

Staphylococcus aureus colonization in atopic dermatitis and its therapeutic implications

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Summary

Skin colonization with *Staphylococcus aureus* is a characteristic feature of atopic dermatitis with more than 90% of patients being colonized. Extracellular matrix proteins are important for the adherence of *S. aureus* to human keratinocytes. The bacterium interferes in the inflammatory process of atopic dermatitis in various ways, among which the ability to release superantigens in a high percentage of clinical isolates is of great importance. As the colonization correlates significantly with the severity of eczema, anti-staphylococcal treatment measurements are widely used. In cases of atopic dermatitis exacerbation with wide-spread weeping lesions, a systemic antibiotic treatment is warranted, with erythromycin no longer being recommended due to an increased resistance rate. In localized superinfected lesions the topical application of an antibiotic-glucocorticoid preparation may offer advantages to the mere steroid application. Based on efficacy and resistance data, fusidic acid is the antibiotic of choice. There is evidence that phototherapy in atopic dermatitis may be even more effective when combined with anti-staphylococcal measurements. In the future new therapeutical options may be available.

Discussion on the importance of microbial factors on the pathogenesis of eczema and the therapeutical implications for the treatment of eczema began more than 100 years ago.¹ Since then, our knowledge concerning the complex interactions between microbes and skin inflammation has improved dramatically and today the Gram-positive bacterium, *Staphylococcus aureus*, is recognized as an important triggering factor for the maintenance of skin inflammation and acute exacerbations of the genetically determined skin disease atopic dermatitis (AD).

Staphylococcus aureus skin colonization in atopic dermatitis

The microbial flora of AD patients shows striking differences in terms of the presence of *S. aureus* (Table 1). The relative rarity (2%–25%)² of colonization by *S. aureus* on normal skin sites is in sharp contrast to the high carriage rate found in patients with AD, ranging from 76% on unaffected areas and up to 100% on acute, weeping lesions.^{3–5} We investigated the colonization features of 50 children with AD presenting at our out-patient clinic. Bacterial swabs were taken from eczematous lesions according to the individual distribution pattern and from areas suspicious for chronic

colonization, including the nares and axillas in all patients. Forty-five (90%) of the children had cutaneous colonization with *S. aureus*, of which 32 (71%) harboured the strain in their nares and only 45% in their axillas (unpublished data). These findings stress the importance of the nares as a localization that is preferentially harbouring by *S. aureus*, and it seems necessary to include this localization into anti-staphylococcal therapeutic strategies.

Relevant factors for enhanced skin colonization in atopic dermatitis

The factors responsible for the preferred colonization of atopic skin are not known in detail. The first step in any bacterial infection process is the adherence of the bacterium to the host cell. By introducing a new adhesion assay we studied the role of *S. aureus* surface-associated proteins in the attachment to HaCaT keratinocytes, and we showed that there are several proteins involved, such as staphylococcal protein A, coagulase, clumping factor and fibronectin-binding proteins.⁶ Other factors whose relevance to the increased colonization of atopic skin with *S. aureus* is presently being discussed are listed in Table 2.

Table 1. Resident flora of normal and atopic skin

Resident skin flora	Normal	AE
Micrococcaceae		
Coagulase-negative staphylococci	+	++
<i>Staphylococcus aureus</i>	—	++
Peptococcus	+	+
Coryneform organisms		
Corynebacteria	+	+
Propionibacteria	+	+

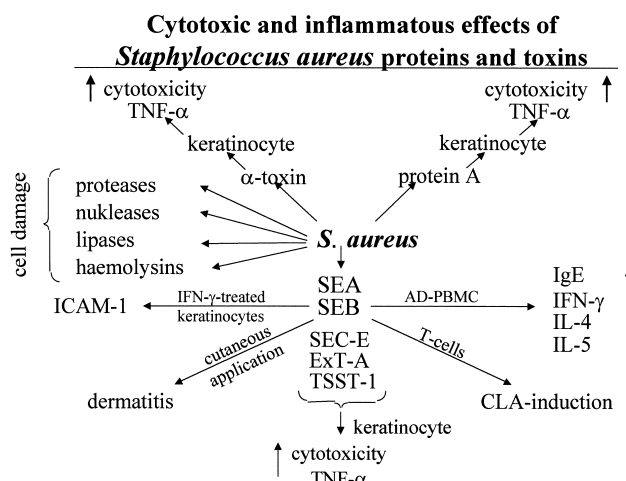
Mechanisms of *S. aureus*-induced skin inflammation in atopic dermatitis

Staphylococcus aureus induces inflammatory reactions via a range of activities, including protein and toxin secretion (Fig. 1). Among these are the *S. aureus* superantigens that are produced by 57%–65%^{10,11} of isolated strains, which have been intensively studied during the last years and have been characterized as substances with potent inflammatory and immunological effects.¹²

Peripheral blood mononuclear cells from patients with AD stimulated with *S. aureus* enterotoxin B (SEB), secreted significantly more IL-4, IL-5, and IgE, and markedly less interferon-gamma than those from healthy controls, a finding that indicates that SEB produced by *S. aureus* strains colonizing the skin of patients with AD induces the expansion of Th-2 clones, leading to increased IgE synthesis and eosinophil activation.¹³ Direct pro-inflammatory effects on keratinocytes through the release of tumour necrosis factor- α were induced by incubation of keratinocytes with staphylococcal protein A, α -toxin and the superantigenic toxins SEA and SEB.¹⁴ *In vivo* the application of SEB on atopic skin induced an inflammatory reaction.¹⁵

Table 2. Characteristics of AD relevant to *S. aureus* colonization

pH	pH values are shifting towards alkalinity ⁷ with adherence of <i>S. aureus</i> to human keratinocytes being highest at pH 7–8 ⁶
Extracellular lipids of the stratum corneum	Quantitative and qualitative changes in lipid composition ⁸ could result in diminished antibacterial activity ⁹

Figure 1. Cytotoxic and inflammatory effects of *S. aureus* proteins and toxins.

Anti-staphylococcal treatment in atopic dermatitis

The improved knowledge of the pathophysiological importance of *S. aureus* in AD, combined with the positive correlation between the severity of eczematous lesions and the colonization with *S. aureus*,¹⁶ forms the rationale for an anti-staphylococcal therapy in patients with AD.

In cases of exacerbation of AD with weeping lesions the oral administration of anti-staphylococcal drugs is most effective.^{17,18} As a significant number of *S. aureus* isolates are resistant to erythromycin, the antibiotics of choice are the penicillin-resistant penicillins such as flucloxacillin, the oral cephalosporins such as cephalexin^{17,18} or fusidic acid.¹⁹ In cases of penicillin allergy, fusidic acid or clindamycin is recommended.

There exist different therapy options for localized superinfected lesions.²⁰ It has been shown that the topical application of a 0.3% solution of gentian violet twice daily to bilateral lesional skin and uninvolved skin for 4 days in *S. aureus* colonized AD patients, results in a clinical improvement and a reduction of bacterial numbers that is statistically significant in comparison with treatment using the vehicle.²¹ Our results indicate that by combining topical glucocorticosteroids with an antibiotic or an anti-infective, an identical clinical efficacy may be achieved by using steroids of less potency, thereby reducing the possible side-effects from topical steroids. Among the antibiotics, fusidic acid seems to be the drug of choice due to its inhibition of staphylococci at very low concentrations, regardless of the patient's susceptibility to methicillin or oxacillin.²² Although the

substance has been on the market since the 1960s and is widely used, the number of primarily resistant *S. aureus* strains has been relatively constant over the years, and has not exceeded 1%–2%.²³ When blood and cerebrospinal fluid strains of *S. aureus* isolated between 1989 and 1995 from England and Wales were analysed, the rate of resistance significantly increased to methicillin, erythromycin, clindamycin, ciprofloxacin, gentamicin, trimethoprim and rifampicin, but showed a stable resistance to fusidic acid.²⁴

Even in the absence of clinical signs of active infection, patients with AD profit from a reduction of *S. aureus* density due to the presence of these bacteria on the skin. In those cases antiseptics such as chlorhexidin or triclosan can be added to emollients and successfully used for the treatment of larger skin areas.^{25,26}

Combination of anti-staphylococcal measurements and phototherapy for atopic dermatitis with high density numbers of *S. aureus* isolates

Phototherapy for the treatment of both chronic stages of the disease (especially conventional UVA/UVB therapy, 311 nm UVB therapy) and acute, severe exacerbation of AD (especially UVA1 or systemic PUVA therapy) is a beneficial treatment option.²⁷ An anti-staphylococcal effect of UV therapy has been reported.²⁸ Findings from UVA1 studies imply that an additional anti-staphylococcal therapy might improve the beneficial effect of phototherapy, because non-responders to UVA1 therapy were characterized by higher *S. aureus* colonization rates than patients that did respond.²⁹

Future therapeutical approaches

In the future, new therapeutical options may become available. Due to the anti-staphylococcal activity of some skin lipids like sphingolipids,⁹ a topical administration of these compounds seems promising. Data on the effect of nitric oxide on staphylococcal killing could result in new topical treatment options.³⁰ *Staphylococcus aureus* has an increased adherence to corneocytes and keratinocytes of patients with AD. A possible therapeutic approach to prevent staphylococci from colonizing human skin could be to block the responsible structures. Even an immunological therapeutic approach would be possible by treating *S. aureus*-sensitive patients with injections of allergen-antibody complexes, as this has been shown to be effective in patients with AD and hypersensitivity to *Dermatophagoides pteronyssinus*.³¹

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