Chiara Maria Teresa Boggio, Federica Veronese, and Marta Armari contributed equally to this article. The order of the co-first authors has been randomy selected.

Paola Savoia and Barbara Azzimonti contributed equally to this article.

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SUMMARY Atopic dermatitis (AD) is a prevalent chronic inflammatory skin disorder, affecting 10%–20% of the population, characterized by dryness, intense itching, and recurrent rashes. The pathophysiology of AD is multifactorial, involving skin barrier dysfunction, immune dysregulation, genetic factors (such as filaggrin mutations), and environmental factors. The skin microbiota also plays a pivotal role in AD, serving both as a target and a driver of the disease. In AD, the delicate balance of the skin microbiota is disrupted, leading to a decrease in beneficial bacteria such as *Streptococcus*, *Cutibacterium*, and *Corynebacterium*. Concurrently, bacterial pathobionts, notably *Staphylococcus aureus*, proliferate and express their virulence factors excessively. This imbalance exacerbates symptoms by damaging the skin barrier, releasing toxins, and triggering a Th2-driven immune response, thus weakening the skin defenses and making individuals with AD more susceptible to bacterial, fungal, and viral infections, thereby complicating treatment and worsening disease outcomes. Effective AD management requires a thorough understanding of the interplay among the skin microbiota, the immune system, and microbial pathobionts. Strategies that restore the microbial balance, preserve the skin barrier, and modulate the immune response show significant potential for reducing infections and improving AD symptoms, highlighting the microbiota's dual role in AD pathology. This review examines the complex role of the skin microbiota in AD, emphasizing how dysbiosis both drives disease progression and influences immune responses, and vice versa. It also explores emerging microbiota-targeted therapies aimed at improving disease outcomes.

KEYWORDS atopic dermatitis, skin microbiota, *Staphylococcus aureus*, *Staphylococcus epidermidis*, chronic inflammatory skin disorders, skin barrier disfunction, immune dysregulation

INTRODUCTION

It is well established that the human microbiota is a dynamic entity that can act as both a friend and a foe for its host, depending on many factors, both intrinsic and extrinsic, modifiable or not, and ultimately on the host immune system response (1). Under normal conditions, the commensal microflora, especially that of the upper respiratory airways, the skin, and the gut, acts as a biological barrier protecting against primary or opportunistic pathogen colonization. However, when its balance is altered, some commensal components decrease in abundance, whereas pathobionts may take over and shift from commensals to pathogens, leading to endogenous and exogenous infections, inflammatory conditions, immune disorders, and also cancer (2–4). In this way, a vicious cycle that may lead to further microbial imbalances is established (5, 6).

Atopic dermatitis (AD) is one of the most emblematic examples of dysbiosis-associated skin disorders. It is a chronic inflammatory condition mainly characterized by dryness, itching, and recurrent rashes that highly impact the patient's life quality (7). Despite the advances of drug research, effective management of this disorder still poses many challenges, as current treatments often fail to deliver optimal outcomes (8, 9). To address this gap, a more comprehensive, multidimensional approach is recommended. Key strategies include appropriate skincare regimens to help improve skin barrier function and microbial balance, whereas other approaches focus more on immune response restoration. Moreover, skin and gut microbiota modulation, by both healthier eating habits and pre-, pro-, syn-, and post-biotic practices, represents a promising therapeutic approach to reduce infections, improve symptoms, and potentially alter the disease course (10).

Nevertheless, the exact causal relationship between skin microbiota unbalance and AD remains complex and partially understood, with evidence suggesting a bidirectional interaction. On one side, dysbiosis marked by the overgrowth of *Staphylococcus aureus* is frequently observed in AD.

In fact, this halophilic bacterium is thought to contribute to inflammation and worsen AD symptoms by producing several virulence factors, such as toxins, and triggering

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immune responses (11, 12). The imbalanced microbiota may contribute to the onset and/or exacerbation of this condition, leading to skin barrier disruption, lipid content changes, and inflammation, further reducing beneficial bacterial diversity and favoring *S. aureus* overgrowth, implying that the disease itself contributes to the dysbiosis maintenance (11, 12). This reciprocal vicious cycle establishes a complex feedback loop, in which it is unclear, and thus an ongoing field of research, whether changes in the microbiota are a primary cause or a consequence of AD.

With these premises, starting from a description of the clinical AD features, this literature review aims to clarify this "Hamletic doubt" and provide an informative updated synthesis on the multiple roles of the skin microbiota in AD, focusing not only on its bacterial component but also on fungi and viruses, as simply commensals or pathobionts, and on their mutual interactions too. Additionally, the review explores emerging therapeutic perspectives for managing AD and addressing atopic dysbiosis.

Methods

In this literature review, the MEDLINE NIH National Library of Medicine (NLM) electronic free medical bibliographic PubMed and Scopus publicly available databases were consulted by looking for the keywords and terms "microbiota," "microbiome," "skin microbiota," "skin microbiome," "skin bacteriota," "skin virota," "skin micota," "bacteria," "viruses," "epitheliotropic viruses," "mycetes," "fungi," "bacteriophages," "phageome," "*Staphylococcus* spp.," "*Staphylococcus aureus,*" "*Staphylococcus epidermidis,*" "*CoNS,*" "*Streptococcus* spp.," "*Corynebacterium* spp.," "*Candida* spp," "*Malassezia* spp.," "*Cutibacterium acnes,*" "Human Herpes virus," "Molluscus contagiosus," "Human Papillomavirus," "inflammation," "inflammatory skin diseases," "atopic dermatitis," "acne," "immune system," "cytokines," "carotenoid pigment," and both in single and/or in combination, and the Medical Subject Heading (MeSH) controlled vocabulary, in paper titles and abstracts to retrieve the highest quality indexed and most cited original peer-reviewed scientific *in vitro, in vivo,* and *ex vivo* research studies and reviews (final consultation: March 20, 2025).

The bibliographic literature search was focused on original scientific international articles. English language was not used as an exclusion criterion, since articles written in German were also included in the study.

ATOPIC DERMATITIS

Incidence

AD, also referred to as atopic eczema (AE), is the most common chronic relapsing inflammatory skin disorder. It is characterized by dryness, intense itching, and recurrent eczematous lesions and is often associated with other atopic conditions, such as asthma and allergic rhinitis, in a phenomenon known as "atopic march" (13).

It affects approximately 10%–20% of the global population, with a lifetime prevalence of 15%–20% in children and 2%–10% in adults (14, 15). Epidemiological data show that AD tends to be more prevalent in developed countries, notably in North America, Western Europe, and parts of East Asia, than in developing regions. Contributing factors include higher levels of urbanization, dietary changes, and increased exposure to pollutants in industrialized settings. In addition, reduced microbial exposure during early childhood, common in highly sanitized environments, may alter both the gut and skin microbiome, disrupting immune regulation and favoring allergic responses. Over the past three decades, AD incidence has increased dramatically, rising 2-fold to 3-fold (16). According to a 2013 study from the Global Burden of Disease (GBD) project, AD has been identified as the leading contributor to the global burden of skin diseases (17, 18). Such trends underscore the pressing need for further research into environmental, immunological, and microbiome-related factors that drive AD pathogenesis, and for the development of targeted strategies to manage this growing global health concern.

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Pathophysiology

AD is a multifactorial disease with a complex and not fully understood pathophysiology. It involves skin barrier dysfunction, genetic predisposition, immune deregulation, pro-inflammatory cascades, altered microbiomes, and environmental factors, such as diet and antibiotics (Fig. 1). Indeed, the exposome plays a key role in its evolution, as it affects the host microbiota and immune response (16, 19).

Skin barrier disruption increases *trans*-epidermal water loss (TEWL) and skin pH rise, facilitates allergen and irritant penetration, and reduces the levels of essential lipids and proteins. Hülpusch et al. found that *S. aureus* skin abundance is influenced by cutaneous pH and can predict the worsening of AD severity by contributing to the inflammatory profile maintenance (20). Mutations in the gene encoding filaggrin (FLG), a crucial skin barrier protein, are common in AD and are associated with a weakened barrier and increased infection risk, particularly in severe, early-onset, and persistent cases (19). Immune dysregulation, especially the dominant Th2 response in the acute phase of AD and a shift to Th1 in chronic lesions, drives the inflammatory processes. Key Th2 cytokines (i.e., IL-4, IL-5, and IL-13) stimulate B cells to switch into IgE production, which in turn sensitizes mast cells via the high-affinity IgE receptor (FcεRI). Upon re-exposure to an allergen, sensitized mast cells undergo degranulation, releasing histamine and other pro-inflammatory mediators that intensify itching and acute inflammation (21, 22). Meanwhile, IL-5 promotes eosinophil recruitment, further amplifying tissue damage and inflammation. Thus, chronic IgE binding to mast cells perpetuates immune cascades and leads to sustained inflammation (21–23). Moreover, repeated itching and scratching episodes cause microtrauma, disrupt the skin barrier, and initiate a self-sustaining loop of barrier breakdown, allergen penetration, and persistent immune activation (10). Over time, Th1 cytokines—particularly IFN-γ—become more prominent, fostering skin thickening and hyperpigmentation. In parallel, Th22 cells produce IL-22, a critical driver of keratinocyte proliferation and epidermal hyperplasia (10). The interplay between Th2-

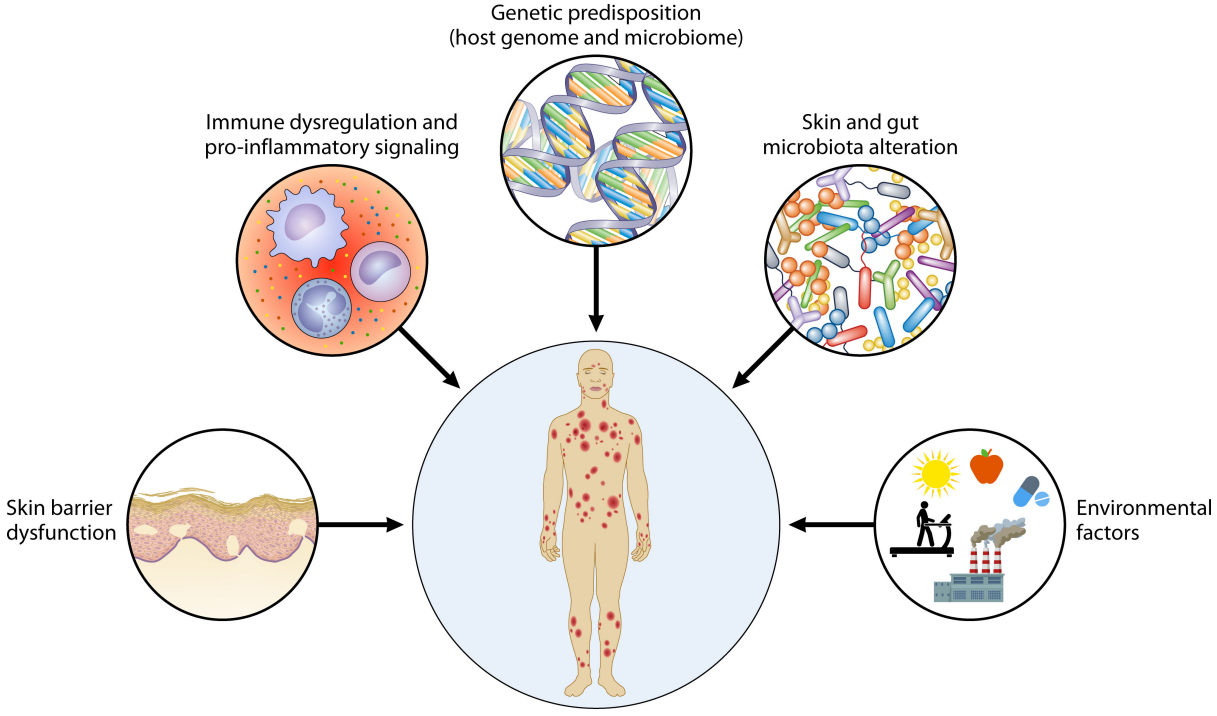

FIG 1 Factors involved in AD pathogenesis. Overview of the key factors contributing to the development and progression of AD, including skin barrier dysfunction, immune dysregulation, genetic predisposition, microbiota imbalance, and environmental triggers. The figure was created with BioRender and revised by Patrick Lane (ScEYEnce Studios).

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and Th1/Th22-driven responses establishes a more complex, mixed cytokine milieu that underlies the chronic, relapsing course of AD and poses therapeutic challenges. (Fig. 2).

Environmental stimuli, like exposure to urban pollution, dry climate, unsuitable UV light exposure, widespread chemical use, and changes in household routine, reduce skin microbiota diversity, thus weakening its protective function. Beneficial bacteria like *Streptococcus* and *Cutibacterium spp*. are often reduced, especially during flare-ups. Instead, *S. aureus* overgrows and exacerbates symptoms, promoting skin inflammation by releasing toxins and superantigens and activating the immune system, thus worsening barrier function, also by protease production rising (19, 24). Moreover, the damaged skin barrier (e.g., reduced filaggrin expression) makes *S. aureus* colonization easier (25).

The exposome can affect the gut microbiota as well, with gut dysbiosis also influencing the AD course. According to recent cohort studies, and similarly to the skin, AD patients have a peculiar dysbiotic gut signature, described by an overpresentation of harmful or pro-inflammatory bacteria such as *S. aureus*, *Escherichia coli*, and *Clostridium difficile*, and by a reduction in Bifidobacteria, Bacteroidetes, and Bacteroides. Worthy of note, the overabundance of *E. coli* and *Clostridia* may lead to eosinophilic inflammation, thus contributing to the atopic vicious cycle (11, 12, 19). The consequent AD gut barrier compromise also allows microbial products (e.g., lipopolysaccharides) to enter the bloodstream, triggering inflammation and influencing T-cell responses, promoting the typical Th2-skewed immune AD profile, and exacerbating allergic inflammation, both at local and systemic levels (19). Although less understood, the bidirectional gut-skin relationship (the so-called gut-skin axis) enables dysbiosis in one to influence the other, worsening systemic immune response and inflammation (19). Besides the immunological pathways, the gut microbiota influences AD development through metabolic and neuroendocrine routes. Increased histamine secretion can intensify itching, while the altered release of neurotransmitters and neuromodulators further contributes to AD symptoms (26).

Clinical presentation

AD presents a heterogeneous range of clinical features and symptoms. Lesions typically appear as poorly demarcated, scaly, and erythematous papules and plaques, commonly located on flexural surfaces such as the knees, elbows, and wrists. Other frequently affected areas include the face, neck, and hands. The hallmark symptom of AD is persistent and severe itching, which significantly impacts daily activities and disrupts sleep, contributing to a marked decline in patients' quality of life. AD clinical features vary based on the patient's age and whether the condition is in an acute or chronic phase. Hello and colleagues described three broad clinical patterns:

Chronic, persistent form

approximately 20%–30% of childhood AD cases persist into adulthood. This patient's category often experiences severe manifestations that are difficult to manage, characterized by diffuse, symmetrical, and flexural dermatitis, frequently accompanied by facial eczema.

Relapsing course

This occurs in 12.2% of patients whose childhood AD appears to resolve during adolescence but recurs in adulthood. These patients commonly develop chronic hand eczema, particularly when engaged in wet work (such as certain occupations, domestic tasks, or childcare).

Adult-onset form

In approximately 18.5% of total AD cases, the condition first manifests in adulthood, usually between the ages of 20 and 40, though it can also develop in elderly individuals.

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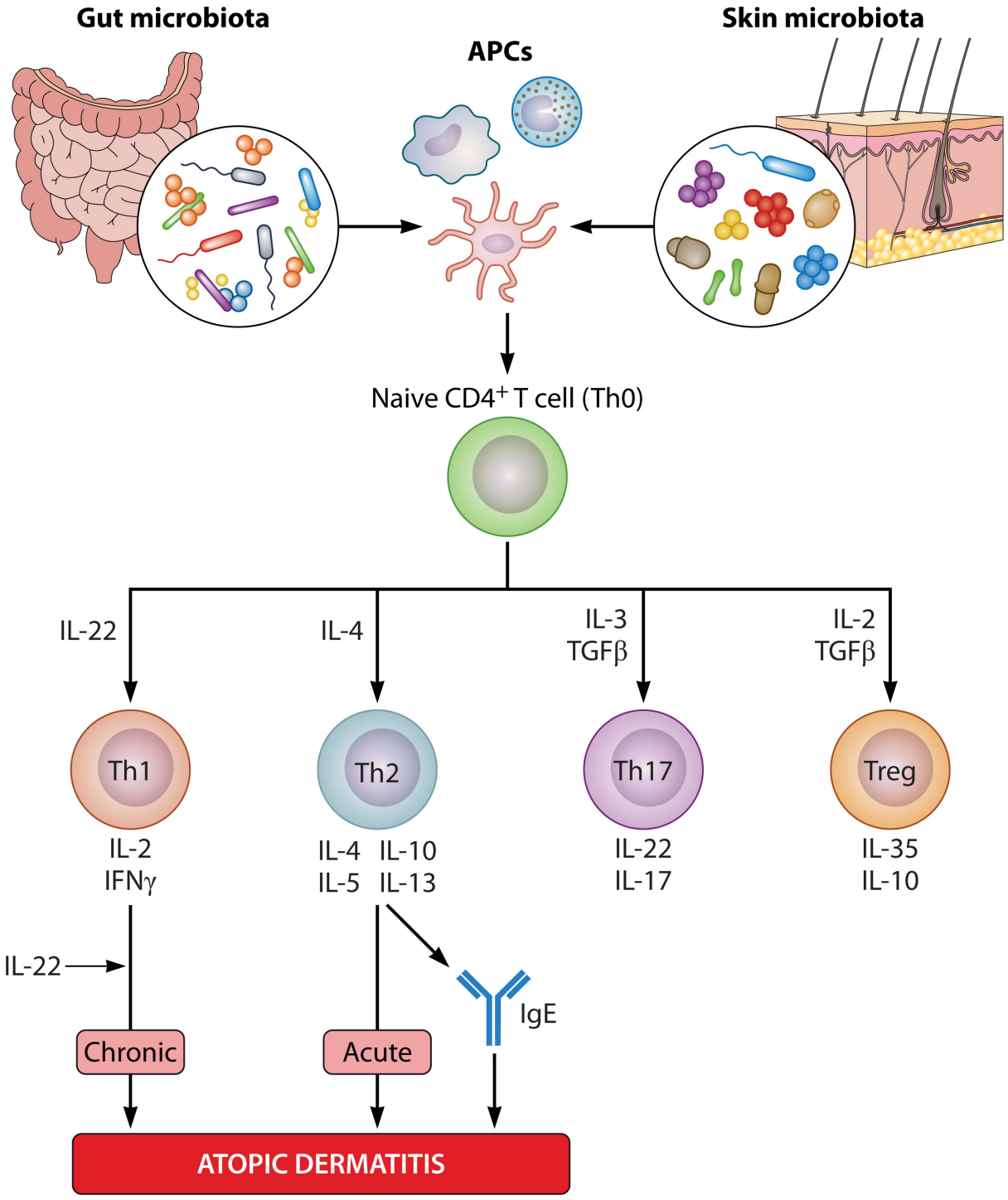

FIG 2 Microbiome-immune interaction in AD. APC: antigen-presenting cells. The interaction between the microbiome and the immune system plays a key role in the activation of APCs, influencing the typical AD inflammatory response and infection susceptibility. The figure was created with BioRender and revised by Patrick Lane (ScEYEnce Studios).

Diagnosis often requires ruling out other conditions, with a skin biopsy sometimes necessary to confirm the diagnosis (27, 28).

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Clinical phenotypes

AD exhibits various overlapping phenotypes. The characteristic presentation is lichenified/exudative flexural dermatitis, frequently associated with head and neck and/or hand eczema (7).

Head and neck eczema affects predominantly or uniquely the face and neck, including the eyelids and lips. Chronic cases often present hyperpigmented and lichenified areas on the neck, colloquially referred to as a dirty neck. In adolescent patients, if the head and neck eczema extends to the trunk seborrheic areas (i.e., upper chest and back), it can be defined as *portrait dermatitis* or *seborrheic dermatitis-like dermatitis* (7, 29–32).

Hand eczema occurs in 60%–70% of people diagnosed with AD, making chronic hand eczema a key clinical sign, particularly in adult patients. Three morphological clinical forms can be observed: (i) acute relapsing dyshidrotic eczema (*pompholyx*), (ii) chronic form of irritant contact dermatitis, and (iii) chronic dry fingertip dermatitis (7, 29–32).

Generalized eczema is a form of severe diffuse AD, affecting the face, neck, flexures, and all regions of the body with variable degrees. There are two clinical patterns, the inflammatory (acute, exudative with crusted eczematous lesions accompanied by profuse scaling, frequently associated with signs of superinfection), and the lichenoid ones (chronic, characterized by lichenifications, crusts, excoriations, and xerosis) (7).

Nummular eczema, common in Chinese and Indian adults with AD, shows round, inflamed lesions, typically located on the lower limbs. It is also observed in patients with allergic contact dermatitis (7).

AD is a potential differential diagnosis of *erythroderma*. Over 90% of the skin is red, dry, lichenified with pruritus, general discomfort, asthenia, and peripheral dermopathic adenopathies. This form is more frequent in elderly patients (7, 28, 33, 34).

Nodular prurigo is an AD variant seen in approximately 30% of patients aged 40–50 years, and it appears with extremely pruriginous papules generally at the shoulders and arms (7, 34).

Psoriasiform dermatitis is characterized by flexural eczema and no thick psoriatic plaques associated with intense itching (Fig. 3) (7, 34).

Diagnosis

The diagnosis of AD is primarily clinical, guided by the criteria proposed by Hanifin and Rajka in 1980 (Table 1). In certain cases, particularly in elderly patients, skin biopsy may be required to confirm the diagnosis or to differentiate AD from other conditions, such as cutaneous lymphoma (27, 28). Although there are no specific serological markers for AD, approximately 80% of the patients exhibit the extrinsic AD subtype, which is associated with elevated total serum IgE levels in response to specific protein allergens. In contrast, the intrinsic subtype is characterized by normal total IgE levels (16, 35, 36). Blood eosinophil counts may also be elevated, but since they tend to fluctuate more rapidly than IgE levels, they can serve as an indicator for monitoring changes in disease activity (35). Another laboratory marker of AD is lactate dehydrogenase (LDH), which may provide additional insights into disease severity and progression (35).

Treatment

Treatment selection for AD depends primarily on disease severity, commonly assessed via the Eczema Areas Severity Index (EASI) score. Complementary patient-reported outcome measures, such as the Dermatology Life Quality Index (DLQI) and Numerical rating scale (NRS) for itch and sleep, refine therapeutic decisions (16, 38). Basic care includes regular moisturization, gentle cleansing, and avoidance of identified allergens and irritants (8, 9).

For mild AD, first-line management typically involves topical corticosteroids and calcineurin inhibitors. In moderate-to-severe AD, a short course of systemic corticosteroids, oral antihistamines to alleviate pruritus, phototherapy, or systemic agents (e.g., cyclosporine) may be required. When cyclosporine is contraindicated or proves

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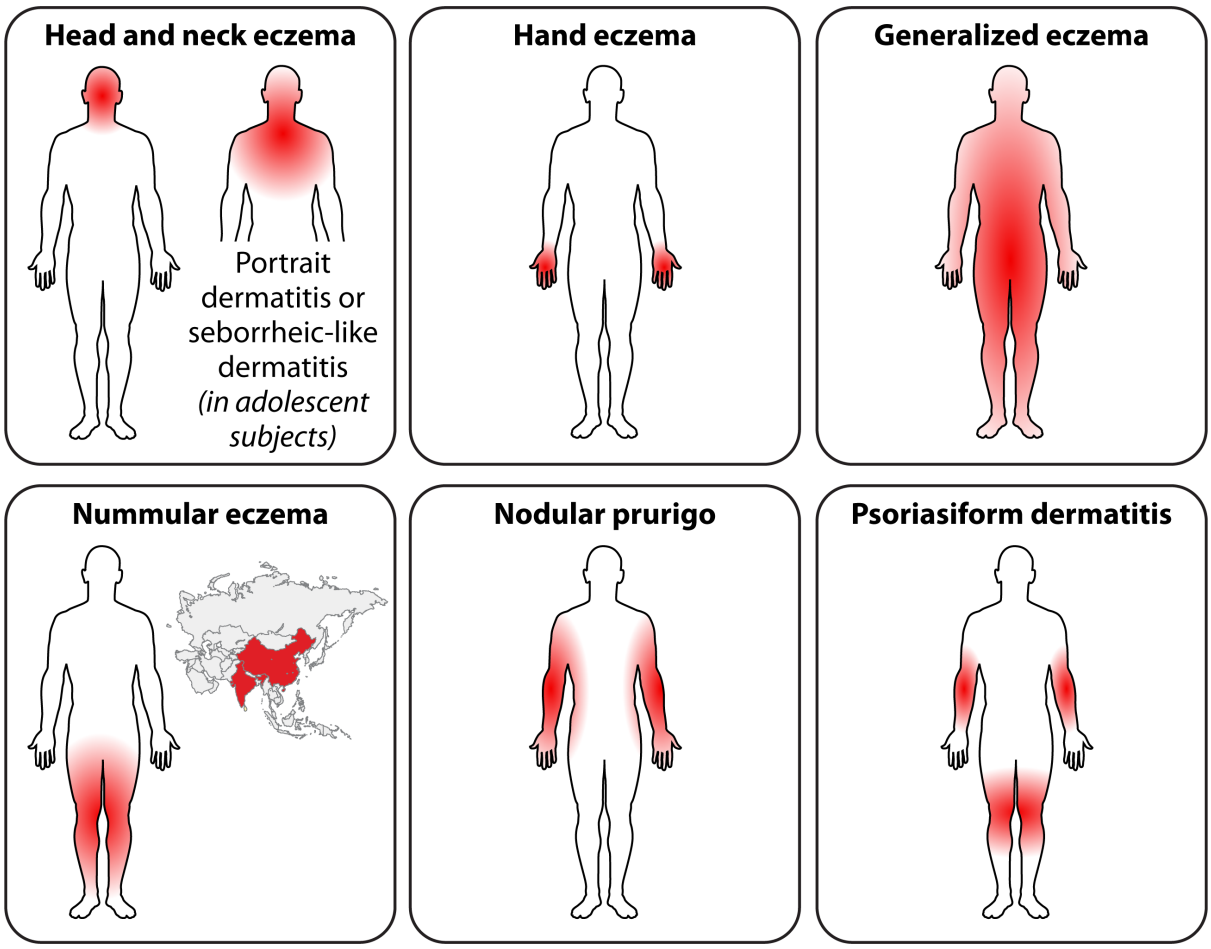

FIG 3 Clinical AD phenotypes. Depiction of the diverse clinical phenotypes of AD, highlighting variations in presentation based on lesion distributions. The figure was created with BioRender and revised by Patrick Lane (ScEYEnce Studios).

ineffective, targeted biologics and JAK inhibitors are important alternatives. Currently, approved biologic therapies for AD include dupilumab (an IL-4/IL-13 inhibitor) and the IL-13 inhibitors tralokinumab and lebrikizumab. Meanwhile, JAK inhibitors block specific enzymes (JAK1, JAK2, JAK3, and TYK2) implicated in pro-inflammatory cytokine signaling and can be administered either topically (e.g., ruxolitinib or delgocitinib, which are currently in Phase II and III trials), or orally. Three oral JAK inhibitors—upadacitinib (JAK1-selective), abrocitinib (JAK1-selective), and baricitinib (JAK1/JAK2)—are approved for AD. Conventional immunosuppressants, such as azathioprine or methotrexate, as well as biologics like omalizumab, may be used off-label when other options fail or are not tolerated (8, 9).

Growing evidence suggests that skin and gut microbiota offer an additional therapeutic target in AD. Probiotic supplementation can modulate gut microbial composition, prevent opportunistic pathogen colonization, influence bacterial metabolism, and restore immune balance (8, 9). Thus, probiotics may help reduce inflammation and improve AD clinical manifestations. Conventional immunosuppressants, however, may adversely affect the skin microbiome by altering immune responses and increasing susceptibility to bacterial and fungal overgrowth. The extent to which newer AD therapies (e.g., biologics and JAK inhibitors) interact with the microbiome still requires further investigation.

Recent research on pre-, pro-, syn-, and post-biotics underscores their potential in reducing inflammation and reinforcing skin barrier function (39, 40). Prebiotics may foster the growth of beneficial gut and skin commensals, whereas probiotics may

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TABLE 1 AD diagnostic criteria as defined by Hanifin and Rajka[a]

Feature type	Criteria
Major features (3 of 4 present)	Pruritus
	Typical morphology and distribution of skin lesions
	Chronic or chronically relapsing dermatitis
	Personal or familiar history of atopy
Minor features (3 of 23 present)	Xerosis
	Ichthyosis/palmar hyperlinearity/keratosis pilaris
	Immediate (type I) skin test reactivity
	Elevated serum IgE
	Early age of onset
	Tendency towards cutaneous infections/impaired cell-mediated immunity
	Tendency towards non-specific hand or foot dermatitis
	Nipple eczema
	Cheilitis
	Recurrent conjunctivitis
	Dennie-Morgan infraorbital fold
	Keratoconus
	Anterior subcapsular cataracts
	Orbital darkening
	Facial pallor/erythema
	Pityriasis alba
	Anterior neck folds
	Itch when sweating
	Intolerance to wool and lipid solvents
	Perifollicular accentuation
	Food intolerance
	Course influenced by environmental/emotional factors
	White dermographism/delayed blanch

[a]Criteria from reference 37.

diminish AD severity by modulating the immune responses and restoring microbiota balance, especially when administered during pregnancy and infancy. Synbiotics, which combine prebiotics and probiotics, appear to enhance regulatory T-cell function and reduce inflammatory cytokines more effectively than probiotics alone (39, 40).

Postbiotics represent a promising new frontier in AD treatment support (41). They can regulate immune responses, stimulate production of essential skin lipids, strengthen tight junction proteins, and inhibit harmful bacteria like *S. aureus*. Early clinical data suggest that topical or oral postbiotics can improve AD symptoms such as redness, itching, and eczema severity (42). Although these interventions show significant promise as adjunct therapies, further research is needed to determine the optimal compounds, strains, dosages, and treatment durations.

Detailed discussions on these approaches are provided in the "Future Perspectives" section.

SKIN MICROFLORA IN AD

The skin is colonized by many microorganisms, including pathobionts, which establish synergistic, mutualistic, and/or antagonistic interactions among one another to maintain the host's health and homeostasis. The skin microbiota composition is site- and age-specific, varying among males and females, also influenced by the host lifestyle, since it is continuously exposed to many stressors (43–46). Cutaneous appendages, namely hair follicles, sweat, and sebaceous glands, have their own specific features and microbiota (47). Indeed, skin dysbiosis has been associated with various dermatological issues, including AD (48).

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AD-associated skin dysbiosis varies much, mainly depending on the specific body niche features (i.e., moist, dry, or sebaceous), age (pediatric versus adult patients), as well as lesional and non-lesional areas (49, 50). However, although there are several reports regarding the involvement of specific bacterial genera and species in AD, strain-specific differences are yet to be fully investigated; therefore, they may represent a key step in understanding at best the skin microbiota involvement in AD and more generally in the host health (49, 51, 52).

The skin microbiota includes mainly bacteria, fungi, and viruses, divided into sub-communities. Bacterial communities have been more deeply studied, whereas fungi and viruses, often referred to as mycobiome/mycobiota and virome/virota, respectively, are key components of both the normal and impaired microflora (53–55).

In the following sections, the main representatives will be described in relation to healthy versus atopic skin.

Bacterial agents

The role of bacteria in AD has been largely studied, with skin dysbiosis now recognized as a critical factor in the disease progression (19). *S. aureus* is the main player in this condition, often being the most abundant species on atopic skin. De Tomassi et al. combined 16S rRNA gene sequencing and qPCR to analyze bacterial composition and abundance on the skin of patients with severe AD. The study revealed marked *S. aureus* overgrowth, accompanied by a reduction in microbial diversity compared with healthy skin. Monitoring its abundance could help assess the disease severity and develop targeted therapeutic strategies (56). Bacterial skin infections are common complications of AD and pose significant health risks, as they can progress to systemic infections with potentially life-threatening outcomes. A considerable number of patients are also colonized with methicillin-resistant *S. aureus* (MRSA), further complicating treatment by limiting the efficacy of standard antimicrobial therapies (57). Several other bacteria may be associated with AD, although a major role is reserved for decreased microbial diversity (58)

Staphylococcus spp

The *Staphylococcus* (59) genus is a group of gram-positive saprophytic bacterial species belonging to the Staphylococcaceae family and Firmicutes phylum. It is a common colonizer of healthy skin surfaces and mucous membranes and can also be responsible for a wide range of local and systemic infections in susceptible individuals.

This genus is traditionally divided into two main groups based on the production of bacterial coagulase: the coagulase-positive one, which includes *S. aureus*, and the coagulase-negative one, with *Staphylococcus epidermidis* as the most prominent member. Although most *Staphylococcus* species are distributed throughout the human body, some others have site-specific preferences, such as *S. aureus* primarily for the nose, and *S. auricularis* for the ear canal. At the skin level, *S. epidermidis* is the prevalent species, followed by *Staphylococcus hominis* and *Staphylococcus capitis* (60).

Staphylococcus aureus

Several studies suggest that 20% of healthy adults persistently carry *S. aureus*, whereas 60% are only intermittently colonized (61). Thanks to its specific cell wall protein agglutination factor B (ClfB) and iron-regulated surface determinant A (IsdA) and to the mediation of the extracellular matrix components such as cytokeratin 10 (62), *S. aureus* adheres to the keratinized squamous epithelial cells of the anterior part of the nostrils, where it escapes the host's innate and adaptive immune responses.

Despite its commensality, in dysbiosis-promoting conditions, *S. aureus* can behave as a human opportunistic pathogen. Indeed, it can be associated with a variety of disorders, being responsible for a wide range of acute and chronic diseases, local and systemic endogenous and exogenous infections, or postoperative wound complications

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(63). Due to its ability to spread into the bloodstream, *S. aureus* can cause bacteremia and systemic diseases, contributing to the progression of both local and systemic infections (64). Furthermore, its role is particularly evident in dysbiotic conditions, such as AD, where it can exacerbate inflammation. Moreover, it is linked to moderately mild to severe respiratory and skin infections, including abscesses, furuncles, and wounds; although usually not life-threatening, they can be accompanied by significant morbidity and pain (64).

As first observed in the 1970s by Leyden and colleagues, the typical AD dysbiosis is mainly characterized by overgrowth and virulence of *S. aureus* and is associated with alterations of the epithelial barrier and/or malfunction of the immune system (65). A wide range of cell-associated and secreted virulence factors allows it to evade and subvert the immune system even in immunocompetent hosts (66). As observed by the pooled analysis of Kong and colleagues, *S. aureus* is dominant in both damaged and healthy skin areas, with 70% of AD patients carrying *S. aureus* on skin lesions and 39% of them also on healthy skin (67, 68). Several other studies confirmed these results, with percentages ranging from 30% to almost 100% (25, 69–71). A study on 149 healthy newborns highlighted how, in the pediatric population, *S. aureus* colonization precedes AD development and that its presence on the axillary skin is associated with a significantly increased AD risk and higher prevalence at 3 months in infants who developed AD than in those who did not (20% vs 5.7%). Cox regression indicated that a positive test for *S. aureus* increased nearly 5-fold the AD risk (72).

Some enzymes produced by *S. aureus*, such as exotoxins, exhibit broad-spectrum harmful and exfoliative properties that can damage skin barriers, thus exacerbating AD inflammatory responses, although data remain scarce. Regarding the *S. aureus* quorum sensing (QS) system and accessory gene regulator (agr) pathway, they are well described in the literature to promote pathogenicity (73–75). Nakamura and colleagues found that the *agr* system of *S. aureus* is essential for epidermal colonization and contributes to AD development. Studies in mouse models and human samples demonstrated that *S. aureus* with an active *agr* system damages the skin barrier and promotes inflammation, favoring AD onset and severity (76).

These systems modulate virulence in response to changes in the host environment during infection, contributing to disease severity (77). In this direction, Tamai and colleagues demonstrated that the *S. aureus agr* QS system plays a key role in the pathogenesis of AD by regulating the expression of several virulence factors (73). The agr locus contains the two main RNA II and RNA III transcripts. RNAII, regulated by the P2 promoter, includes the agrBCD operon, which is involved in the production and secretion of the autoinducing peptide AIP, responsible for the activation of the TCSTS signal transduction system. RNAIII stimulates the synthesis of toxins such as δ-toxin and phenol-soluble modules (PSM), which participate in increasing the skin inflammation typical of AD (78).

Indeed, through the RNAIII transcript, the synthesis of toxins, such as δ-toxin and phenol-soluble modules (PSM), which contribute to intensifying the skin inflammation typical of AD, is enhanced. The same pathway also upregulates genes associated with bacterial invasion, such as leukocidins, enterotoxins (α-toxin, β-hemolysin, toxic shock syndrome toxin 1, and leucotoxins), exoproteases, and lipases (79).

The *agr* system regulates the transcription and synthesis of key virulence staphylococcal hemolysins. Among these, alpha-hemolysin (also known as alpha-toxin) is recognized for the hemolytic, dermonecrotic, and neurotoxic effects and largely damages keratinocytes (80). Literature evidence suggests its involvement in Herpes Simplex Virus 1 (HSV-1) infection in human keratinocytes and AD mouse models through ADAM10-mediated pathways (81, 82). Moreover, alpha-toxin activates the proteolytic activity of ADAM10, thus leading to the degradation of cellular E-cadherin and consequent loss of keratinocyte cohesion, typical of AD (83, 84). *S. aureus* delta-hemolysin, instead, may aggravate AD through activation of mast cells. As shown by Nakamura and colleagues, these cells, once stimulated by the toxin, release histamine and other inflammatory molecules that

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intensify the allergic skin response (85). Interestingly, *S. aureus* strains, isolated from the AD skin, produce higher amounts of δ-toxin compared with non-pathogenic strains. In mouse models, skin colonization by δ-toxin-producing *S. aureus* strains led to increased IgE production and to greater levels of inflammation compared with mice colonized with mutant strains lacking this toxin (79).

S. aureus enzymes play a pivotal role in AD pathogenesis and symptoms as well. Proteases are a key example, as they play a key role in damaging the epidermal barrier, allowing the bacteria to penetrate the deeper epidermal and dermal layers. In AD mouse models, this process strongly activates Th2- and Th17-type immune responses (86, 87). Among these, V8 protease is of particular interest. Deng and colleagues discovered a key mechanism by which *S. aureus* contributes to itching and skin damage, creating a vicious cycle that aggravates the AD disease. They revealed that the V8 protease can activate a receptor known as PAR1 in sensory skin neurons. This interaction triggers neuronal signals that induce an intense sensation of itching, pushing the subject to scratch repeatedly. Scratching, however, although it provides temporary relief, makes the situation worse. Repetitive movements damage the skin barrier, increase inflammation, and create an environment even more favorable for *S. aureus* over colonization and proliferation. In this way, the bacterium amplifies itching, thus leading to scratching, which facilitates bacterial skin colonization and inflammation. Through the elimination of this protease and by pharmacologically blocking the receptor, itching and skin damage are significantly reduced, giving a marked symptom and skin lesion severity amelioration (88, 89).

Staphylococcal hyaluronidases and collagenases compromise the skin barrier by catalyzing the degradation of hyaluronic acid and extracellular matrix, respectively (90–92). As a result, the skin permeability increases, with a higher risk of bacterial colonization and infections. These features are typical of AD, but the role of *S. aureus*-derived enzymes in AD pathogenesis is mostly unknown (93).

Another intriguing example is staphylococcal enterotoxin (SEA), encoded by the *sea* gene, which is the most common toxin in staphylococcus-related food poisoning (94, 95). Orfali and colleagues discovered that this toxin influences the CD4+ T cell response in patients with AD, altering their functional and genetic profile. AD patients show an impaired immune response compared with healthy subjects following stimulation with SEA. In AD, the polyfunctional CD4+ T cell response is reduced, especially in the CD4+ CD38+ cell subpopulation. In addition, exposure to SEA promotes the expression of EGR2 and IL-13, linked to T cell anergy, which could contribute to the disease's chronicity. These findings suggest that staphylococcal enterotoxins contribute to a tolerogenic immune profile in AD patients, leading to a less efficient response against infections (96).

Kobayashi and colleagues explored the mechanisms that regulate *S. aureus* abscess formation, emphasizing the critical role of neutrophils in containing the infection. They highlighted how *S. aureus* manipulates the immune environment to enhance its survival. Among them, *S. aureus* capsule protects it from neutrophil-mediated killing and immune responses, contributing to its hematic spread and persistence. These processes promote chronic inflammation, typical of persistent AD-associated skin infections (97).

The golden carotenoid pigment staphyloxanthin (STX), produced by *S. aureus*, is a key virulence factor due to its antioxidant properties. As an orange-red triterpenoid, membrane-bound carotenoid STX is important in the environmental fitness of *S. aureus* (98). Furthermore, STX maintains the structural integrity of the bacterial membrane and is associated with bacterial survival under stressful conditions (99). Several enzymes participate in the biosynthesis of STX. The process begins with CrtM, a dehydrosqualene synthase, which catalyzes the condensation of two molecules of farnesyl diphosphate, forming 4,4′-diapophytoene. Subsequently, CrtN, a dehydrosqualene desaturase, dehydrogenates 4,4′-diapophytoene to form 4,4′-diaponeurosporene. Finally, the latter undergoes a series of modifications, including oxidation, glycosylation, and esterification, to give rise to STX (100).

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STX not only enhances the resilience of *S. aureus* in hostile environments but also contributes to its pathogenicity, making it an important target for research and potential therapeutic interventions.

STX can improve the antioxidant properties of *S. aureus* and the resistance to neutrophils. This yellow carotenoid pigment acts as an antioxidant, having multiple conjugated double bonds that facilitate the detoxification of reactive oxygen species generated by the host immune system (101). *S. aureus* strains may differ in their ability to produce STX. A prominent example of this difference is represented by MSHR1132T and FSA084T strains. MSHR1132T, isolated from an indigenous Australian patient, is characterized by the absence of pigmentation, appearing creamy white. The absence of STX in MSHR1132T and related strains indicates a potential biological difference from pigmented strains, which could influence their pathogenicity and resistance to oxidative stress (102).

A crucial mechanism used by phagocytic cells to eliminate pathogens is the release of reactive oxygen species, produced by the enzyme nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and myeloperoxidase (MPO) (103, 104). It has been hypothesized that bacterial carotenoids, such as those produced by *S. aureus*, may have a protective role against these defensive molecules (105).

By genetically mutating crtM and crtN genes (encoding dehydrosqualene synthase and dehydrosqualene desaturase) to eliminate pigment production, Liu et al. demonstrated that pigment-deficient strains are more susceptible to immune defenses. This suggests that targeting carotenoid biosynthesis could be a promising strategy for developing new treatments against *S. aureus* infections (106).

Another factor to be considered in AD development and progression is the strain diversity within the *S. aureus species*. As an example, the study of Byrd et al. identified specific *S. aureus* strains associated with pediatric AD, including the ST188 clade, which was found to be predominant. This strain stands out for its ability to persistently colonize atopic skin, thanks to a genetic profile characterized by increased expression of virulence genes, including those coding for superantigens and exfoliative toxins. The study also highlighted the presence of other *S. aureus* clones with adaptive characteristics specific to atopic skin, including strains belonging to the CC1 and CC8 clonal complexes, known for their ability to produce enterotoxins and modulate the host's immune response. These strains show an enrichment in antimicrobial resistance genes and an increased ability to form biofilm, making them particularly difficult to eradicate. Genomic analysis also suggested that *S. aureus* strains isolated from AD patients tend to be genetically distinct from those found in healthy subjects (70). The study by Conte et al. analyzed 38 *S. aureus* strains isolated from AD patients and healthy carriers, using whole genome sequencing (WGS) and phenotypic analyses. The main results indicated that strains from AD patients show significant genetic heterogeneity and share a set of virulence factors and antimicrobial resistance genes, such as mecA, blaZ, and ermC. In addition, these strains exhibit less variability in gene content, indicating that the inflammatory conditions of AD may exert selective pressure, leading to a gene repertoire optimization. Significant enrichments were observed in genes related to mechanisms such as post-translational modifications, protein turnover, and chaperonins, as well as intracellular trafficking, secretion, and vesicular transport. Phenotypically, all AD strains were strong or moderate biofilm producers, whereas less than half showed invasive capabilities (51).

Staphylococcus epidermidis

S. epidermidis is a ubiquitous human skin commensal. It can both benefit and harm its host through various microbial and eukaryotic cell-microbial interactions, which are usually strain- and context-dependent (107–110). Since it lacks the enzyme coagulase, it is part of the CoNS group, being the most representative member (111).

S. epidermidis is generally regarded as a beneficial colonizer of the normal skin microflora. It is involved in many physiological functions, such as containment of

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opportunistic pathogen growth and virulence, barrier development and repair, immune modulation, and host homeostasis maintenance (112, 113). Although it mainly colonizes moist or sebaceous areas, as well as the mucosae, this species can be found in all skin microenvironments at different densities, depending on their physio-chemical properties (112, 114, 115). Skin colonization by *S. epidermidis* is mediated by adhesins that recognize skin and extracellular matrix ligands, such as accumulation-associated protein (Aap), which binds to corneocyte glycans, and serine aspartate repeat-containing (Sdr) proteins, which recognize ECM components (112). Its adhesins, also involved in biofilm formation, are key virulence factors (108). Early *S. epidermidis* colonization during neonatal life seems to be essential for skin barrier development, leading to a tolerogenic T-cell response to commensal microorganisms without impairing the immune response against pathogens (116). Besides, *S. epidermidis* may reinforce the epithelial barrier through sphingomyelinase (SMase)-assisted ceramide production, as demonstrated by Zheng and colleagues (117). Furthermore, it is involved in pathogen colonization resistance through direct and indirect mechanisms. It secretes antimicrobial peptides (AMPs) that can selectively counteract *S. aureus,* but also increases the keratinocyte production of AMPs, thus modulating the innate response (118), also promoted through the keratinocyte aryl hydrocarbon receptor (AhR) pathway (119). As far as the adaptive immune response is concerned, *S. epidermidis* induces IL-17A + CD8+ T cell response (120).

Besides being a human commensal, *S. epidermidis* can also behave as an opportunistic pathogen. As such, it is widely recognized as responsible for device-associated infections in immunocompromised patients (121, 122) and involved in the etiopathogenesis and worsening of many skin diseases, AD included (70). Several studies report *S. epidermidis* overgrowth on AD lesions, which worsens the existing interactions between the host and the skin microbiota, leading to further dysbiosis, skin damage, and disease progression (77, 112, 123). Interestingly, Byrd and colleagues demonstrated through metagenomic sequencing the prevalence of clonal *S. aureus* isolates and heterogeneous *S. epidermidis* strain communities in AD patients (70).

If we delve into strain-related topics, it is important to highlight that despite the growing interest in strain-specific influence on host health and homeostasis, *S. epidermidis* remains a relatively overlooked species compared with *S. aureus*. Phylogenetically distinct *S. epidermidis* strains can colonize the skin of the same healthy subject. The strain variety could depend on microbial interactions within the skin microbiota itself, for instance, through metabolic competition or secretion of antimicrobial molecules (110). Focusing on AD*, S. epidermidis* genetic variability and strains, as well as its cutaneous distribution, play a pivotal role in AD dynamics, with the possible definition of AD subtypes according to the composition of staphylococci during the acute phases of the disease (52).

Many *S. epidermidis* features could link its presence to AD. According to Cau and colleagues, some *S. epidermidis* strains produce the extracellular cysteine protease A (EcpA), which damages the epithelial barrier, induces a keratinocyte inflammatory response, and correlates with disease severity (123). Similar data were obtained by Williams and colleagues. In their study, the authors highlighted how EcpA drives early skin inflammation, later amplified by *S. epidermidis* phenol-soluble modulins (PSMs) through keratinocyte cytokine secretion. Finally, they remarked that overabundant *S. epidermidis* could be responsible for skin disease through the *agr* quorum sensing system, which controls both PSM gene and *ecpA* expression (124).

S. epidermidis proinflammatory activity has been highlighted as well. Previously, it was believed that, being a normal skin colonizer, this bacterium does not exhibit any distinct proinflammatory activity. However, in AD-derived primary normal human epidermal keratinocyte (NHEKs) models, *S. epidermidis* activates the inflammation-associated transcription factor NF-kappaB and induces the expression of proinflammatory cytokines. In addition, in human 3D skin equivalents, proinflammatory mediators

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are induced, whereas barrier molecules (i.e., filaggrin, keratin 1, and keratin 10) are downregulated (125).

Despite staphylococci colonizing the whole skin, it has been reported that staphylococcal biofilm can be found on lesional sites, but not on non-lesional ones (112, 126). However, discordant data are reported, as Gonzalez and colleagues first demonstrated the presence of staphylococcal biofilm on both lesional and non-lesional sites in AD pediatric subjects (126). Interestingly, *S. epidermidis* strains isolated from AD lesions show great biofilm production (126, 127). Similarly to *S. aureus*, *S. epidermidis* can form biofilm in correspondence with the sweat ducts, occluding them and leading to subclinical miliaria in patients with filaggrin-deficient stratum corneum, which exacerbates the typical itching (127). The study by Byrd et al. examined the interaction of different S. *epidermidis* and *S. aureus* strains in AD, particularly under the effect of topical corticosteroids. After treatment, a significant reduction in *S. aureus* load was recorded, whereas the population of *S. epidermidis* underwent a selective modulation, with an increase in the less inflammatory strains and a reduction in the more aggressive ones. This suggests that therapy can influence not only inflammation but also the skin microbial balance (70). To assess whether specific *Staphylococcus* strains vary according to AD status, Lane Starr et al. classified them into metagenomes using StrainGST. The analysis revealed a notable absence of *S. epidermidis* FDAARGOS_1361 (ST 153) in lesional samples, whereas it was detected in five out of seven control samples and four out of eight non-lesional samples. In contrast, three other *S. epidermidis* strains (ST 5, 89, and 387) were identified exclusively in AD swabs. These findings suggest that the association of *S. epidermidis* with disease activity may be strain-dependent (128).

Other coagulase-negative staphylococci (CoNS)

The so-called CoNS represent a highly heterogeneous group of staphylococci that colonize human skin and mucosae (129). It includes nearly 40 species, among which *S. epidermidis*, *S. hominis*, *Staphylococcus haemolyticus*, *S. capitis*, *Staphylococcus saprophyticus*, *Staphylococcus caprae*, *Staphylococcus lugdunensis*, *Staphylococcus simulans*, *Staphylococcus warneri*, *Staphylococcus pettenkoferi*, and *Staphylococcus massiliens* are the most isolated (129, 130). It is difficult to provide a comprehensive description of this group since it is mainly composed of genetically and functionally uncharacterized staphylococci. Overall, the absence of the enzyme coagulase is a defining feature among them. These bacteria have been regarded as less or non-pathogenic bacteria for a long time, and with similar behavior, but they range from beneficial species to pathogenic ones with different virulence potential (109, 111). In fact, they are one of the most frequent nosocomial infectious agents, being responsible for catheter-related and bloodstream infections (131).

Similar to the other staphylococcal species previously described, CoNS colonize the skin and the mucosae, with a preference for moist sites, and are one of the most abundant colonizers of all skin sites in eubiotic conditions (109, 129). Their physiological role (i.e., maintenance of skin homeostasis, counteraction of skin inflammation, and colonization resistance) overlaps with that reported for *S. epidermidis*, although evidence regarding the individual CoNS species is limited (112, 130, 132). Antimicrobial secretion is a common feature among CoNS isolates, such as some *S. hominis* and *S. capitis* strains (112, 133–136). At the same time, other commensal species represent a growing threat. Among the CoNS, *S. haemolyticus* possesses the highest level of antimicrobial resistance and frequently causes a broad spectrum of infections (137, 138). Several other CoNS strains carry methicillin resistance genes (i.e., *mecA* gene) and tend to develop multidrug resistance, especially in nosocomial environments, whereas commensal CoNS and their AMPs can act as the host's guardians against pathogenic *S. aureus* (137). However, although many CoNS can cause infection in eczematous sites, few reports of CoNS and AD have been published with discordant results.

Some analyses showed an increased abundance of specific CoNS in AD and their correlation with disease severity, both in infants and adults. *S. capitis* seems to be

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involved in AD flares and in other typical clinical manifestations, like scalp dermatitis (139). Based on literature evidence, it could be hypothesized that *S. capitis* may play a role in AD, although it is still unclear (140). Interestingly, other researchers demonstrated how staphylococcal communities are similar between lesional and non-lesional AD skin, whereas they differ between AD patients and healthy subjects. According to Edslev and colleagues, absolute abundances of different CoNS correlate with disease severity, that is, severe AD forms are associated with absolute abundance of *S. capitis* and *S. lugdunensis* on non-lesional sites, whereas milder AD is associated with absolute abundance of *S. hominis* (141).

Other studies instead support the hypothesis that dysbiotic AD skin lacks these protective CoNS. CoNS strains can compete with *S. epidermidis* and contain its deleterious potential. If they are absent, the *S. epidermidis agr* system may no longer be inhibited, thus leading to EcpA production and skin barrier damage (123). Additionally, CoNS also counteracts *S. aureus*, as later described.

It can be supposed that the diverse CoNS relative abundance in AD samples could be species-specific and may also depend on specific dermotypes (87).

Pseudomonas aeruginosa

P. aeruginosa is a ubiquitous bacillus that can be found in the environment (i.e., soil, water) and on both animals and humans. It behaves as an opportunistic pathogen that rarely causes infections in healthy subjects, whereas it is frequently associated with nosocomial infections, especially in immunocompromised patients or those affected by cystic fibrosis (142, 143). *P. aeruginosa* infections occur in a wide range of organs and may have different grades of severity (144). Although it can be retrieved in diverse environments, *P. aeruginosa* is not often found on healthy human hosts (145). According to the literature, this bacterium is part of the transient skin microflora in case of impaired epithelial barrier or can be found in just 2% of non-hospitalized individuals in correspondence with moist niches, whereas it is a normal gut colonizer in 10%–15% of healthy subjects (146, 147).

P. aeruginosa is often involved in skin disease pathogenesis and progression, with chronic wound healing impairment, folliculitis, and green nail syndromes as representative conditions, but also because of bacteremia (145). At the same time, evidence regarding its role in AD is limited, as it is not frequently found in AD lesions or in very low amounts (148, 149).

Cutibacterium acnes

C. acnes, previously known as *Propionibacterium acnes*, is the most abundant commensal of the human skin flora (150). Like many other microorganisms, it can play a double role. On one hand, its commensal role has been confirmed by several studies. On the other hand, it is emerging as an opportunistic pathogen, but further studies are needed. Indeed, it is mainly known for its involvement in acne vulgaris pathophysiology (151). Its pathogenic role has only been suggested, and it is yet to be confirmed (152). In eubiotic conditions, *C. acnes* can be found mostly in sebaceous follicles. Recent findings suggest that due to its anatomical and physiological features, each skin pore is colonized by a single *C. acnes* lineage (153). It plays key roles both in homeostasis and in disease evolution, in skin barrier function and pH control, while modulating host immunity (both innate and adaptive) and counteracting pathogen colonization and/or overgrowth (i.e., *S. aureus*) (152). Different phylotypes are responsible for different outcomes in terms of health and disease, as has been described for acne vulgaris. More in detail, several studies reported how some *C. acnes* strains are associated with healthy skin and others with acne and its severity (152, 154).

C. *acnes* seems to concur in AD pathogenesis and progression. Atopic skin shows both a decreased abundance of C. *acnes*, a sebaceous gland number, and dimension reduction, thus a limited sebaceous secretion, which could lead to a further loss of the same species (155, 156). AD is not only characterized by a reduced *C. acnes* abundance

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but also by a decrease in triacylglycerols (TAGs) content and higher TEWL. TAGs have a positive effect on the skin barrier, as they can provide fatty acids for ceramide synthesis, and their synthesis at keratinocyte level is induced by C. *acnes*. Thus, a loss in C. *acnes* content could help explain the lipidic alteration in atopic skin (157, 158).

C. acnes protective role in AD and healthy skin has been suggested (18). Notably, *C. acnes* secretes L-carnosine. This metabolite, enriched in AD, could have anti-oxidative and anti-inflammatory effects through the heme oxygenase 1 (HO-1) pathway (139). Despite the fact that interesting results regarding phylogenetic diversity have been obtained, further investigation is needed.

Streptococcus spp

The *Streptococcus* genus includes over 100 species that can behave as commensals, pathogens, and opportunistic pathogens (159, 160). They are divided into beta or non-beta hemolytic streptococci and can be classified according to the Lancefield classification into 20 different groups, depending on the cell wall composition (161). They colonize the oral cavity and the nasopharynx and can also be found on the skin and are responsible for a variety of diseases (160).

Streptococcus genus can be found on dry epithelial surfaces. It is frequent on the skin of healthy pediatric subjects, for instance, in the perioral area, and is more abundant in people with elastic skin. Overall, *Streptococcus* spp. could influence skin structure and barrier function as well as skin aging (161–163). Among the streptococci, despite being part of the skin and oral microbiota, *Streptococcus mitis* has been recognized as a new emerging pathogen in pediatric patients (164). It regulates oral immune balance and interacts with oral keratinocytes, but with effects on skin health yet to be understood (165, 166). On the other hand, *Streptococcus pyogenes*, a group A Streptococcus (GAS), is not commonly isolated from healthy skin, being one of the best-known examples of transient skin colonizers, particularly in the concurrence of pathologic conditions. *S. pyogenes* is often associated with skin and soft tissue infections (SSTIs), as well as psoriasis, and may infect keratinocytes by forming biofilm (167–170).

The *Streptococcus* spp. relative abundance seems to vary in AD patients, similarly to what happens for *Cutibacterium* and *Corynebacterium* species. During AD flares, these species are less abundant, probably due to the antimicrobial metabolites secreted by staphylococcal colonizers (i.e., *S. aureus*) (68). SSTIs are among the complications of AD (171). GAS species have been isolated from pediatric skin samples: they first colonize the epithelial surface, then they evolve into more invasive infections with severe health consequences, potentially leading to hospitalization (172). Indeed, *S. pyogenes* is the second most common infection agent (both SSTI and systemic) in AD patients (58, 173). Regarding Group B Streptococci (GBS), recent findings seem to suggest that the AD risk in children may increase when vaginally delivered from mothers that underwent intrapartum antibiotic prophylaxis (174).

Corynebacterium spp

Corynebacterium spp. are lipophilic slow-growing bacteria that can be easily found on skin and upper respiratory surfaces. They are recognized as human commensals, and their behavior is strictly context-dependent (18, 175). *Corynebacterium* is one of the most abundant genera in skin normal flora and mainly found in moist niches, like *Staphylococcus* spp., and dry areas (49).

Limited data are available on *Corynebacterium* spp. due to the technical challenges of culturomics analysis. Most *Corynebacterium* species are not associated with any dermatological disease and may help the skin immune system in counteracting pathogen colonization (176–178). Nevertheless, there are some exceptions, such as for *Corynebacterium minutissimum* and *Corynebacterium tenuis*, which are responsible for erythrasma and trichomycosis axillaris, respectively (177). Among the normal skin flora, opportunistic *Corynebacteria*, such as *Corynebacterium jeikeium,* can be found as well (179).

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As previously introduced, AD-associated dysbiosis includes a general decrease in *Corynebacterium* spp (49). Despite this, metagenomic analysis evidenced that the relative abundance of *Corynebacterium kefirresidentii* increases in AD flares compared with healthy controls.

Fungal agents

Data concerning the role of fungi in AD development and exacerbation remain limited, particularly when compared with the extensive research on bacterial involvement. The primary candidates in the pathogenesis of AD are represented by *Malassezia* and *Candida* spp., although controversial results are reported (180). In general terms, such yeasts have been mostly detected in special AD sites, like the head and neck regions, thus confirming their high prevalence in sebaceous gland-rich and intertriginous areas. Notably, the reported effectiveness of antimycotic drugs in AD cases is a further element supporting their involvement (181, 182).

Malassezia spp.

Malassezia is a lipophilic yeast belonging to the Basidiomycota genus, which includes 19 different species. Initially classified under the genus *Pityrosporum* and grouped into three different species (i.e., *Pityrosporum ovale, Pityrosporum orbicolare*, and *Pityrosporum pachydermatis*), these organisms were later recognized as different *Malassezia furfur* serovars (183). Nowadays, *Malassezia* spp. comprises the A, B1, B2, and C groups, with B1 and B2 being the most detected in human skin (i.e., *Malassezia restricta* and *Malassezia globosa* belonging to the B1 group, and *Malassezia sympodialis* to B2). It is commonly retrieved in sebaceous areas like the face, scalp, thorax, and the upper back.

Malassezia is a normal component of the human mycobiota, but it can also act as an opportunistic pathogen. *Malassezia* can be retrieved either in healthy or diseased skin, such as in pityriasis versicolor, seborrheic dermatitis, folliculitis, and AD (181). The yeast colonization begins early in life, with maternal and caregiver contacts representing the contagion source. Moreover, the heightened sebaceous gland activity induced by the maternal hormones may explain the easy skin colonization of the newborn's skin by *Malassezia* (183). Notably, *Malassezia* presence on the skin decreases with age, correlating with reduced sebaceous secretion in elderly individuals and confirming its reliance on lipid-rich environments (184). *Malassezia* species produce lipases, which break down the sebaceous lipids on the skin surface, releasing free fatty acids and other lipid byproducts. These free fatty acids can irritate the stratum corneum, compromise corneocyte integrity, and disrupt intercellular lipid bilayers, leading to increased TWEL, further weakening the skin barrier (185).

Choi and colleagues identified different well-represented *Malassezia* species in AD patients compared with healthy individuals, with *M. restricta* being the most detected in AD and the only species reported in healthy controls (186). The role of *M. restricta* in AD pathogenesis has been confirmed by Lee and colleagues, evaluating the correlation between the yeast itself and biological drugs (i.e., ruxolitinib, anti-IL-4R) in experimental models (185). At the same time, in AD patients, the identification of yeast has been reported to be less frequent in lesional versus non-lesional skin, with *Malassezia sympodialis* predominance (187). Accordingly, a previous study has detected a relative depletion of *M. globosa* in AD patients, in which a predominance of *M. sympodialis* and *Malassezia dermatitis* was found (188). The AD-altered skin barrier allows *Malassezia* spp. to penetrate and interact with keratinocytes and local immune cells, either directly or through specific proteins and enzymes, thus leading to the upregulation of some proinflammatory factors and to the release of Th2 pattern cytokines, thereby promoting Th17 (189, 190). Another possible mechanism played by the yeast in AD development is represented by the activation of IgE-mediated sensitization to *Malassezia* antigens. Accordingly, Celakovska and colleagues highlighted the correlation between sensitization to some yeast molecular components (mainly *M. sympodialis* Mala s6 and s11) and AD severity; moreover, Mala s11 (Manganese superoxide dismutase *M. sympodialis*)

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sensitivity correlated with high IgE serum levels (191). The yeast's capability to deliver antigens is greater in alkaline environments, as it occurs at the cutaneous level in many AD patients, and this could help explain the important role of IgE sensitization toward *Malassezia* components (182). Indeed, higher sensitizations to *M. sympodialis*, *M. restricta,* and *M. globosa*, as measured by total and specific IgE levels, were significantly associated with severe AD, even if their presence on the skin is rather low (192). *Malassezia* sensitization was also found to correlate with peculiar AD localization, like the head and neck, with a typical worsening when sweating (193).

Candida albicans

The yeasts of the *Candida* genus are considered commensal and saprophytic microorganisms commonly detected in the human body. The main species is *C. albicans*, ordinarily isolated from mucosal areas (i.e., gastrointestinal tract, genital site in women) as well as skin surfaces, especially cutaneous folds. The shift from commensalism to pathogenicity is usually favored by some predisposing factors, such as diabetes, immunosuppression, senescence, and antibiotic agents; furthermore, some intrinsic *Candida* virulence factors also enhance these processes (181).

Candida spp. detection in AD patients has been previously shown to be higher compared with healthy subjects, either from the skin or the gastrointestinal tract (181). More recently, different studies have reported a higher detection of *Candida spp*. in skin swabs from AD subjects, with a predominance of *C. albicans* and *Candida parapsilosis* (186, 192). In addition, a high rate of sensitization to *Candida* spp. (mainly *C. albicans* m5 antigen) has been demonstrated, with a positive correlation with increased AD severity (192), and detection of IgE antibodies specifically directed toward *C. albicans (194*). Of note, *C. albicans* IgE can cross-react with other fungal agents, like *Malassezia* and other *Candida* species, thus leading to falsely elevated levels of specific antibodies (181).

When evaluating the PBMC proliferative response to *C. albicans* exposition in AD patients, a significant augmented production of IFN-γ, IL-2, IL-4, IL-5, and IL-17 was reported, with the yeast mostly recognized as a Th1-inducer agent (195, 196). However, it must be considered that the different morphological status, that is, yeast versus hyphal form, can activate the Th1 or Th2 cytokine response, respectively, thus inducing different AD clinical features and severity (182).

Furthermore, it has been recently clarified that the yeast modulates the immune response processes by acting on cellular interaction and adhesion mechanisms mediated by the small extracellular vesicles and their effect on specific dendritic cell receptors (i.e., Siglec-7 and −9) and sialic acid. Such a pathway was found to be altered, possibly impairing the physiological response to fungal agents (197).

Viral agents

Viruses play a significant role in the onset, exacerbation, and complication of AD. The incidence of viral infections, particularly those caused by Herpes Simplex Virus (HSV), Molluscum Contagiosum, and Human Papillomavirus (HPV), is notably higher in AD patients compared with the general population (198, 199). In fact, the defective skin barrier and mutations in the filaggrin gene that characterize AD facilitate viral entry, increasing susceptibility to infections (198, 199).

Alterations in the skin microbiota of AD patients may also influence viral colonization and infection. Disruption of the microbial balance can reduce competition against pathogenic viruses, favoring their growth. Furthermore, the Th2-dominant immune response can impair the host's ability to effectively combat viral infections (58). Conversely, viral infections can activate the immune system, potentially exacerbating the Th2-skewed response, leading to increased inflammation, worsening symptoms, and more frequent flare-ups (200, 201).

Notably, many AD patients use topical or systemic corticosteroids or other immunosuppressants to manage their symptoms. Unfortunately, these treatments can suppress immune function, reducing the skin's ability to reduce viral load (58).

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Human herpesvirus

The Herpesviridae family consists of DNA viruses with the unique ability to establish lifelong latency in their host following the initial infection. The most notable family members are Herpes Simplex Virus (HSV) types 1 and 2, which remain latent in sensory ganglia (58).

Individuals with AD face an elevated risk of developing HSV infections and may experience a severe, disseminated infection form called eczema herpeticum (EH), or Kaposi's varicelliform eruption (KVE), first described in 1887. This condition is characterized by painful lesions that initially appear in affected AD areas but can spread to healthy skin or even to internal organs, posing a significant risk to the patient's life. In this scenario, prompt antiviral treatment is essential to manage the life-threatening consequences (202). A multicenter analysis from the German registry demonstrated that EH occurred in 21.8% of AD patients. Among those with EH, 54.8%, representing 12% of the study population, experienced multiple episodes. Interestingly, no significant differences were observed in demographic or disease characteristics, nor were there associations with previous conventional treatments (202). The relationship between EH and a history of *S. aureus* infections was explored by Moran and colleagues, who found a sixfold increased risk of EH in patients with such infection. Notably, the presence of IgG antibodies against the *S. aureus* antigen SE*I*X was linked to the development of EH, reinforcing the hypothesis that *S. aureus* skin infections may heighten susceptibility to HSV (203). Conversely, HSV-infected keratinocytes can trigger the release of IL-1, IL-6, and TNF-α, amplifying local inflammation and potentially exacerbating AD flares.

Recent evidence suggests that several genetic variants may help identify a subgroup of AD patients more susceptible to develop EH (204). These variants often involve loss-of-function mutations in the filaggrin gene and in other genes involved in maintaining skin barrier integrity and hydration. Also, dysregulation in genes involved in inflammation processes and the maintenance of immune response has been demonstrated (205).

Recent studies, including a meta-analysis, have indeed demonstrated a broader association between AD and infections by other human herpesviruses (HHVs), such as Cytomegalovirus (CMV), mainly in pediatric subjects, and Epstein-Barr Virus (EBV) more frequently in adult AD patients (206).

Molluscum contagiosum virus (MCV)

MCV is a poxvirus responsible for the development of characteristic skin-colored, dome-shaped, umbilicated papules called Molluscum Contagiosum (MC). The infection has distinct modes of transmission and presentation, depending on the patient's age and immune status. In children, MC is commonly transmitted via direct skin contact, whereas in adults, it can be sexually transmitted, often presenting in the genital area or lower abdomen.

In individuals with a fully functional immune system, MCV typically follows a self-limited course, whereas in people with a weakened immune system, the infection can become more widespread and persistent, leading to clusters of lesions that are harder to treat. Children with AD are particularly vulnerable to MCV infection due to the compromised skin barrier, which facilitates the virus's entry (207). A study including 615 children affected by MC, 13.17% of whom had AD, demonstrated that those with AD experienced a significantly higher lesion count and more itchiness compared with those without AD (208). The risk of developing MC in adult AD patients is indeed significantly higher, estimated to be 2.85 times greater than in the general population (209).

Filaggrin gene mutations are recognized as an additional risk factor for MCV infection (210). However, the study published by Kojima and colleagues suggests that these mutations do not significantly influence the number of lesions at presentation or the time of infection resolution. This implies that although the skin barrier impairment

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increases susceptibility to infection, once the virus is present, other factors (likely related to immune function) determine the clinical course (211).

Human papillomavirus (HPV)

HPVs are a group of ubiquitous DNA viruses that are often associated with skin and mucosae and are known for their role in the development of several tumors (212). Among them, several beta and gamma HPV genera are part of the skin virome of healthy subjects and can be included among the commensal microorganisms. They have been found in the skin of 45% of healthy infants and 80% of healthy adults, leading to subclinical manifestations. However, in individuals with a compromised or weakened immune system, for instance, Epidermodysplasia Verruciformis (EV) patients, these pathobionts may promote skin carcinogenesis (213, 214).

Patients with AD are more susceptible to HPV infections due to a combination of factors, including the previously cited impaired skin barrier function and immune dysregulation. Additionally, the intense itching associated with AD leads to frequent scratching, which causes microtears and abrasions, providing entry points for HPV to infect basal skin cells. This heightened susceptibility can result in an increased incidence of cutaneous warts and other HPV-related skin conditions in individuals with AD.

Moreover, a recent murine study by Bergot and colleagues demonstrated that the expression of the high-risk HPV16 E7 oncoprotein in keratinocytes is associated with skin thickening, acanthosis, and spongiosis. The study also found elevated levels of thymic stromal lymphopoietin (TSLP) and an increased presence of innate lymphoid cells in infected skin, suggesting a potential role in the development of AD-like lesions (215).

Warts caused by HPV can be more extensive and persistent in individuals with AD, as previously reported in the literature (216, 217). Moreover, cases of extended HPV-associated skin verrucosis (218) and acquired EV (219) have been reported, as well as HPV-related squamous cell carcinoma (SCC) cases (220).

A retrospective case-control study involving 1,160 women conducted by Morgan and colleagues demonstrated an association between AD and cervical high-risk HPV infection (221). However, an increased risk of developing cervical cancer has not been demonstrated, even among women receiving long-term immunosuppressive treatment for AD (222).

In 2024, Du Than and colleagues analyzed, through an AmpliSeq-HTS approach, the virome composition of an AD patient, demonstrating the presence of 31 HPVs/human polyomavirus (HPyVs) species, with high variability in the viral composition over time for lesional sites, in contrast with a more stable signature observed in non-lesional skin (223).

In addition, conventional systemic immunosuppressants, such as cyclosporine, methotrexate, azathioprine, or high-dose corticosteroids, can compromise the immune system's ability to detect and eliminate viruses, potentially increasing the susceptibility of AD to HPV infection and HPV-related lesions (224). Although newer biologic agents and small molecule therapies tend to be more selective and may carry a different infection risk profile compared to broad immunosuppressants, they can still increase the risk of viral infection (225). There is some real-world evidence of an increased risk of HPV infections in AD patients treated with dupilumab (226) and upadacitinib (227). However, large-scale long-term data regarding HPV risk in patients on these newer therapies remain limited.

Bacteriophages

The human virome also includes several bacteriophages, or simply phages. Their role is to selectively target and infect specific bacteria, without directly affecting the human host. Recent evidence highlights how the loss of phages in the skin microflora corresponds to higher concentrations of potentially pathogenic bacteria. Bacteriophage dysbiosis has been reported in psoriasis and acne, with a reduction of these viruses in the affected sites (228). However, the relationship between AD and bacteriophage populations is still unclear. A recent work by Wielscher and colleagues focused on the

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phageome composition in normal versus atopic human skin to investigate whether it shifts during AD and its eventual involvement in AD pathogenesis. Despite the limited number of subjects and the high inter-individual variability, the researchers identified 28 phages (i.e., Bonferroni significant contigs) that significantly differ between normal and atopic skin. Overall, it seems that cutaneous phageome changes from healthy and inflamed skin, with skin-protecting phages decreasing as the inflammation worsens (229).

Another study by Bjerre and colleagues reported how *Cutibacterium* (formerly called *Propionibacterium*) phages and *Staphylococcus* phages are the most abundant in both atopic and healthy individuals in a small sample population. Their results support those previously reported by Wielscher and colleagues, as specific *Propionibacterium* and *Staphylococcus epidermidis* phages were found more abundant in AD subjects, with *Staphylococcus* phages increased on lesional areas (230).

Figure 4 summarizes the skin dysbiotic pattern previously described, focusing on atopic versus non-lesional skin.

MICROBIAL INTERACTIONS IN AD

Microorganisms coexist in the human body as polymicrobial communities, sharing colonization spaces and competing for resources. Interactions between these communities generally favor the persistence of microorganisms beneficial to health, highly influencing local communities and counteracting pathogen colonization (231). In cases of dysbiosis and polymicrobial infections, disrupted interactions among microorganisms can further exacerbate the existing condition. When dysbiosis and polymicrobial infections occur, the altered modes of interaction between microorganisms can further aggravate the situation, worsening the imbalance already present (Fig. 5).

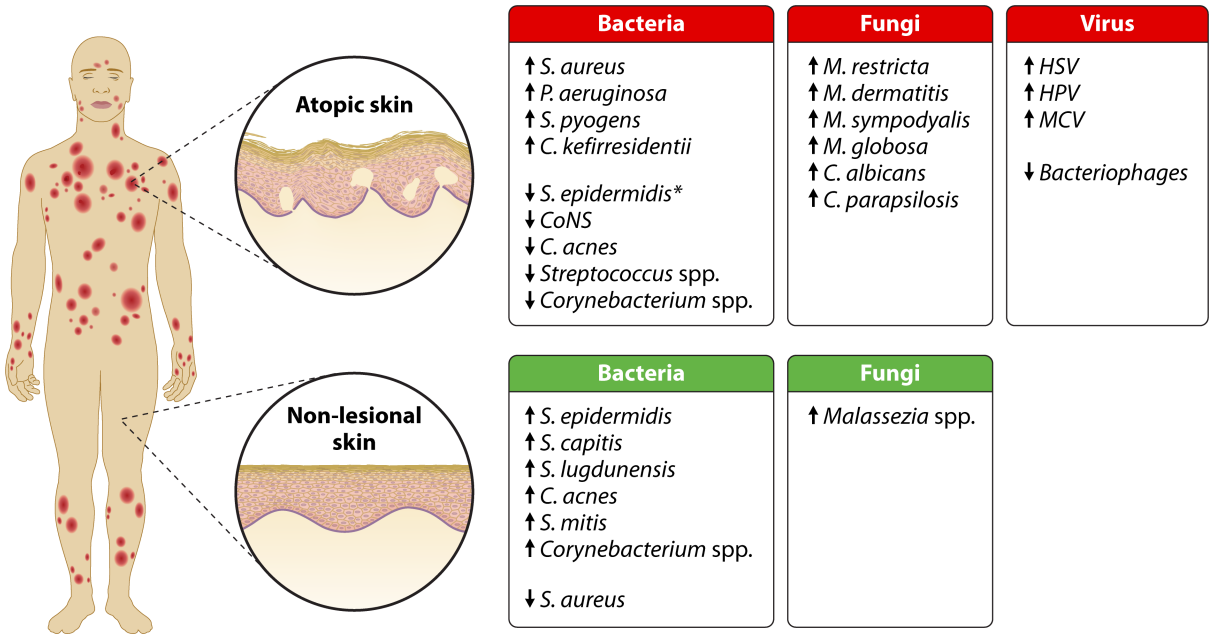

FIG 4 Skin dysbiotic pattern in atopic vs. non-lesional skin. Illustration of the microbial compositions of atopic and non-lesional skin. The upper panel represents the atopic skin microbiome, with the bacterial, fungal, and viral species overrepresented and downregulated (evidenced by arrows). The lower panel depicts non-lesional skin, displaying balanced microbial diversity with the microbial species represented (indicated by arrows). The figure was created with BioRender and revised by Patrick Lane (ScEYEnce Studios).

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Control of *Staphylococcus aureus* by CoNS

Staphylococcus epidermidis

The interplay between *S. epidermidis* and *S. aureus* is of increasing interest. Like other staphylococci, *S. epidermidis* uses the *agr* system for QS, which consists of four protein components (AgrA–D) and a signaling molecule known as the autoinducing peptide (AIP) (232). Otto and colleagues found that cross-inhibition exists between the QS pheromones of *S. aureus* and *S. epidermidis*. They studied several subgroups of *S. aureus*, each characterized by genetic variants of the *agr* QS system. It has been observed that almost all subgroups of *S. aureus* are sensitive to the pheromone of *S. epidermidis*, which means that it can inhibit the *agr* system of *S. aureus* (233).

The presence of both these species during AD flares opens a series of questions regarding their respective roles. On one hand, it can be suggested that the increased abundance of *S. epidermidis* in AD lesions may be an antagonistic or compensatory mechanism against *S. aureus* through AMP secretion (68). At the same time, other studies reported how *S. epidermidis* could increase *S. aureus* virulence, for instance through *S. epidermidis* peptidoglycan-linked mechanisms (234, 235).

Multi-staphylococcal biofilms are a common occurrence in infections and on AD lesions (112, 235). Their relationship remains unclear and multifaceted, probably in a strain-dependent way, as *S. epidermidis* can inhibit, potentiate, or simply coexist with *S. aureus* biofilm. When co-cultured *in vitro,* these bacteria, isolated from the same AD subjects, showed cooperative interactions (235). The possible synergy between these staphylococci could enhance the resistance against antimicrobial compounds, being responsible for the disease outcome and determining the response to treatment (68, 112, 235).

In the study by Williams and colleagues, it was confirmed that the self-inducing peptide of the *agr* type I system of *S. epidermidis* is active against *S. aureus* USA300 LAC *agr* type I and protects human keratinocytes, whereas the *agr* types II and III of *S. epidermidis* showed no activity. Analysis of clinical samples from subjects with AD highlighted the presence of these strains on human skin and suggested that the severity

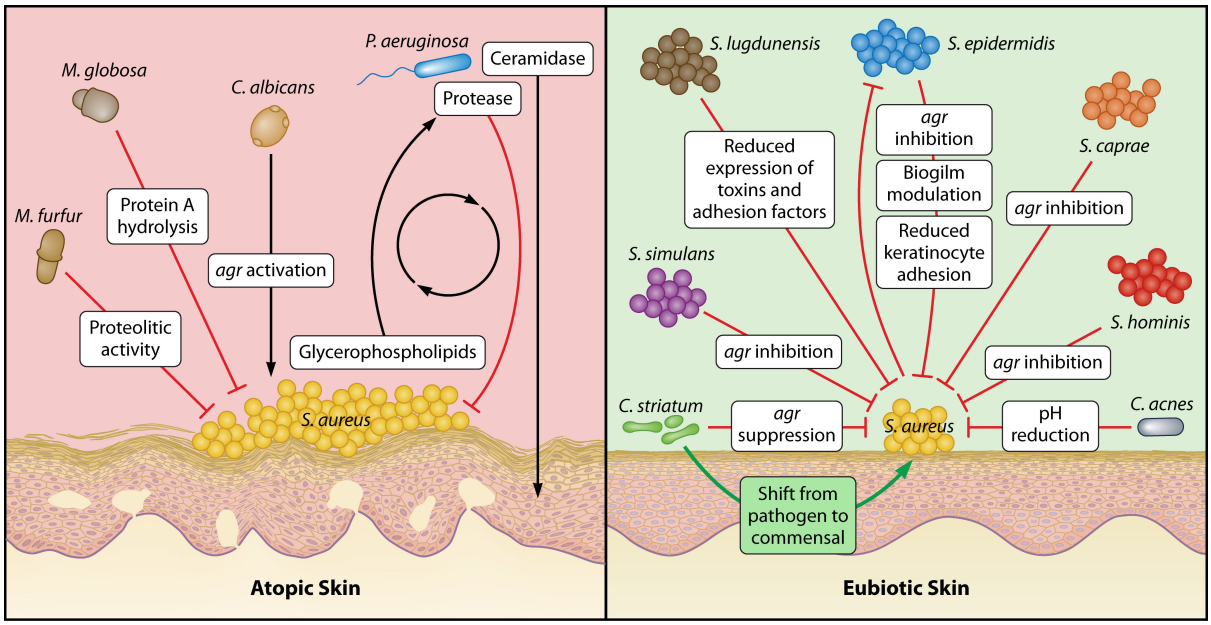

FIG 5 Microbial interactions in atopic vs. non-lesional skin. Comparison of microbial networks in atopic and non-lesional skin, illustrating key differences in interactions and community stability. The left panel displays the atopic skin microbiome, characterized by disrupted microbial networks with weaker connections and an overrepresentation of pro-inflammatory taxa. The right panel shows the non-lesional skin microbiome, featuring robust, balanced microbial interactions and a greater prevalence of commensal species. The figure was created with BioRender and revised by Patrick Lane (ScEYEnce Studios).

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of disease flare episodes is related to a decrease in the abundance of *S. epidermidis agr* type I compared with *S. aureus*. This imbalance would favor the expression of PSMα and the progression of the disease. This study demonstrates the benefits of restoring commensal strains of CoNS to prevent the activity of the *S. aureus agr* system on the affected skin (236).

In the study by Numata and colleagues, it emerged that *S. epidermidis* can inhibit the absorption of *S. aureus*, which aggravates inflammation in AD lesions, into keratinocyte cells. The presence of *S. epidermidis*, or its secretions, significantly reduces the absorption of *S. aureus*. This protective effect is linked to thermolabile substances secreted by *S. epidermidis* and suggests that this bacterium could have a role in preventing infections and maintaining the balance of the skin microbiome, with possible therapeutic applications for AD (237).

Iwase and colleagues discovered that a protease, called Esp, secreted by *S. epidermidis* strain JK16, can inhibit biofilm formation and nasal colonization by *S. aureus*. Esp not only prevents *S. aureus* biofilm formation but also destroys pre-existing biofilms. It also makes *S. aureus* more susceptible to one component of the immune system, the human beta-defensin 2 (hBD2), an antimicrobial peptide that is part of the innate immune system. Alone, beta-defensin 2 has low bactericidal activity against *S. aureus* in biofilms, but in combination with Esp, it becomes much more effective in destroying *S. aureus* cells. This bacterial interference mechanism represents a new way to inhibit *S. aureus* colonization (238).

The study by Nakatsuji and colleagues highlighted how *S. epidermidis* can play a protective role against *S. aureus* through the production of AMPs. In subjects with healthy skin, *S. epidermidis* releases AMPs that selectively kill *S. aureus*, preventing its growth and reducing its ability to colonize the skin. These AMPs not only show a powerful, specific antimicrobial action but also act in synergy with LL-37, an AMP produced by the human immune system, amplifying the effectiveness of the natural antimicrobial defense (239).

Staphylococcus hominis

As previously mentioned, *S. hominis* contributes to the natural defense against pathogens. In patients with AD, however, a significant reduction in AMPs-producing *S. hominis* strains is observed, which leads to greater vulnerability to colonization by *S. aureus*. Indeed, Altunbulakli and colleagues showed how *S. hominis* is more abundant in samples from healthy subjects and from non-lesional atopic areas, whereas lesional sites show a significant loss in this commensal (71), thus associating this microbial imbalance with AD symptom worsening. The study by Nakatsuji and colleagues identified *S. hominis* as a protective skin commensal, particularly regarding its ability to fight *S. aureus*. They found that *S. hominis* strain A9 produces AMPs (i.e., lantibiotics) capable of selectively inhibiting the growth of *S. aureus* without disturbing other components of the skin microbiota. The *S. hominis*-produced AMPs have proven to be particularly effective in limiting the ability of *S. aureus* to colonize and proliferate on the skin (239).

Staphylococcus caprae

S. caprae, a coagulase-negative bacterium of the skin flora, could play a protective role in inflammatory skin diseases, AD included, by interfering with *S. aureus*. Paharik and colleagues reported that a commercially available *S. caprae* (DSM 20608) produces PSMs capable of blocking the *S. aureus agr* QS system. This inhibition reduces the expression of toxins and adhesion factors, limiting the pathogen's ability to colonize and damage tissues (240). Moreover, in Altunbulakli and colleagues' work, it has been reported that *S. caprae* abundance in AD and healthy subjects follows a pattern like that of the previously described S. *hominis* (71).

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Staphylococcus simulans

Brown and colleagues highlighted how *Staphylococcus simulans*, another skin commensal, can modulate the virulence of *S. aureus* in the aggravation of skin pathologies such as AD. The researchers found that *S. simulans* produces peptides that inhibit the *S. aureus* QS system, particularly *agr*. By interfering with this mechanism, *S. simulans* reduces the production of α-toxin by *S. aureus*, and thus pathogen colonization and skin damage (241).

Staphylococcus lugdunensis

In the work of Zipperer and colleagues, it was demonstrated that *S. lugdunensis* produces an antibiotic peptide called lugdunin, which inhibits the growth of *S. aureus* and reduces its ability to colonize the skin. Lugdunin works by binding to the lipoteichoic acid (LTA) of *S. aureus*, interfering with the interaction between the pathogen and the host. Furthermore, lugdunin inhibits the production of toxins responsible for *S. aureus* virulence, such as α-toxin, which damages cell membranes and causes tissue destruction; leukocidin, which acts on white blood cells, compromising the immune response; and enterotoxins, which contribute to inflammatory responses and can worsen skin infections. Reducing these toxins prevents *S. aureus* from causing tissue damage and limits its ability to trigger infections (242).

Relationship between *S. aureus* and *P. aeruginosa*

As previously mentioned, evidence on *P. aeruginosa* involvement in AD is limited. Nonetheless, *P. aeruginosa* AN17, a ceramidase (CDase)-positive strain, was isolated from atopic skin (243, 244). What emerged is that the CDase does not hydrolyze skin ceramides in physiological conditions and in the absence of detergents. However, *S. aureus* could secrete some anionic glycerophospholipids, thus potentially stimulating CDase-mediated hydrolysis. In addition to this, several *P. aeruginosa* strains, AN17 included, secrete staphylolytic proteases that lyse *S. aureus* cells, thus leading to the release of their content in the surrounding environment and the ceramide hydrolysis in a vicious cycle of events (149, 244). Finally, *P. aeruginosa* CDase induces the release of pro-inflammatory mediators via the S1P pathway in a 3D keratinocyte model, thus suggesting how S1P could be involved in AD progression (149).

Relationship between *S. aureus* and *C. acnes*

Recent findings support the protective role of *C. acnes* against *S. aureus* in AD. *C. acnes* inhibits *S. aureus* through several mechanisms, like metabolite secretion and reduction of microenvironmental pH. When this commensal is less present in the host microflora, the inhibition of *S. aureus* is reduced, thus potentially leading to its overgrowth (245). Regarding AD, Jung and colleagues developed an *in vitro S. aureus*-infected skin organoid to mimic AD. Pre-treatment with *C. acnes* showed protective effects on the epidermal barrier of these infected models with an increase in epithelial filaggrin expression (246).

Relationship between *S. aureus* and *Corynebacterium* spp.

Corynebacterium spp. are known for counteracting *S. aureus*. For instance, *Corynebacterium pseudodiphtheriticum* secretes anti-microbial factors in the upper respiratory mucosae, whereas *Corynebacterium striatum* is a suppressor of staphylococcal *agr* system. They inhibit streptococcal invasion and virulence, especially in the nasal cavity, where they act as antagonists of *S. pneumoniae* (175). Focusing on *S. aureus*, an interesting result was reported by Ramsey and colleagues. Microbe-microbe interactions determine the behavior of specific microbial populations through several molecular mechanisms. The authors demonstrated how *in vitro* co-infection of *Corynebacterium striatum* and *S. aureus* can affect the latter's virulence, shifting S. *aureus* toward commensalism. Despite these data were obtained in a different disease model, namely

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diabetic foot infections (DFI), it could be worth investigating whether this phenomenon also occurs in AD (247).

Relationship between *S. aureus* and *Malassezia*

Some reports have highlighted the possible protective role of *Malassezia* in counteracting the *S. aureus* role in AD. More in detail, Li and colleagues showed that the *M. globosa* strain secreting Aspartyl Protease 1 (MgSAP1) was able to act toward *S. aureus* biofilm formation through the hydrolysis of bacterial-produced protein A, an important *S. aureus* virulence factor (248, 249). Subsequently, the same researchers studied the effect *in vitro* and in animal models of the homolog protein in *M. furfur* (MfSAP1), which was chosen due to its strict similarity with MgSAP1 and ease in genetic manipulation. First, they observed the effect of MfSAP1 in favoring skin colonization mediated by its proteolytic effect; second, its capability to promote cutaneous inflammation in the murine model with barrier-skin defect was clearly demonstrated (248, 249).

Relationship between *S. aureus* and *C. albicans*

Co-inoculation of *C. albicans* and *S. aureus* in mice causes 100% mortality, whereas inoculation of either organism alone is non-lethal. Todd and colleagues demonstrated that this was due to *C. albicans'* capability to increase the virulence of *S. aureus* by improving the *agr* QS system. Their co-culture elevates the levels of α-toxins produced by *S. aureus*, both *in vitro* and in mice. Although treatment with α-toxin-neutralizing antibodies partially reduces mortality, the purified toxin alone is not sufficient to cause lethality, suggesting that synergism requires live microorganisms and/or additional virulence factors (250).

Vila and colleagues report on the discovery of the effect of farnesol, a molecule secreted by *C. albicans*, on the behavior of *S. aureus* in a context of interspecific interactions. It has been observed that farnesol inhibits the production of STX through a competitive binding mechanism of farnesol to the CrtM enzyme, involved in the synthesis of STX. Furthermore, exposure to farnesol induces oxidative stress in *S. aureus*, activating a defense response based on thiol-based redox systems, regulated by global virulence factors. This activation makes *S. aureus* more resistant to oxidizing agents (e.g., hydrogen peroxide) and phagocytosis by immune cells (251).

FUTURE PERSPECTIVES

Current understanding of the microbial involvement in AD underscores the significant impact of skin dysbiosis on the disease onset and progression and highlights the importance of preserving or restoring its eubiosis. In future research and clinical practice, it will be crucial to explore and detail both topical and systemic therapeutic options that can target the complex interplay between the host immune system and the skin microbiota in AD, as preclinical studies suggest that microbiota-focused approaches may benefit AD patients (252, 253). Dupilumab is a notable example. Evidence suggests that it not only exhibits a favorable safety profile but also significantly reduces *S. aureus* colonization on both lesional and non-lesional skin while enhancing microbial diversity (252, 254). In contrast, data on the effect of JAK-STAT inhibitors on the host microbiota in AD are still scarce; hence, further investigations are required (255).

For systemic approaches, in addition to the existing previously mentioned immunomodulatory agents and biological therapies, there is growing interest in oral probiotic supplements formulated with beneficial strains—often from genera such as *Lactobacillus* and *Bifidobacterium*—that may help modulate immune responses and enhance the skin microbial diversity, via the gut-skin axis and immunological pathways (256–259).

On the topical side, beyond conventional corticosteroids and calcineurin inhibitors, new formulations containing prebiotics, probiotics, synbiotics, or postbiotics show promise in restoring a healthier microbial balance on the skin (252, 254, 255). Topical probiotics, such as formulations promoting ceramide production and reducing *S. aureus* burden, have also demonstrated efficacy (260). An innovative approach involves

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Roseomonas mucosa, a gram-negative skin commensal that has been tested as a potential candidate for in-human "topical microbiome transplantation," as described by Myles and colleagues, in AD patients. Three *R. mucosa* isolates from healthy donors were selected based on prior *in vitro* and *in vivo* animal screenings and applied topically to affected skin (clinical trial NCT03018275) (261). However, further assessments are required to fully understand the role of this skin commensal in AD. Indeed, different isolates (e.g., from healthy versus atopic donors) can differently impact the disease (253). Moreover, *R. mucosa* is recognized as an emerging opportunistic pathogen, with the host skin microbiota serving as its main reservoir, warranting caution and consideration (262).

Recent findings on the use of probiotics have shown considerable variability, depending also on the experimental protocols and on the patients enrolled in the different research studies. Moreover, safety concerns regarding live probiotic supplementation in specific populations (i.e., pregnant and/or breastfeeding mothers, newborns, and infants) should be considered (258). Prebiotics are another option, but they have not been extensively studied yet in relation to AD, and evidence is still scarce (263). Still, several dermo-cosmetic products are enriched with prebiotics (e.g., inulin, fructooligosaccharides, galactooligosaccharides) and/or postbiotics (such as bacterial lysates and fermented products), besides the usual emollients used to moisturize and restore the damaged skin barrier. Pre- and post-biotics exhibit many health-promoting properties that make them valuable ingredients in cosmetic formulations, as they have antioxidant and anti-inflammatory activity, helping the skin barrier protection, while supporting the resident microbiota (264, 265). Prebiotics can enhance the growth of both beneficial and, sometimes, pathogenic bacteria. As an example, inulin and fructooligosaccharides (FOS) are well recognized for promoting beneficial microbes, including Bifidobacteria and Lactobacilli (266, 267).

However, we must also consider that specific prebiotics could also support the proliferation and virulence of opportunistic or potentially pathogenic bacteria in particular conditions (268, 269); therefore, further investigations are required before absolutely claiming these properties (270, 271).

Synbiotics have also been used for either prevention or treatment of AD, for instance, in pediatric subjects. However, results remain inconsistent due to the variability in terms of treatment timing, duration, and administration route (272, 273).

Plant-derived products have been historically used to treat several inflammatory conditions like AD due to the bioactive compounds they contain. From a microbial perspective, these extracts can both inhibit pathogens and support the resident microbiota by fostering a bidirectional relationship with it (274, 275). Finally, having prebiotic activity, they can also be exploited to obtain high-value-added products with postbiotic potential (276).

Fecal matter transplantation (FMT) has emerged as a potential therapeutic approach to restore gut homeostasis in inflammatory disorders characterized by intestinal dysbiosis, including moderate-to-severe AD. Clinical trials have yielded promising results, demonstrating FMT as a safe and effective intervention for AD. However, further studies are required to confirm these findings and to better understand the underlying mechanisms (277, 278). In the paper by Aroniadis and Brandt, the risks associated with FMT are described. Despite the benefits, such as the treatment of *Clostridium difficile* infections, the main risks include the possible transmission of unknown pathogens, adverse reactions such as cramps and diarrhea, and the alteration of the balance of the intestinal microbiome, which can lead to dysbiosis. The authors also highlight the need for further long-term studies to monitor the effects of the treatment, especially in contexts other than *C. difficile* infections. In general, even with relatively low risks when treatment is performed correctly, it is essential to carefully monitor patients to promptly identify any complications and continuously improve donor selection protocols (279).

Finally, phage therapy has been introduced for AD as well. This targeted therapy utilizes bacteriophages to combat bacterial infections, particularly those caused by antibiotic-resistant bacteria, without significantly harming the commensal microbiota.

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This makes phages a promising alternative to antibiotics, especially in an era where antibiotic resistance is a global health threat. A crucial point of phage therapy is its ability to address biofilm-related infections, which are difficult to treat with traditional antibiotics. Furthermore, phages can also be employed against intracellular pathogens, thanks to engineering and delivery technologies to overcome cellular barriers (280). One promising area could be the use of phages to treat chronic skin infections, such as those caused by *S. aureus*, which are common in AD patients. Their use to reduce local bacterial load could improve disease management, limiting the use of antibiotics and slowing down the natural bacteria propension, nowadays out of control, to develop multidrug resistance (281–283).

CONCLUSIONS

The skin microbiota plays a pivotal role in the pathogenesis and progression of inflammatory skin disorders, notably AD. Although significant strides have been made in understanding the microbiome influence on skin health, the precise dynamics between its microbial components in AD are still not fully understood. The self-reinforcing cycle observed in dysbiotic and inflammatory conditions is a crucial aspect that warrants deeper investigation. In this intricate scenario, the question arises: is the microbiota a victim of the inflammatory environment, an executioner driving disease exacerbation, or does it embody both roles simultaneously? Evidence suggests that the skin microbiota in AD is both affected by and contributes to the disease process. Dysbiosis—characterized by a decrease in microbial diversity and by an overrepresentation of pathobionts like *S. aureus*—can compromise the skin barrier and modulate immune responses, thereby exacerbating inflammation. Conversely, the inflammatory milieu of AD can alter the skin microenvironment, making it more conducive to pathogenic colonization and further disrupting microbial balance.

Understanding the dynamic, bidirectional relationships between skin microorganisms, host immune response, and inflammatory status is essential to provide new insights into AD pathogenesis and possible therapeutic approaches.

Future research should focus on unraveling these complex interactions through integrative approaches that combine microbiology, immunology, and clinical science. Metagenomic and metabolomic analyses could provide deeper insights into microbial functions and host-microbe interactions. Additionally, longitudinal studies, observing microbiota changes during disease flares and remissions, could shed light on causative versus consequential relationships.

Such insights may pave the way for novel therapeutic strategies focusing on restoring skin microbiota eubiosis, strengthening the skin barrier, and modulating immune responses. Promising approaches include microbiota transplantation, targeted antimicrobial therapies, and the use of pre-, pro-, and post-biotics to disrupt the cycle of inflammation and dysbiosis in AD.

In conclusion, delving into the intricate interplay between the skin microbiota and the host in the context of AD holds promise for both a deeper understanding of the disease and the development of innovative, microbiota-centered interventions. Determining whether the microbiota acts as a victim, an executioner, or both is more than an academic pursuit; it represents a critical step toward more effective, personalized treatments for individuals with AD.

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AUTHOR AFFILIATIONS

[1]Laboratory of Applied Microbiology, Department of Health Sciences (DiSS), Center for Translational Research on Allergic and Autoimmune Diseases (CAAD), School of Medicine, Università del Piemonte Orientale, Novara, Italy
[2]Dermatology Unit, Department of Health Sciences (DiSS), School of Medicine, Università del Piemonte Orientale (UPO), Novara, Italy

AUTHOR ORCIDs

Chiara Maria Teresa Boggio http://orcid.org/0000-0003-4625-3858
Federica Veronese http://orcid.org/0000-0001-6438-5171
Marta Armari http://orcid.org/0009-0000-1243-1615
Elisa Zavattaro http://orcid.org/0000-0003-4537-3014
Elia Esposto http://orcid.org/0000-0001-6791-5932
Paola Savoia http://orcid.org/0000-0002-1636-8411
Barbara Azzimonti http://orcid.org/0000-0001-6364-6595

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AUTHOR BIOS

Chiara Maria Teresa Boggio is a biologist who graduated in 2019 in Biodiversity and biological evolution at the University of Milan. After obtaining the professional qualification to practice as a biologist, she worked for several years as a contract professor at the University of Eastern Piedmont (UPO), combining teaching and research (ORCID ID: 0000-0003-4625-3858). She is currently a research fellow (PRIN-PNRR 2022 P2022N2XWH project) in the applied Microbiology Laboratory of Prof. Dr. Barbara Azzimonti at UPO, where she studies the role of the skin microbiota, and particularly the impact of Staphylococcus aureus in atopic dermatitis. At the same time, she is expanding her skills through a I level Master's in "Clinical microbiology and Parasitology: diagnostic techniques and application", with the aim of deepening the dynamics between microorganisms and human health.

Federica Veronese is a permanent medical manager at AOU Maggiore della Carità Hospital, Novara, since 2018. She works in the Clinical Section of Dermatology headed by Professor Paola Savoia. She obtained her MD in 2007 at University of Eastern Piedmont and specialized in Dermatology and Venereology in 2016 at the University of Turin. Her main interests include the pathogenesis, diagnosis, and novel treatments of skin cancers and inflammatory skin diseases. Her research comprises 56 publications in peer-reviewed journals (H-index 10; ORCID ID: 0000-0001-6438-5171) and over 50 presentations at national and international conferences. Clinically, she focuses on non-melanoma skin cancers, particularly actinic keratosis in immunosuppressed patients and atopic dermatitis. She is sub-investigator in multiple clinical trials. She currently participates in PRIN-PNRR 2022 P2022N2XWH project.

Marta Armari is a Biotechnologist by training and is a PhD candidate (Food, Health, and Longevity Studies, XXXIX Cycle) at University of Eastern Piedmont (UPO), Italy. She graduated from the University of Milan with a BSc in Biotechnology and a MSc in Pharmaceutical Biotechnologies. During her internships, she focused on Plasmodium falciparum drug resistance and the effects of P. falciparum hemozoin of macrophage polarization and differentiation. As a PhD candidate, she is now part of the Applied Microbiology Laboratory under Prof. Dr. Barbara Azzimonti's supervision. Her research has shifted to human skin microbiota, skin pathogens, skin dysbiosis and related disorders. Specifically, she is focused on the employment of vegetal extracts and derived postbiotics toward methicillin-resistant Staphylococcus aureus. Additionally, she is studying the involvement of gut and skin microbiota in skin diseases, such as psoriasis and atopic dermatitis. ORCID ID: 0009-0000-1243-1615.

Elisa Zavattaro is Associate Professor of Dermatology at the University of Eastern Piedmont (UPO), Novara, Italy, providing her clinical practice at the Dermatology Unit in the Hospital AOU Maggiore della Carità, Novara. She obtained her MD in 2000 and specialized in Dermatology and Venereology in 2005 at UPO. Subsequently she attended a Master in Surgical Dermatology at the University of Siena and then obtained a PhD degree in Clinical and Experimental Medicine at UPO. Her main interests include the pathogenesis, diagnosis, and novel treatments of skin cancers, with a special focus on the management of skin cancer in immunosuppressed patients. Her research comprises 100 publications in peer-reviewed journals (H-index 19; ORCID ID: 0000-0003-4537-3014). She serves on the editorial boards of Frontiers in Medicine (Dermatology), Dermato, and Cancers. She has participated in many clinical trials as sub-investigator and she was responsible for the Unit 2 in the "Ricerca Sanitaria Finalizzata" RF-2011-02347709 project.

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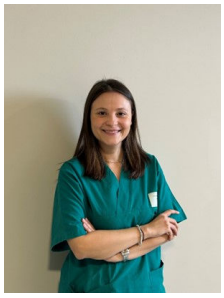

Elia Esposto is a medical manager at AOU Maggiore della Carità Hospital, Novara, since 2022. She works in the Clinical Section of Dermatology headed by Prof. Savoia. She obtained her MD in 2016 at University of Eastern Piedmont, specialized in Dermatology and Venereology in 2022 at the University of Turin and obtained master's degree in pediatric dermatology in 2024 at University of Bologna. Her main interests include the pathogenesis, diagnosis, and novel treatments of skin cancers and inflammatory skin diseases. Her research comprises 25 publications in peer-reviewed journals (ORCID ID: 0000-0001-6791-5932). Clinically, she focuses on melanoma, pediatric dermatology and atopic dermatitis. She is sub-investigator in multiple clinical trials.

Paola Savoia is full professor of Dermatology at the University of Eastern Piedmont, Novara, Italy, and has headed the Clinical Section of Dermatology at AOU Maggiore della Carità, Novara, since 2016. She obtained her MD in 1990 and specialized in Dermatology and Venereology in 1994 at the University of Turin. Her main interests include the pathogenesis, diagnosis, and novel treatments of skin cancers and inflammatory skin diseases. Her research comprises 225 publications in peer-reviewed journals (H-index 40; ORCID ID: 0000-0002-1636-8411) and over 250 presentations at national and international conferences. Clinically, she focuses on melanoma, non-melanoma skin cancers, and primary cutaneous lymphomas. She serves on the editorial boards of Frontiers in Medicine (Dermatology), Dermato, and Medicina (Dermatology). She is principal or sub-investigator in multiple clinical trials and sits on the AOU Maggiore della Carità Clinical Trial Centre Board. She coordinated the "Ricerca Sanitaria Finalizzata" RF-2011-02347709 project and currently coordinates the PRIN-PNRR 2022 P2022N2XWH project.

Barbara Azzimonti is an Assistant Professor of Microbiology and Clinical Microbiology and leads the Laboratory of Applied Microbiology at University of Eastern Piedmont (UPO), Italy. She earned her BS in 1996 and qualified as a Biologist in 1998 (University of Milan). Visiting scientist at DKFZ, Germany (2001-2002), she then specialized in Clinical Pathology (2003). She holds certifications from the Advanced Course in Food Science and Applied Nutrition (2018) and from the International School on Microbiota in Digestive Diseases (2024). Her research focuses on microbiota in skin and oropharyngeal diseases, 3D modelling, and antimicrobial resistance. With an H-index of 27 (ORCID 0000-0001-6364-6595), she has about 70 international publications. She co-leads the PRIN-PNRR 2022 project and collaborates with medical and biotech companies. Actively engaged in outreach, she received the Recti Eques Paladini Italiani della Salute Award (2021).

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