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Edslev, Sofie M.; Agner, Tove; Andersen, Paal S.

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REVIEW ARTICLE

Skin Microbiome in Atopic Dermatitis

Sofie M. EDSLEV[1], Tove AGNER[2] and Paal S. ANDERSEN[1,3]
[1]Department of Bacteria, Parasites, and Fungi, Statens Serum Institut, [2]Department of Dermatology, Bispebjerg University Hospital, Copenhagen, and [3]Department of Veterinary and Animal Sciences, University of Copenhagen, Frederiksberg, Denmark

Atopic dermatitis is a common inflammatory skin disease with a complex pathogenesis that includes imbalanced immune system signalling, impaired skin barrier and enhanced *Staphylococcus aureus* skin colonization. The skin bacterial communities are characterized by increasing abundance of *S. aureus*, leading to reduced diversity compared with the bacterial communities on healthy skin, and increasing disease severity. In contrast, fungal communities are richer and more diverse on the skin of patients with atopic dermatitis, although distribution of the most common species is similar in patients and controls. Filaggrin deficiency in atopic dermatitis skin might be related to the enhanced skin colonization by *S. aureus*. In addition, *S. aureus* expressing variant virulence factors have been shown to elicit atopic dermatitis-like phenotypes in mice, indicating that specific *S. aureus* strains can induce flare-ups. This review aims to provide an overview of the recent literature on the skin microbiome in atopic dermatitis.

Key words: atopic dermatitis; skin microbiome; *Staphylococcus aureus*; filaggrin.

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Corr: Paal S. Andersen, Department of Bacteria, Parasites, and Fungi, Statens Serum Institut, Artillerivej 5, DK-2300 Copenhagen S, Denmark. E-mail: psa@ssi.dk

SIGNIFICANCE

Atopic dermatitis is a common skin disease characterized by dry and itchy skin with eczema flares. The disease is associated with changes in the skin microbiota, which constitutes all microorganisms present on the skin surface. The greatest difference is due to increased abundance of *Staphylococcus aureus*, a bacterium that can cause skin infections and probably contributes to aggravation of the disease. This review aims to provide an overview of recently published literature regarding changes in the skin microflora in atopic dermatitis and its association with disease severity and exacerbation.

Atopic dermatitis (AD) is a common inflammatory skin disease that affects 10–20% of children and 2–10% of adults in developed countries (1, 2). The pathogenesis of the disease is complex and includes impaired skin barrier function and an imbalanced immune system with enhanced Th2, Th17, and Th22 signalling (3). Furthermore, patients with AD have an increased burden of *Staphylococcus aureus* skin colonization, which is associated with disease severity and exacerbation (4–8). Within recent years, where it has become possible to examine complete microbial communities using advanced DNA sequencing technologies, it is evident that cutaneous *S. aureus* is associated with decreased bacterial diversity on AD skin (8–13). The aim of this review is to provide an overview of the recent literature on the skin microbiome as well as microbe-host interactions in AD.

There is no single established accepted definition of the term "microbiome" in the scientific community. Often, this term is defined as the composition of all microbial genes in a community (14), but it has been argued that this definition rather describes the "metagenome" and that the word "microbiome" should be defined as all microorganisms in a habitat (the "microbiota"), their genomes, and the surrounding environmental conditions (15). In this review, the latter definition is used.

Skin microorganisms can be identified using culture-based assays, and complete microbial communities can be examined by DNA sequencing (**Box 1**) followed by diversity and taxonomy analysis (**Box 2**). Recently, Grogan et al. (16) have summarized the techniques used for studying the skin microbiome, and the methods are therefore not described in detail in this review.

HEALTHY SKIN MICROBIOME

The skin is an important first-line defence against pathogenic microbial invasion. Tight connections between corneocytes in the stratum corneum form a physical barrier, and antimicrobial peptides and lipids secreted from keratinocytes and glands provide a chemical barrier (17). In addition, commensal skin microorganisms can impede growth of pathogens, either directly by secreting antimicrobial molecules, or indirectly by occupying space and competing for nutritional resources (18, 19).

The skin microbiota consists of diverse organisms, including bacteria and fungi. In adults, the microbial community composition is rather stable over time, despite of the constant exposure to external microorganisms from other humans and the surrounding environment (20). However, the composition of the microbiota changes during puberty, with children having a more diverse microbiota compared with adults (21–23).

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Box 1. Assays for examination of microbial organisms and communities

- Culture assays: Plating and culturing of samples in order to detect and isolate specific viable microorganisms of interest. Advantages of this method are the possibility to use isolated strains for additional analysis, e.g. testing for antimicrobial resistance and examine the gene content using molecular methods. Also, it is known that the detected microbes are alive and viable. Disadvantages are that it is difficult to detect microorganisms that do not grow easily under standard laboratory conditions and that it is not possible to examine the microbial community as a whole.
- Whole genome sequencing: Sequencing genomes of specific microorganism of interest allows to examine the genetic content and thus properties of the single strain. This method is especially useful for comparing strains and their relatedness, e.g. to examine the similarity of strains isolated from distinct skin sites within individuals. A disadvantage of this method is that only selected strains are examined.
- Targeted amplicon sequencing: Sequencing of selected variable regions of the 16S rRNA gene can be used to identify most bacteria in a sample, making it possible to examine the composition of the bacterial community. The transcriptional spacer regions ITS1/2 and variable regions of the 18S rRNA gene can be used to study eukaryotic microbial communities, such as fungal communities. An advantage of targeted amplicon sequencing is thus the ability to examine whole microbial communities, though this method has its limitations as it often is impossible to differentiate between related species. Another disadvantage of this method is that all available target DNA is sequenced, including DNA from microbial contaminants and human skin cells, which especially constitutes a problem for low biomass samples, such as skin samples.
- Metagenomic shot-gun sequencing: Shot-gun sequencing is used to examine the complete genomes of the microbiota. This allows to detect all species constituting the microbiota at the strain level as well as examining specific properties of the community, e.g. metabolic pathway genes. A disadvantage of shot-gun sequencing is that deep-sequencing is required in order to obtain a high resolution making the method very expensive. As a consequence, most metagenomic studies are based on minor sample sets. Another disadvantage, which also applies to the amplicon DNA sequencing method, is the lack of discrimination between live and dead organisms.

Bacteria constitute the greatest proportion of the microbiota, representing more than 70% of species in most skin areas (24). 16S rRNA gene sequence analysis has shown that *Corynebacterium, Cutibacterium* (formerly *Propionibacterium* (25)), *Micrococcus, Staphylococcus, Streptococcus*, Betaproteobacteria, and Gammaproteobacteria are common skin-colonizing bacteria (9, 21, 23, 24, 26). Microbial richness and Shannon-diversity are influenced by the microenvironmental conditions on the skin, including pH, moisture, sebum content, and topography (24, 26, 27). Sebaceous skin sites (e.g. facial areas and the upper part of the chest and back) are dominated by *Cutibacterium acnes* and are less diverse and rich compared with moist skin (e.g. nares, axillary vault, antecubital fossa, and popliteal fossa) and dry skin (e.g. volar forearm) (24, 26). *C. acnes* is also the most abundant species in dry skin, whereas no single bacterial species is over-represented in moist skin, although *Corynebacterium* spp. and *Staphylococcus* spp. relative abundances are greatest (24). Fungi constitute 1–5% of the skin microbiota (24), with *Malassezia* being the most common and abundant habitant (27, 28).

Box 2. Diversity and taxonomy analysis

- Alpha-diversity: Diversity within samples.
  - Richness: the total number of species or unique sequences in a sample.
  - Shannon Index: a diversity measure that takes into account both species richness and evenness.
- Beta-diversity: Diversity between samples.
  - Pairwise comparison of community structures can be measured using distance-based methods, e.g.:
    - Weighted UniFrac: Dissimilarity measure based on species presence/absence data. Takes into account the phylogenetic relatedness of species.
    - Unweighted UniFrac: Dissimilarity measure based on the relative abundances of species. Takes into account the phylogenetic relatedness of species.
    - Jaccard: Dissimilarity measure based on species presence/absence data. Does not take into account the phylogenetic relatedness of species.
    - Bray-Curtis: Dissimilarity measure based on the relative abundances of species. Does not take into account the phylogenetic relatedness of species.
  - Ordination plots: Visualization of beta-diversity based on the pairwise distance measures. Samples with similar community structures are clustered together. The axes determine the degree of variance between samples.
  - Hierarchical clustering: Samples are clustered in a dendrogram based on the pairwise distance measures.
- Taxonomy analysis: Analysis of species distributions in a community/sample.

SKIN MICROBIOME IN ATOPIC DERMATITIS

AD is clinically characterized by red, dry, and itchy skin, with eczema flares and disease exacerbation. Interestingly, the clinical presentation of AD changes with age (29). Infants (< 1 year) are primarily affected by acute lesions of the cheeks, scalp, neck, trunk, and extensor parts of the extremities. Children (2–12 years of age) are mostly affected by eczema at the antecubital and popliteal fossa, and adolescents and adults by chronic lesions comprising the head, neck, hands, and flexural areas (and sometimes widespread disease). Consequently, published studies on the skin microbiome in AD have focussed on distinct skin areas depending on the age group investigated. A major genetic risk factor of AD in Asian and Caucasian populations is loss-of-function mutations in the *FLG* gene encoding the skin protein filaggrin (30). Filaggrin is essential for the alignment of keratin in the corneocytes, and filaggrin breakdown products act as natural moisturizing factors (NMFs) important for proper skin hydration. Thus, filaggrin is important for maintaining a functional skin-barrier. Th2 and Th22 cytokines can down-regulate *FLG* expression, and thus lead to filaggrin deficiency in AD independently of loss-of-function mutations in *FLG* (3). Filaggrin deficiency and reduced levels of NMFs and free fatty acids, followed by an increase in skin pH, lead to an altered skin ecology in AD (31–34). Also, microbial communities are altered on AD skin compared with normal healthy skin, as described below.

Bacterial community on atopic dermatitis skin during infancy

As in healthy control skin, the skin microbial composition in AD differs between age groups, with distinct bacteria being over-represented at different ages (10, 21). Two case-control studies have compared the bacterial community composition on skin from infants with and without AD (35, 36). Zheng et al. (35) examined the bacterial community composition in perioral skin in infants with clinical signs of AD at the sample site and in age-matched healthy controls. The microbial diversity was lower on AD skin compared with healthy control skin, with the largest difference observed between patients with severe AD and healthy controls. *Streptococcus* was the most common bacterial genus at the perioral skin, with mean relative abundances exceeding 40% in both healthy

control skin and lesional skin from patients with mild/moderate AD. However, in the severe AD patient group, relative abundances of *Streptococcus* spp. were significantly reduced and replaced with *Staphylococcus* spp, primarily *S. aureus*. In contrast, bacterial communities on skin from the cheeks, nose tip, antecubital fossa, and popliteal fossa were generally similar in infants with or without AD (36). Importantly, the AD group consisted of infants who not necessarily had developed AD or had active disease at the sampling time-points, which very well can influence the results. *S. aureus* was not identified in any of the skin samples (36), despite the fact that *S. aureus* is frequently detected on antecubital and popliteal fossa skin regions in older children and adults with AD (8, 10). Although this could indicate that *S. aureus* colonization at the antecubital and popliteal fossa is not an essential marker for AD during disease development in the first year of life, culture-based analysis has indicated the opposite (37). Thus, Meylan et al. (37) found that frequencies of *S. aureus* colonization at axillary and antecubital fossa skin were significantly higher at the time of diagnosis among infants and toddlers (0–2 years of age) developing AD compared with non-AD age-matched controls. However, frequencies of *S. aureus* colonization were less than 15% and thus remarkably lower compared with the prevalence in older children and adults with AD (6). In addition, *S. aureus* colonization of the anterior nares, which is a major habitat for *S. aureus* in both healthy and AD individuals (6, 38), was not considered to be a risk factor for AD development among infants with familial predisposition (39). Thus, a possible role of cutaneous *S. aureus* colonization during development of AD still needs further investigation.

Bacterial community on atopic dermatitis skin during childhood and adulthood

Several studies have shown that bacterial communities on skin of children and adults with established AD are less diverse, and are dominated by increased proportions of *S. aureus* compared with communities on healthy skin (8–13, 21, 35). Quantification of cutaneous *S. aureus* abundances has shown that the proportional increase of *S. aureus* is due to a significant greater absolute abundance of *S. aureus* on AD lesional and non-lesional skin compared with healthy control skin (40–42). No difference in absolute abundances of the 3 common skin bacteria *Corynebacterium*, *Cutibacterium*, and *Streptococcus* were observed between AD and healthy control skin in children (40). Thus, the increased relative abundance of *S. aureus* on AD skin is probably not due to decreased colonization with these bacteria, but mainly a result of an enhanced burden of *S. aureus* on the skin. This could also explain that the total bacterial load is significantly greater on AD skin compared with healthy control skin (**Fig. 1**) (40, 43).

Kong and colleagues (8) were the first to examine the temporal bacterial variation on antecubital and popliteal fossa skin in children during and after an AD flare episode (8, 12). Bacterial diversity was significantly reduced during flares at both skin sites, compared with baseline and post-flare samples. The decreased diversity during AD flares was associated with increased relative abundances of *S. aureus*, which exceeded 40% in many of the samples. The increase in relative abundances of *S. aureus* was accompanied by a decrease in the relative abundance of *Streptococcus salivarius* (8, 44), a commensal bacteria of the oral cavity, intestines and skin that has been shown to possess anti-inflammatory potentials *in vitro* (45). In addition, higher proportions of *S. salivarius* contributed to greater bacterial diversity on the skin of the cheek, volar- and dorsal forearm in healthy infants with a family history of atopic diseases and thus at higher risk of developing AD (44). The proportional abundances of *S. aureus* decreased significantly at the post-flare sample time-point, but were still slightly higher compared with *S. aureus* proportional abundances in the healthy control samples (8, 12). Yet, no significant difference in alpha-diversity was observed between baseline, post-flare, and healthy control skin, which could indicate that skin bacterial diversity is only reduced during flare-ups. Several studies have compared alpha-diversity on lesional and non-lesional AD skin, but with different conclusions. Three studies found that the bacterial diversity was lower on lesional skin compared with non-lesional skin (13, 21, 46), whereas 2 other studies found that the diversity was equally reduced on affected and un-affected AD skin compared with healthy control skin (9, 10). Neither age nor sampling sites can explain the

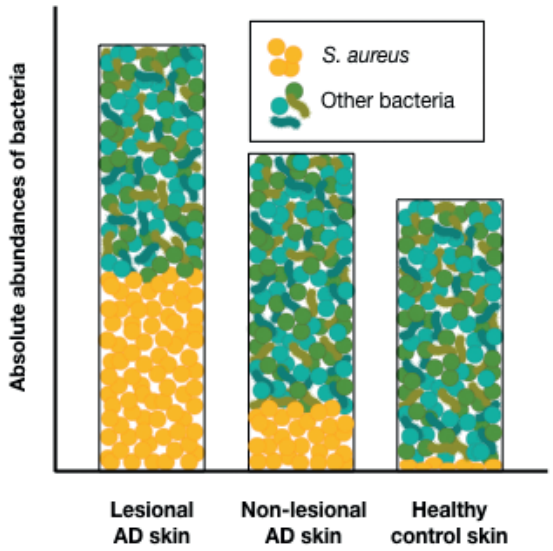

Fig. 1. Absolute abundances of bacteria in atopic dermatitis (AD) skin and healthy skin. Bacterial densities are significantly greater on AD lesional skin compared with healthy control skin, which mainly is due to significantly increased abundances of *S. aureus* in AD lesional skin. *S. aureus* absolute abundances are also increased in AD non-lesional skin, but not as much as in lesional skin.

conflicting results. These studies might indicate that it is not the eczema itself that drives the changes in diversity, but other AD-related factors in or on the skin that not only are associated with lesional skin areas (e.g. *S. aureus* colonization, lipid composition or pH).

Clausen et al. (9) discovered that the bacterial community composition (beta-diversity) varied significantly between lesional and non-lesional skin areas in adult AD patients, with the greatest variance being due to a different distribution of Staphylococcal species. One-third of the lesional skin samples were dominated by *S. aureus* (relative abundances greater than 50%), whereas only a few non-lesional skin samples were characterized by high proportions of *S. aureus*. Instead, coagulase-negative staphylococcal species (CoNS), such as *S. epidermidis* and *S. hominis*, dominated the bacterial community on non-lesional skin in a majority of patients. In accordance, Baurecht et al. have shown that relative abundances of CoNS are reduced and *S. aureus* abundances increased in acute and chronic lesional skin compared with non-lesional AD skin (46). Though the identified CoNS are common colonizers of moist skin, their abundances were lower on healthy control skin compared with non-lesional AD skin at the antecubital fossa (9, 46). It could thus be hypothesized that the skin ecology in AD supports enhanced staphylococcal growth on both lesional and non-lesional skin, and that changes in the distribution among the staphylococcal species towards greater abundances of *S. aureus* can contribute to the development of eczema locally on the skin. However, no changes in the proportion of either *S. epidermidis*, *S. hominis* or *S. capitis* at the antecubital- and popliteal fossa during or after a flare-up episode was identified among paediatric AD patients (12), suggesting that a potential role for the CoNS spp. in AD still needs to be clarified. Furthermore, species level analysis might not be sufficient, as distinct strains within a species can have distinct phenotypes. For example, Nakatsuji et al. have shown that CoNS strains isolated from the skin of healthy individuals more often are capable of killing *S. aureus* compared with CoNS strains isolated from AD skin (42). Also, colonization of specific subspecies of *S. aureus* seems to be favoured in AD, as *S. aureus* clonal complex 1 (CC1) strains are more often detected on skin and in nares from AD patients compared with healthy controls (47). The increased prevalence of CC1 *S. aureus* colonization might be due to intrinsic factors in AD, e.g. CC1 *S. aureus* colonization have been associated with carriage of loss-of-function mutations in *FLG* (7), or due to extrinsic factors, such as treatment practice leading to selection of antibiotic resistance (48, 49).

Eukaryotic microbial community on atopic dermatitis skin

Few studies have examined the eukaryotic microbial community on AD skin, and only in adults and Asian populations (50–52). Focus has been on fungal communities, which was found to be richer and more diverse on AD lesional skin compared with healthy control skin (50, 51). *Malassezia*, especially *M. globosa* and *M. restricta*, was the dominant fungus in both AD lesional skin and healthy control skin (50, 51). An increase in the proportional abundance of *M. dermatitis* and *M. sympodialis* was identified on the skin of individuals with a history of AD (no active disease) compared with individuals without AD (52). However, no differences in the proportions of these 2 species were found between lesional skin of AD patients with active disease and healthy control skin (51, 53). Another fungal species, *Candida albicans*, was found to be over-represented on AD lesional skin on the cheeks (presence in 100% of samples), compared with healthy control skin from the same area (presence in 10% of samples) (51). The literature regarding skin eukaryotic microbial communities in AD is limited, and thus, additional studies with more attendees are needed in order to validate the presented results.

Atopic dermatitis disease severity is associated with changes in skin microbial communities

Significant differences in alpha- and beta-diversity across AD severity scores have been identified in both lesional and non-lesional skin sites, with patients with more severe disease having the lowest bacterial diversity on the skin (9, 10, 13, 54). Brandwein et al. (10) found that the bacterial community composition in antecubital- and popliteal fossa in patients with mild/moderate AD was more similar to the community composition of healthy control skin than to skin areas in patients with severe AD, regardless of whether samples were collected from lesional or non-lesional skin. This finding supports the hypothesis that the AD phenotype, such as an overall impaired skin barrier and skin inflammation, has a widespread effect on the skin microbial community and not only on lesional skin areas.

S. aureus skin and nasal colonization is significantly more prevalent among patients with more severe disease (6, 7, 55, 56), and increased relative abundances of *S. aureus*, at least at the antecubital fossa, have been associated with increasing AD severity scores (10–13). However, conflicting results regarding total *S. aureus* densities on skin in relation to AD severity have been published. Thus, *S. aureus* absolute abundances have been associated with increasing severity scores among adult patients (13, 57), whereas no association was detected in a paediatric AD population (54).

Studies investigating eukaryotic microbial communities on AD skin are sparse, but one study implies that there is an association between AD severity scores and the fungal community on skin, as beta-diversity analysis showed distinct community compositions in samples from patients with severe AD compared with samples from those with mild/moderate AD (51).

MICROBE-HOST INTERACTIONS IN ATOPIC DERMATITIS

Microbiome studies have made it evident that microbial communities on AD skin differ from those of healthy skin, and that the greatest difference is due to an over-representation and greater abundance of *S. aureus* on AD skin. What are the mechanisms behind these differences? Functional analysis studies suggest that the AD phenotype, including impaired skin barrier function, increased pH, and skin inflammation, can promote changes in the skin microbial communities (43, 58, 59). Moreover, *S. aureus* can induce skin inflammation and aggravate AD (12, 60–62). Thus, a vicious circle might exist, with filaggrin deficiency in skin leading to enhanced colonization of *S. aureus*, which through the expression of virulence factors then can induce skin inflammation and contribute to further skin barrier impairment, and, in turn, can facilitate the maintenance of an imbalanced skin microbial community (**Fig. 2**). The mechanism behind these connections is elaborated below.

Atopic dermatitis pathogenesis facilitates changes in skin microbial communities

In AD, loss-of-function mutations in the *FLG* gene have been associated with changes in the overall bacterial community composition on non-lesional AD skin (9, 46), as well as with an increased risk of *S. aureus* colonization on lesional skin and in anterior nares (7). These studies indicate that filaggrin can influence bacterial growth and colonization on the skin. In accordance, presence of the filaggrin breakdown products urocanic acid (UCA) and pyrrolidone carboxylic acid (PCA), which contribute to skin acidification, have been shown to reduce *S. aureus* growth *in vitro* (58). More neutral pH, reflecting the skin pH in AD, has been associated with increased expression of *S. aureus* genes involved in colonization, including the gene encoding clumping factor B, which mediates adherence to keratinocytes (58, 59). Thus, increased *S. aureus* colonization among AD patients with *FLG* loss-of-function mutations (7) might be due to changes in skin pH caused by UCA and PCA deficiency. In addition to increased *S. aureus* adherence in epidermis, filaggrin deficiency is also associated with enhanced migration of *S. aureus* into the dermis skin layer. Nakatsuji et al. (43) showed that skin barrier impairment in mice, induced by genetic predisposition (*FLG* loss-of-function mutations) and physical skin disruptions (tape stripping), led to enhanced penetration of *S. aureus* into the dermis where it could activate the host immune system. In humans, the absolute abundance of *S. aureus* was significantly greater in dermis of AD lesional skin compared with healthy control skin, indicating that *S. aureus* can migrate more easily into the deeper skin layers of patients with AD with a disrupted skin barrier (43). Disrupted AD skin is also more permeable to allergens, which can trigger type I allergic responses in sensitized individuals. To corroborate this, patients with AD are also more often hypersensitive to a wide range of microbial allergens, including allergens from *S. aureus* and the skin colonizing fungal species *Malassezia furfur* and *Candida albicans*, compared with the general population (63–65).

AD skin might not only be more susceptible to *S. aureus* colonization, but also more vulnerable to *S. aureus* virulence. Alpha-haemolysin (also known as alpha-toxin), a virulence factor secreted by *S. aureus*, has thus been shown to adhere more easily to keratinocytes in AD skin compared with keratinocytes in healthy skin (66, 67). Alpha-haemolysin adheres to sphingomyelin lipids in the membranes of keratinocytes, leading to cell lysis and contribution to skin barrier disruptions (68). The density of sphingomyelin lipids, and thus the amount of free adherence sites for alpha-haemolysin, is regulated by the enzyme acid sphingomyelinase. Filaggrin deficiency as well as Th2 cytokines promote down-regulation of acid sphingomyelinase, thus enhancing alpha-haemolysin binding efficiency (66, 67). Thus, filaggrin deficiency in AD probably both favours *S. aureus* colonization and enhanced *S. aureus* mediated cytotoxicity and immune activation (**Table I**).

S. aureus *as an inducer of clinical atopic dermatitis*

Byrd et al. (12) have shown that *S. aureus* isolated from AD skin, but not *S. aureus* from normal healthy skin, was able to induce skin inflammation in wild-type mice with no genetic predisposition. Skin inflammation, assessed by epidermal thickening and cutaneous infiltration of immune cells, including Th2 and Th17 cells, was more pronounced in mice inoculated with *S. aureus* from patients with more severe AD. This study highly suggests

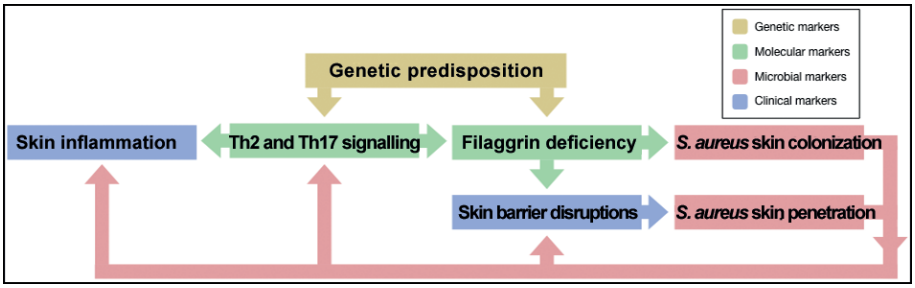

Fig. 2. Proposed connections between human factors involved in AD pathogenesis and *S. aureus* colonization and virulence.

Table I. The effect of filaggrin deficiency on *S. aureus* skin colonization and virulence

Effect of filaggrin deficiency		
Primary outcomes	Secondary outcomes	Refs
Increased skin pH	Enhanced *S. aureus* growth and colonization	(58, 59)
Impaired skin barrier	Enhanced *S. aureus* migration through the epidermal barrier and into dermis	(43)
Increased density of sphingomyelin lipids in keratinocyte membranes	Enhanced binding of alpha-haemolysin (cytotoxic *S. aureus* virulence factor)	(67)

that certain strains of *S. aureus* are able to elicit lesions similar to those observed in AD. The detected effect of *S. aureus* is probably mediated by the production of virulence factors, such as phenol-soluble modulins (PSM) and enterotoxins.

Several studies indicate that *S. aureus* induced skin inflammation and barrier disruption in mice are dependent on secretion of PSM-alpha, which promotes interleukin (IL)-17A mediated pro-inflammatory responses *in vitro* (human keratinocytes) and *in vivo* (mice) (60, 69, 70). Another PSM, known as delta-toxin, was also able to mediate *S. aureus* induced skin inflammation in mice, an effect that probably is mediated by delta-toxin induced mast cell degranulation, IgE production and enhanced IL-4 expression (62, 71). Interestingly, PSM-alpha transcripts are significantly more abundant in *S. aureus* isolated from AD skin compared with those from *S. aureus* isolated from healthy control skin (60), and delta-toxin production has been found to be considerably higher among *S. aureus* from lesional skin compared with non-lesional skin on patients with AD (62). These findings might explain why *S. aureus* strains isolated from AD lesional skin were better at eliciting skin inflammation compared with *S. aureus* from healthy skin (12).

S. aureus enterotoxins have also been proposed to be important mediators of *S. aureus* induced skin inflammation. Thus, topical application of staphylococcal enterotoxin B (SEB) to skin have been shown to cause erythema and epidermal thickening in both healthy volunteers and patients with AD (72), an effect which likely is mediated by enhanced T-cell signalling (72, 73). Studies indicates that *S. aureus* from AD skin more often carry genes encoding enterotoxins (*sea*, *seb*, *sec*, and *sed*) and more often produce these toxins compared with *S. aureus* isolated from non-AD individuals (73, 74). Furthermore, carriage of enterotoxin producing *S. aureus* has been associated with increased AD severity (assessed by SCORAD) (73, 75).

In one study, alpha-haemolysin was also found to be produced more frequently by AD *S. aureus* (91% of isolates) compared with production rates among *S. aureus* from healthy volunteers (33% of isolates) (61), which in combination with AD genetic predisposition for enhanced binding efficiency of the toxin (66, 67) could make alpha-haemolysin a potent inducer of skin barrier disruptions in AD (61). However, two other studies found lower proportions of *S. aureus* producing alpha-haemolysin on AD skin (30–63% of isolates) (76, 77) and a third study reported an alpha-haemolysin gene (*hla*) expression frequency of 59% among *S. aureus* nasal isolates from healthy carriers (78), highlighting that population-based differences and use of distinct assays can influence the results. Thus, future studies need to elucidate whether alpha-haemolysin, and other *S. aureus* toxins, is upregulated in *S. aureus* colonizing AD skin.

The above-mentioned studies support the hypothesis that *S. aureus* virulence is a major driver of AD disease exacerbation and might even be a direct cause of flare-ups. In order to cause disease, *S. aureus* must first colonize the skin. *S. aureus* isolated from AD skin has an enhanced binding activity of clumping factor B, leading to increased adhering to corneocytes, compared with *S. aureus* from healthy skin (79). In addition, CC1 *S. aureus*, which is a dominant clone in AD (7, 79, 80), had a slightly higher binding affinity compared with other *S. aureus* lineages (79). Thus, the increased prevalence of *S. aureus* skin colonization in AD might both be due to host factors and *S. aureus* factors (58, 59, 79). A summary of the described *S. aureus* virulence factors shown to be involved in AD is given in **Table II**.

EFFECT OF ATOPIC DERMATITIS TREATMENTS ON SKIN MICROBIAL COMMUNITIES

Topical application of corticosteroid (glucocorticoids) based creams is a common treatment of AD lesions. Prospective studies examining the effect of topical corticosteroid treatment on skin microbial communities in AD, have shown that 4–6 weeks of treatment led to significant increases in bacterial Shannon-diversity and richness (40, 81), whereas 7–10 days of treatment had no influence on alpha-diversity, though an clinical improvement was observed (35). Thus, a possible effect of topical corticosteroid on skin microbial communities is dependent of several weeks of continuous treatment. Comparative studies also imply that topical corticosteroid

Table II. Virulence factors upregulated in *S. aureus* isolated from atopic dermatitis skin compared with *S. aureus* from healthy control skin

Virulence factors	Clinical outcomes	Mediators	Refs
PSM-alpha	Skin inflammation Skin barrier disruptions	IL-17A signalling Protease activity	(60, 70)
Delta-toxin	Skin inflammation	IL-4 signalling Mast cell degranulation IgE release	(62, 71)
Alpha-haemolysin	Skin barrier disruptions	Keratinocyte lysis	(61)
Enterotoxin B	Skin inflammation	T-cell signalling	(72)
Clumping factor B	*S. aureus* colonization	Cell adherence	(79)

PSM: phenol-soluble modulin; IL: interleukin.

treatments have an effect on the skin microbial community, as AD patients undergoing topical corticosteroid treatments prior to sample collections often have a more diverse bacterial population with lower relative abundances of *S. aureus* compared with non-treated patients (8, 9, 81). This effect might be due to direct inhibition of *S. aureus* as well as to a general improvement on skin conditions due to the anti-inflammatory properties of corticosteroids (82).

A keystone treatment practice in AD is application of emollients and moisturizers, which restore skin barrier integrity and prevents flare-ups. Despite extensive use, little is known about what effect this treatment approach has on skin microbial communities, but one study indicates that emollient application leads to decreased proportions of *Staphylococcus* spp. on AD lesional skin (83). Although it indeed would be interesting to examine the long-term effect of emollient usage on the skin microbiome, it might be challenging and ethically unjustifiable to set up such study, as it would include an AD patient group that will be denied treatment with emollients and moisturizers for a longer period.

One study has examined the effect of dupilumab treatment, an anti-inflammatory systemic therapy offered to adults with severe and chronic AD, on the skin bacterial community (13). Sixteen weeks of treatment led to increased alpha-diversity and a decrease in relative and absolute *S. aureus* abundances on lesional as well as non-lesional AD skin. However, this effect was lost 18 weeks after treatment termination. Dupilumab inhibits IL-4/IL-13 signalling, and the study thus shows that reduction of Th2-mediated signalling may influence *S. aureus* skin colonization.

Another common treatment practice, at least in some countries, is topical application of fusidic acid, which is a narrow-spectrum antibiotic used against *S. aureus*. Unfortunately, bacterial growth of other common bacterial species on skin, including CoNS, are also inhibited by fusidic acid (84), and recent studies have shown a high prevalence of fusidic acid resistant *S. aureus* on AD skin and nares (48, 49), signifying that alternative treatment regimens are needed for the control of *S. aureus* colonization. Future treatment approaches could include *S. aureus* anti-virulence therapy (71) or application of commensal skin bacteria with anti-*S. aureus* properties (42). Oral administered antibiotics might also impact the cutaneous bacterial community composition and select for antibiotic resistance among skin bacteria (85–87).

CONCLUSION

Multiple studies have shown that increased abundance of *S. aureus* and loss of bacterial diversity on skin are associated with disease severity and flares in children and adults with AD. The enhanced burden of *S. aureus* skin colonization is probably facilitated by AD-related changes in the skin, including reduced levels of filaggrin and NMFs leading to increased skin pH and skin barrier impairment. In addition, deficiency of commensal bacterial strains with *S. aureus* inhibitory properties may contribute to the increased density of *S. aureus* on AD skin. Functional assays indicate that cutaneous *S. aureus* can exacerbate AD by expressing virulence factors that can induce skin inflammation and skin barrier disruption. Thus, changes in the composition of the skin bacterial community may be an important inducer of the clinical manifestations in AD patients with established disease. Whether bacterial community dysbiosis is also considered to be present prior to AD development is still unclear, and needs further investigation. Increasing knowledge regarding *S. aureus* as a potent promoter of AD exacerbation, has highlighted the skin microbial community as a potential target for future treatment strategies, and is a research field of great interest. Future studies are needed to explore the potentials, efficiency and safety of these novel anti-bacterial treatment approaches.

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