

Atopic eczema: role of microorganisms on the skin surface

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The pathophysiology of atopic eczema (AE) is still poorly understood. One possible concept favors IgE-mediated reactivity towards allergens that enter the skin from the outside or through the blood. Microorganisms of the cutaneous flora also might represent a stimulus for allergic skin reactions. Abnormal bacterial skin colonization is a characteristic feature of AE. *Staphylococcus aureus* (*S. aureus*) is the most common pathogen. Binding to host cells involves special receptors, such as fibronectin or laminin. Specific IgE antibodies to *S. aureus* can be detected in the blood. Whereas the clinical relevance of anti-staphylococcal antibodies is still controversial, specific IgE antibodies to *Pityrosporum* species as well as positive type I prick test reactions to these yeasts seem to correlate with the intensity of eczematous lesions in the head and neck regions of patients with AE. Both antimicrobial and antifungal treatment has been shown helpful in some cases of AE.

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Atopic eczema (AE) is a common skin disease with an increasing prevalence during recent decades that both for those affected and those who care for them demands great efforts (38). Apart from basic skin care and antiinflammatory therapy the identification of eliciting factors, such as aeroallergens, microbial allergens, food and food additives or psychosomatic interactions, is essential (36). The general role of allergy in the pathophysiology of AE is still a subject of controversy. However, the etiological role of allergic reactions in the pathophysiology of AE has been demonstrated by the induction of inflammatory eczematous reactions after epicutaneous application of mite or pollen allergens on the apparently non-involved skin of AE patients (3, 35, 37). An important role in this reaction pattern is played by Langerhans cells (LC) on which IgE receptors have been detected (5, 7). IgE-bearing LC have not been found among patients with respiratory atopy, even in those with a high IgE level (7). In this context we discuss the possible role of hypersensitivity reactions against parts of the cutaneous microflora acting as permanent stimuli for allergic skin reactions via an IgE-mediated mechanism.

Normal skin flora

Microbial inhabitants of the skin surface represent a very inhomogeneous group, consisting of the mite *Demodex folliculorum*, the lipophilic yeasts *Pityrosporum ovale* (*P. ovale*) and *Pityrosporum orbiculare* (*P. orbiculare*), viruses like *Herpesvirus homines*, the cause of "cold sores", and a wide range of different anaerobic and aerobic bacteria that have always attracted much attention in research. This especially applies to the aerobes even though they are outnumbered by the anaerobes by a ratio of more than 10 to 1 (33).

Natural bacterial resistance of the skin

The normal skin is resistant to colonization and invasion by most bacteria except resident flora. Defense mechanisms include an intact epidermis, since most of the bacteria (and fungi as well) are not able to penetrate the overlapping cells which are joined by desmosomes, and the relative dryness of an intact *stratum corneum* that limits bacterial growth. However, some organisms, e.g. *Staphylococcus aureus* (*S. aureus*) are able to penetrate the skin via the intercellular space between corneocytes. A further

host defense mechanism is provided by the lipid layer of the skin, which is composed of sebum and epidermal lipids, whereby the resident microflora play a role; the lipid layer consists of oleic, stearic or palmitic acids that exhibit potent antimicrobial effects. In addition, the skin has components both of the humoral, e.g. secretion of IgA and IgG antibodies, and the cellular immune system with protective effects against the invasion of microorganisms (10, 40).

Aerobic bacterial skin flora of patients with AE

Profound changes in cutaneous flora occur in patients with AE (1) (Table 1). The number of colony-forming units (CFU) in patients with AE is significantly increased, as compared with healthy controls (16). In addition, striking qualitative differences appear in the skin of patients with AE: both eczematous and clinically normal skin is colonized by *S. aureus*. A significantly higher colonization of *S. aureus* (14) correlates with a significantly elevated number of organisms in eczematous lesions, ranging from 14×10^6 organisms/cm² in exudative lesions, 5×10^6 in chronic lichenified plaques, and 1.3×10^3 in normal skin (23).

Specific interactions of S. aureus with atopic skin

The increased colonization by *S. aureus* in patients with AE may be caused by enhanced adherence of *S. aureus* to skin, as this bacteria exhibited a statistically much greater degree of adherence to corneocytes of patients with AE, as compared with corneocytes collected from normal controls or those with psoriatic lesions or other skin diseases, a phenomenon that was unique to *S. aureus* isolates (9). Cell surface components of *S. aureus* are shown in Fig. 1.

Fibronectin was characterized as one of the receptors involved in adhesion of *S. aureus* to host cells (4). Fibronectin binds to teichoic acid, an adhesin which is a cell wall component of staphylo-

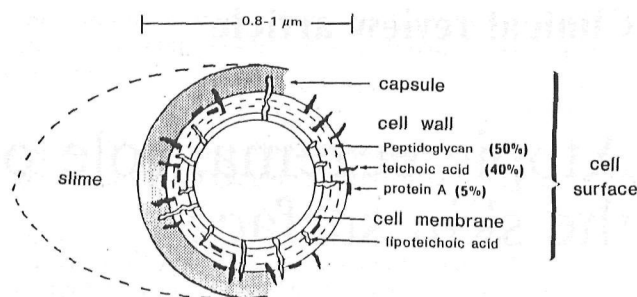


Fig. 1. Cell surface components of *Staphylococcus aureus*

cocci and streptococci (22, 43). The binding of *S. aureus* to fibronectin is time-dependent and irreversible, and it occurs both on live and heat-killed cells (28). Additional adhesins, such as protein A as well as other receptors like laminin, could be involved in these processes (24, 40).

Effect of antimicrobial treatment on AE

The efficacy of antibacterial treatment protocols gives further evidence that bacterial antigens are etiologically involved in the pathophysiology of eczematous lesions which further damage atopic skin. Several studies clearly showed that antibacterial treatment, applied systemically or locally, in combination with steroids is superior to steroids alone (22, 23).

Interaction of S. aureus with the immune system in AE

The colonization both of unaffected as well as eczematous skin in patients with AE has been explained by defective host-defense mechanisms involved in the control of bacterial infections (17). A selective hyporesponsiveness to purified *S. aureus* or cell wall components in T cell-mediated delayed type reactivity in patients with AE was stated to be responsible for the bacterial colonization (18). Recently, it has been shown that T cells from patients with AE respond with a reduced proliferation when they are stimulated with enterotoxin B, as compared with T lymphocytes from normal donors. They also express a different pattern of cytokines. In contrast to T cells from healthy donors, which express predominantly mRNA for IL-2 and IFN γ , the T lymphocytes from patients with AE express mRNA for the cytokines IL-3, IL-4, IL-5 and GM-CSF (Neuber et al., unpublished data). These cytokines then may be involved in the allergic inflammation by a variety of mechanisms, e.g. enhanced release of leukotrienes (30) and other inflammatory mediators, increased IgE synthesis, and eosinophil attraction and activation (21).

Table 1. Resident flora of normal and atopic skin

Resident skin flora	Normal	AE
Micrococaceae		
Coagulase-negative staphylococci	+	++
<i>Staphylococcus aureus</i>	-	++
Peptococcus	+	+
Coryneform organisms		
Corynebacteria	+	+
Brevibacterium	+	+
Propionibacterium	+	+
Acinetobacter	+	+
Pityrosporum	+	++

Disorders in the functional activities of granulocytes and monocytes are not likely to be responsible for the chronic bacterial colonization in AE since they are within the normal range (27).

An inadequate response of the humoral immune response to *S. aureus* or cell wall components by suppressing the synthesis of IgA and IgG antibodies by lymphocytes from patients with AE, as shown *in vitro*, might also be of importance in the colonization of atopic skin with *S. aureus* (29, 31).

The results presented suggest that manifold immunological changes in patients with AE may be the reason for chronic bacterial skin colonization.

S. aureus as an allergen carrier

The presence of specific IgE antibodies against *S. aureus* whole cells or cell wall components gives evidence that *S. aureus* carries allergens that might maintain skin inflammation in AE (2, 26). The clinical relevance of specific *S. aureus* IgE antibodies is controversial. Kapp & Schöpf (20) as well as Friedman et al. (14) conclude that the presence of *S. aureus* is not correlated with disease activity, and do not believe that specific anti-staphylococcal IgE represents an important diagnostic feature in AE. On the other hand, Motala et al. (26) discuss the possibility that anti-*S. aureus* IgE antibodies predict a more chronic and less favorable course of AE. Additionally, patients with AE show both an increased type I (10) and immediate-type (6) response against *S. aureus* extracts in skin tests.

Furthermore, *S. aureus*, teichoic acid, peptidoglycan, and protein A as well as some other bacterial toxins (e.g. α -toxin) induce the release of histamine from mast cells and basophils (15). Not only are Fc ϵ RII (high affinity receptor for IgE) mediated reactions induced by bacteria, but also the expression of the low affinity receptor for IgE (CD23, Fc ϵ RII) is increased when lymphocytes from patients with AE are stimulated with *S. aureus*, as has been shown recently (29). Especially the cell wall product peptidoglycan enhances the expression of CD23 (31).

This component of the cell wall activates also the alternative pathway of complement by promoting the formation of the alternative pathway C3 convertase.

Additionally, platelets from patients with AE generate significantly higher amounts of 12-HETE and express increased numbers of receptors (CD29/CD49f) to extracellular matrix proteins (e.g. fibronectin) when they are stimulated with *S. aureus* (32). These results support the assumption that *S. aureus* antigens and specific allergic type I-reactions are involved in the maintenance of the chronic skin inflammation of AE.

The genus *Pityrosporum*

In addition to bacteria, the normal human skin is colonized by yeasts; among these the genus *Pityrosporum* has received most attention in studies dealing with AE.

This genus includes *Pityrosporum orbiculare*, *P. ovale*, and *P. pachydermatitis*. *P. orbiculare* was the name for the spherical lipophilic yeast that was cultured from the lesions of pityriasis versicolor and that showed no tendency to develop filaments as the characteristic sign of *Malassezia furfur* when studied by direct examination. Therefore *P. orbiculare* and *M. furfur* were thought to represent different phases of the same organism but were clearly differentiated from *P. ovale* (37). Recent investigations, however, have demonstrated a close antigenic relationship between the two species, and today *P. orbiculare* and *P. ovale* are understood to be mere representatives of different stages in a cell cycle of the same species (11). Molecular approaches like DNA contents and DNA fragment analysis should give sufficient information on the exact taxonomy within the genus *Pityrosporum* in the near future.

Distribution of *Pityrosporum* species in human skin

Although human skin is colonized by *Pityrosporum* very early, as shown in a recent study in which the yeast was isolated from infants 1 to 24 months of age (42), the total incidence is much lower in children than in adults (13). The yeasts require addition of lipids when culture is performed. An insufficient lipid supply due to lower sebum production in children than in adults (41) could be the reason for the observed lower incidence. Besides temporary differences there are regional variations in the growth of *P. orbiculare*. In healthy adults the highest numbers were found on the mid-sternum area of the chest and interscapular area of the back (about $3 \times 10^2/\text{cm}^2$ each), reflecting the distribution of pityriasis versicolor regions (12). These numbers were significantly higher than counts resulting from the upper (including back of the hand) and lower extremities (12). Under occlusion the number of counts increased to $2.3 \times 10^3/\text{cm}^2$ (12).

Pityrosporum species and AE

Indications for a possible etiological role of *Pityrosporum* species in the cause of AE derive from clinical and therapeutic experience. Although morphology and distribution of skin lesions in AE change with age, seborrheic areas that are characterized by spacious growth of *Pityrosporum* species are involved in most patients. In a placebo-controlled study patients showing head and neck involvement

also showed a statistically significant improvement of skin lesions when ketoconazole (200 mg) was given daily over a period of 4 weeks (8). In the following years the potency of *Pityrosporum* species as an IgE-binding allergen that is able to initiate inflammatory changes by percutaneous resorption with resulting cell-mediated immunity was impressively demonstrated.

Type I sensitivity to Pityrosporum species

In a large retrospective study of 741 patients prick-tested with an aqueous extract of *P. orbiculare*, a positive type I reaction was related to active AE, and especially to AE in the head-neck region. Negative prick test results were seen for other atopic patients suffering from atopic conjunctivitis, rhinitis and/or asthma without active AE (46). Using an enzyme-linked immunosorbent assay (ELISA), Wessels et al. showed that production of IgE-antibodies against *P. ovale* occurs very frequently in AE, and rarely in patients with atopic diseases without skin involvement (47). By the radioallergosorbent test (RAST), elevated RAST classes (class 3) were the characteristic finding in patients with involvement of the head and neck region, whereas in those with predominant involvement of the extremities an average antibody titer of RAST class 1 was measured (44). In children the occurrence of serum antibodies to *P. orbiculare* measured by RAST correlated well with current eczematous lesions (42).

Late-phase reactions induced by Pityrosporum species

A Scandinavian group ascertained positive reactions in an epicutaneous test with *P. ovale* in 7 of 55 (13%) tested patients with AE (4/33 with head-neck dermatitis, 2/22 without head-neck dermatitis) after 72 h (19). In contrast, results from a Japanese group demonstrated contact sensitivity to *P. ovale* in 75 of 118 (64%) tested patients with AE (45). These differences in the incidence of positive delayed hypersensitivity reactions to the tested microorganisms are probably due to different experimental designs that resulted in different amounts of allergen penetration. Whereas in the Scandinavian study a suspension of killed spores was applied on non-treated skin with an intact stratum corneum barrier, the Japanese study used a chamber-scarification patch test with extracts from *P. ovale*. The question of which method reflects the human situation better cannot be answered at this time. However, scratching the epidermal layer before patch testing clearly carries the risk of causing irritative reactions.

Results from various studies clearly indicate that *Pityrosporum* species must be recognized as a pos-

sible conductor of eczematous lesions in a subgroup of patients with AE.

Conclusion

Although the exact mechanisms of interrelation between skin microorganisms and eczematous inflammation are not yet completely understood, there is enough evidence to form a working hypothesis according to which allergic reactions against microorganisms on the skin surface might play a pathogenic role in elaboration and/or maintenance of skin lesions in at least a subgroup of patients with AE. Antimicrobial treatment both topical and systemic may be helpful in the therapeutic management of these patients.

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