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Atopic dermatitis

Atopic dermatitis (AD) is one of the most common non-contagious inflammatory skin diseases and has a chronic recurrent course [1]. Patients suffer from extremely dry, very itchy, and inflamed skin and are highly susceptible to infection. Often, the quality of life is markedly reduced and the risk of developing additional diseases of the atopic spectrum or mental health sequelae is increased [2]. The clinical picture of AD is the result of the interplay of various factors, such as impairment of the epidermal barrier and immunological mechanisms, psychological factors, and dysbiosis of the cutaneous microbiome [3].

Structural changes of the epidermis cause a partial loss of the physical barrier function primarily mediated by the stratum corneum. While mutations or inadequate processing of the keratinocyte protein filagrin are particularly important, abnormal lipid metabolism and perturbed epidermal differentiation contribute also to the reduced barrier effect of the epidermis [4]. As a consequence, transepidermal water loss is increased in patients with AD, which in turn is accompanied by xeroderma and eventually by severe pruritus. At the same time, irritants and allergens can increasingly penetrate into the epidermis, thus triggering or exacerbating inflammation [4].

While inflammatory processes occur also in non-lesioned areas of the skin of AD patients (subclinical inflammation), they are aggravated in eczematous lesions during a relapse. Accordingly, increased infiltration of Th2 lymphocytes and their production of interleukins (ILs), predominantly IL-4, IL-5, IL-10, or IL-13, is observed during an acute phase. Dermal immune cells, such as Langerhans cells and dendritic cells, increasingly express high-affinity IgE receptors, while the production of antimicrobial peptides (AMPs) by keratinocytes is reduced [5, 6]. These processes promote the additional impairment of the structural barrier. Moreover, atopic skin diathesis seems to be a central intrinsic risk factor for the formation of allergic contact eczema [7].

Apart from the physical and immunological barrier, however, the protective function of the skin is also controlled by a microbiological component. In the following, the skin microbiome as an additional important part of AD pathogenesis will be considered in detail (Figure 1).
Skin microbiome and skin immune system – inextricably intertwined

Human skin is colonized by innumerable microorganisms that coexist in an intricately controlled habitat together with human epithelial cells. Microorganisms and host cells are engaged in a continuous exchange with each other to keep this system in balance. The skin has various mechanisms available to control its microbiome. Apart from the cells of the immune system, these include the pH of the skin, its water content, the epidermal lipid composition, and the expression of AMPs. Depending on localization, age, and individual circumstances, this results in different ecological niches that are occupied by microbes. The foundation for establishing the skin microbiome is already laid at birth, and depending on localization communities with different compositions are formed within a very short time.

The physiological environment of the skin seems to be the key determinant of the microbial composition. Depending on whether the examined skin area is rather dry, moist, or sebum-containing, communities with different diversity are found that are characterized by certain bacteria. A high sebum content, for example, accompanied by high abundance of propionibacteria, while dry regions are dominated by corynebacteria and staphylococci. In contrast, a higher moisture content allows for coexistence of significantly more different bacterial genera.

Knowledge about the formation of the immune system in early childhood, together with insights from animal experiments suggest that the interaction of immune cells with the resident skin flora is vitally important for the maturation of the dermal immune system. The development of a certain immunotolerance towards beneficial microbes is controlled by regulatory T cells. The interaction of microorganisms and various immune cell types ensures maintenance of immune homeostasis even at later times, meaning that conditions are created that leave resident microbes unaffected while the growth of pathogens is registered and inhibited. One example is the utilization of the commensal bacterium Staphylococcus (S.) epidermidis by dendritic cells to calibrate the immune system of the skin. S. epidermidis triggers specific T-cell reactions that differ markedly from the immune response towards pathogens, thus influencing immunomodulatory and barrier-stabilizing processes.

The skin microbiome is not only defined by the interaction of microorganisms and human cells: this complex habitat is also determined by the exchange of microbes among each other. By colonization of all available ecological niches, competing for the already scarce supply of nutrients, and through mechanisms of maintaining the barrier function, commensal members of the skin microbiome impart a so-called colonization resistance towards potentially pathogenic organisms. Perturbations of the balance within the dermal microbiome may compromise barrier function and are observed in various inflammatory skin diseases, such as acne and rosacea. Especially in the last decade, important insights have also been gained for AD with respect to the interrelation between dermal dysbiosis and disease course.

AD is characterized by dysbiosis of the skin microbiome

Two typical characteristics of the skin microbiome of AD patients can be identified: on the one hand, it has a reduced bacterial diversity, and on the other hand, it is often dominated by the bacterium S. aureus. Similar to clinical symptoms, these changes are not constant, but are subject to fluctuations depending on disease phase and treatment. In addition, however, fundamental problems with respect to the physical barrier function affect the dermal microbiome: it was demonstrated that both filaggrin deficiency and altered epidermal lipid composition are accompanied by shifts within the bacterial community.

Whether dermal dysbiosis is exclusively a consequence of AD manifestation or contributes already to its initiation has not been conclusively elucidated. In a study with 149 children whose microbiome was examined at various times within their first two years of life, colonization by S. aureus preceded the manifestation of clinical symptoms in those...
children who developed AD [28]. Although another study from the same year could not identify colonization by S. aureus before onset of clinical symptoms in a smaller patient group, it did find a reduced presence of commensal staphylococci [14]. Similar to healthy individuals, differences can be detected in the skin microbiome of pediatric or adult AD patients, but dysbiosis compared to age-matched control groups is always present irrespective of such changes [29]. Lesional skin differs even more from the control groups than non-lesional skin.

Due to the reduced expression of AMPs, such as LL-37 and beta-defensins, susceptibility to pathogens is generally increased in AD patients [6]. Production of these AMPs is inhibited by Th2 cytokines, such as IL-4 and IL-13 [30]. The human AMPs cooperate synergistically with the AMPs of commensals, such as S. epidermidis and S. hominis. It was, however, demonstrated that affected AD patients are colonized by other strains of these bacterial species than healthy controls. The AD-typical strains were characterized by reduced or completely absent ability to synthesize potent AMPs specifically directed against S. aureus by reduced or completely absent ability to synthesize potent AMPs specifically directed against S. aureus [31]. Therefore, the lack of both human and bacterial AMPs facilitates the uncontrolled spread of S. aureus. Furthermore, changes in the skin microbiome must occasionally be traced to the level of individual bacterial strains in order to draw a comprehensive picture of the interrelation between dysbiosis and AD pathomechanisms. The importance of the microbiome for AD diagnosis is reflected in the so-called microbial index of skin health (MiSH). It has been shown that this score can identify AD with approximately 85 % accuracy based on the analysis of 25 bacterial genera [32]. In addition, it can be used as a predictor for the risk status of the skin and the response to treatment in children [25].

### Table 1

Overview of changes in the bacterial microbiome in patients with atopic dermatitis [59–61].

| Bacterium                        | Regulation | Localization |
|----------------------------------|------------|--------------|
| Corynebacterium                  | ↓          | Skin         |
| Dermaoccus ssp.                  | ↓          | Skin         |
| Methylobacterium spp.            | ↓          | Skin         |
| Propionibacterium acnes          | ↓          | Skin         |
| Staphylococcus aureus            | ↑          | Skin         |
| Staphylococcus epidermidis       | ↑          | Skin         |
| Staphylococcus haemolyticus      | ↑          | Skin         |
| Staphylococcus hominis           | ↑          | Skin         |
| Streptococcus ssp.               | ↓          | Skin         |
| Ssp., species plurais            |            |              |

**S. aureus significantly influences the pathological process of AD**

Whereas detailed studies on the skin microbiome and its composition only became possible with the development of the corresponding methods, the prominent role of *S. aureus* in AD has been known for decades. Already in the 1970s, this gram-positive bacterium was identified as an important disease-related pathogen [33]. It is found much more often on the skin of AD patients than in healthy control groups. Given that colonization is particularly high in AD lesions, intraindividual variations are also observed, depending on whether lesional or non-lesional skin areas are observed. *S. aureus* utilizes the reduced expression of AMPs, the decreased presence of filaggrin filaments, the consequently structurally changed corneocytes, and an IL-4-induced, increased expression of fibronectin and fibrinogen for enhanced adhesion to corneocytes [34–37].

It has been shown on several occasions that the degree of *S. aureus* colonization correlates with disease severity [25, 38, 39]. The already weakened barrier function of the skin can be further compromised by *S. aureus*, given that the pathogen has proteases that further diminish the integrity of the barrier. The protease activity facilitates the penetration into the epidermis resulting in stimulation of Th2 cytokines, such as IL-4 and IL-13. Accordingly, *S. aureus* is found not only on the surface of the epidermis, but also within the dermis of AD lesions [40]. Furthermore, *S. aureus* is expressing its α-toxin, a pore-forming protein that damages the cell membrane of keratinocytes – and again the presence of Th2 cytokines will increase the susceptibility of keratinocytes to α-toxin-induced cell death [41]. Moreover, the biofilm production by *S. aureus* also correlates with the severity of AD and is strongly enhanced in severe types [42]. This promotes chronic colonization of the skin and will increase the disease severity even further. At the same time, the biofilm provides increased tolerance to antimicrobial substances [42].

The spread of *S. aureus* in an acute AD phase is thus ultimately promoted by a mechanistic vicious cycle, because not only do Th2-mediated changes in the skin enhance the adhesion, invasion, and cell-damaging effects of *S. aureus*, but the bacterium itself is also a potent trigger of proinflammatory processes. The expression of a large number of additional molecules, such as bacterial (lipo-)proteins and superantigens, fuel the inflammatory process in the skin [43–46].

**The epidermal microbiome as an approach in AD therapy**

Currently, research is conducted on many different approaches for the treatment of AD [44]. In general, therapy of AD
is individually tailored to each patient and follows a graded approach according to the severity of the disease [45]. The mainstay of each therapeutic approach is the basic therapy; this includes comprehensive information and training of the patient and their relatives, respectively, consistent avoidance of identified provocation factors, and continuous skin care to improve its barrier function. Regular supply of the skin with moisture and lipids and thorough cleansing, which is nevertheless as gentle as possible, are central components of the basic therapy. In addition, anti-inflammatory measures are taken that need to be adapted to the patient's skin condition, age, and the localization of the lesions. First-line medicines are topical glucocorticoids that can be varied based on their potency; furthermore, topical calcineurin inhibitors and, for severe types, systemic immunomodulators are used. Antiseptic interventions are considered in case of superinfections. The use of disinfecting bath additives containing sodium hypochlorite may contribute to a reduction in the use of topical corticosteroids and antibiotics; baths with 0.005 % bleach may improve AD [45].

Targeted support of the skin microbiome as initial treatment approach does not represent any of the mentioned options. Nevertheless, it has already been demonstrated that anti-inflammatory therapy by inhibition of IL-4 receptor-α with the human monoclonal antibody dupilumab is also accompanied by an increase of bacterial diversity and reduced abundance of *S. aureus* [46]. This was attributed to the reduced Th2 immune response, given that the decrease of corresponding biomarkers, the improvement of clinical symptoms (EASI and SCORAD), and the microbial parameters correlated directly with each other. Consistent basic care with emollients will also affect the skin microbiome [47]. Given that impaired barrier function, inflammation, and dermal microbiome are inextricably linked, such findings are not surprising [43, 44, 46].

Some basic therapeutics contain prebiotic or microbiotic ingredients, that is, bacterial sources of nutrients or substances derived from bacteria that are supposed to have a positive effect on the cutaneous microbiome. A more immediate impact might, however, be achieved with living bacteria. While the use of orally administered probiotics for prevention and treatment of AD has been studied and often controversially discussed for quite some time [48–50], only a small number of studies has addressed the topical application of probiotics. This may also be due to the non-trivial question of how to deliver viable bacteria to the skin, given that creams and lotions typically have to be preserved. While older studies address the utilization of bacterial lysates or heat-inactivated bacteria, more recent studies turn to the use of living bacteria. Another potential therapeutic approach for AD caused by pathogenic *S. aureus* is the topical use of certain strains of bacteriophages. Study results show that some phages infect a wide spectrum of pathogenic *S. aureus* strains, but do not attack *S. epidermidis* existing in symbiosis on the human skin [51]. In addition, the treatment with bacteriophage lysis or the combination of phages and surfactants are also being studied as therapeutic approaches [43, 52]. An overview of microbiome-affecting therapeutic approaches is presented in Table 2.

Nakatsuji et al. demonstrated that application of selected coagulase-negative staphylococci (CoNS, *S. epidermidis* and *S. hominis*) could markedly reduce the colonization of AD lesions by *S. aureus* [31]. This effect was based on the AMPs expressed by CoNS and was not achieved with killed bacteria. Autologous transplantation of the patient’s own bacterial strains corresponds to a highly personalized approach. In another study, *Roseomonas mucosa* in sucrose was applied to AD patients in form of microbiome transplantation over a period of six (adults) and 16 weeks (children), respectively [53]. Prior to transplantation, the used *Roseomonas mucosa* strains had been isolated from healthy volunteers. After treatment, antecubital SCORAD, pruritus, and steroid use were reduced, and *S. aureus* colonization was decreased in both age groups. In a follow-up study with children between three and seven years of age, these improvements of clinical symptoms were demonstrated again by means of reduction of SCORAD and EASI, irrespective of the presence of mild or moderate eczema at the time of enrollment [54]. The effects achieved after four months persisted for up to eight additional months, and with exception of one case of self-limited pruritus no adverse effects were observed.

In addition to the idea of isolating commensal bacteria from patients or individuals with healthy skin and transferring them (back), other approaches have examined established bacterial strains from the field of nutritional supplements for topical application, as well. In a recent study, for instance, *Lactobacillus reuteri* was processed in a cream that resulted in reduction of SCORAD and local SCORAD after application for eight weeks, although the effect was not significantly different from the cream without bacteria [55]. Other studies examined the use of combinations of probiotic bacteria in the form of partial baths. Compared to placebo, the examination of a mixture of six different lactobacilli and bifidobacteria demonstrated a significant reduction of various clinical parameters after daily use over a period of two weeks [56]. Moreover, it was shown with a similar study design that probiotic partial baths can significantly reduce colonization by *S. aureus* [57]. Another study monitored clinical symptoms and changes of the microbiome after partial baths with nine different bacterial species (lactobacilli, bifidobacteria, *Streptococcus thermophilus*) [58]. After 14 days, marked reductions of SCORAD and local SCORAD, as well as patient-assessed symptoms were observed. In addition, the daily partial bath reduced *S. aureus* colonization dramatically and resulted in an increase of bacterial diversity...
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Table 2 Overview of possible therapeutic approaches to normalize the microbiome [64, 65].

| Therapeutic approach                                      | Agent                                                                 | Effect                                                                 |
|----------------------------------------------------------|----------------------------------------------------------------------|-----------------------------------------------------------------------|
| Allogenic microbiome transplantation from individuals   | *Roseomonas mucosa* [53, 54]                                         | Reduction of *S. aureus* colonization                                   |
| with healthy skin [54]                                   |                                                                      |                                                                       |
| Autologous microbiome transplantation                    | Competitive coagulase-negative staphylococci (CoNS) [31]             | Reduction of *S. aureus* load in lesions                                |
| Cosmetic bacteria-containing lotion                      | *Lactobacillus johnsonii* NCC533 [62], *Aquaphilus dolomiae* [63],  | Reduction of *S. aureus* colonization                                   |
|                                                          | *Vitreoscilla filiformis* [63]                                        |                                                                       |
| Creams containing bacterial strains from the area        | *Lactobacillus reuteri* [55]                                         | No significant effects detected yet                                    |
| of nutritional supplements                               |                                                                      |                                                                       |
| Partial baths with various bacterial species             | Among others, lactobacilli, bifidobacteria, *Streptococcus thermophilus* [56–58] | Increase of bacterial diversity, decolonization of *S. aureus*         |
| Phages                                                   | Phage SaGU1 [51, 64]                                                 | Specific infection and elimination of *S. aureus*                      |
| Combination of phages and surfactants                    | *Staphylococcus* bacteriophage pSa-3 and Tween 20 [52]              | Dissociation of *S. aureus* aggregates and decolonization             |
| Bacteriophage lysin                                      | Staphefekt [43, 65]                                                 | Decrease of inflammatory symptoms                                      |
| pH shift to a range unfavorable for *S. aureus*          | Acidic or buffered preparations [66]                                | Reduction of *S. aureus* colonization                                   |
| Irradiation                                             | UVB [66]                                                            | Reduction of *S. aureus* colonization                                   |
| Vaccination against *S. aureus*                        | Anti-*S. aureus* antigen [63, 66]                                   | No data available yet                                                  |
| Synthetic antibiotics                                    | ATx201 [44, 67]                                                    | No data available yet                                                  |
| Synthetic antimicrobial oligopeptides                    | Omiganan pentachloride [44, 67]                                      | No data available yet                                                  |

on the skin of study participants. It was assumed that the displacement of *S. aureus* is crucial for this effect [58].

Overall, the use of topical probiotics is, therefore, an intriguing option for the treatment of AD that should be pursued in larger randomized and controlled studies. In this context, the effects achieved with different bacterial strains seem to be by no means mechanistically redundant. The fact that direct manipulation of the skin microbiome is immediately associated with clinical improvement of AD symptoms underscores again the relevance of the dermal microbiome for the disease course of AD and the need for its consideration in the development of novel therapeutic approaches.

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Conflict of interest

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