Role of *Staphylococcus aureus* in Atopic Dermatitis

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**Abstract**

Atopic dermatitis (AD) is a chronic relapsing, itchy inflammatory condition of the skin usually associated with other allergic diseases such as asthma and hay fever. Following the initial occurrence of AD several factors such as environmental allergens, colonization with *Staphylococcus aureus* and allergen specific T cell responses are thought to aggravate the disease. The bacteria skin flora of patients with atopic dermatitis is strikingly different from that in healthy people in terms of the presence of *Staphylococcus aureus*. An altered epidermal barrier, increased bacterial adhesion, defective bacterial clearance and defective cutaneous innate immune response are among various factors contributing to this high bacterial colonization in AD. *Staphylococcus aureus* strains with ability to secrete *Staphylococcal enterotoxins* A - D and the toxic shock syndrome toxin - 1 have been isolated from the skin of up to 65% of AD patients who are colonized with this microorganism. These toxins aggravate the disease by cellular activation to produce cytokines.

**Keywords**: Atopic dermatitis, *Staphylococcus aureus*, Colonization, Superantigens, T-cells, Cytokines
Introduction

Atopic dermatitis (AD) is a chronic relapsing, itchy inflammatory condition of the skin. It is a common skin disease that is also usually associated with other allergic diseases such as asthma and hay fever. It is thought to affect around 10.7% to 30% of children and 2-3% of adults (Bieber. 2008, Hanifin et al. 2007, Sturgill et al. 2004). International Study of Asthma and Allergies in Childhood (ISAAC) involving over 196 centres revealed that there has been a dramatic increase of the overall prevalence of AD, asthma and allergic rhinitis (Asher et al. 2006). This rise was especially seen with allergic rhinoconjunctivitis (Asher et al. 2006). There has also been a 2 to 3 fold rise in AD in industrialized countries where 15 to 30% of children and 2 to 10% of adults are affected (Williams et al. 2006).

Although the rise in allergic diseases is higher in developed countries and especially in the temperate climates, a significant increase has also been observed in many countries in Africa (Zar et al. 2007). The annual incidence estimates for the 6 to 7 year age group ranged from under 2% in Iran to over 16% in Japan and Sweden (Sugiura et al. 1998, Leung et al. 1994). Although there is no data on the prevalence of AD in Sri Lanka, the prevalence of all types of dermatitis (which includes AD) was found to be 9.5% in a suburban population in the Colombo district (Perera et al. 2000).

AD is associated with disruption of the skin barriers and IgE mediated sensitization to food and environmental allergens (Hanifin et al. 2007). The initial mechanisms that induce skin inflammation in patients with AD are not known. However, following the initial occurrence of AD several factors such as environmental allergens, colonization with Staphylococcus aureus and allergen specific T cell responses are thought to aggravate the disease (Gong et al. 2006, Hanifin et al. 2007).

The purpose of this review is to discuss the exacerbation of disease activity by S. aureus.

Skin colonization by S. aureus

The bacterial skin flora of patients with atopic dermatitis is strikingly different from that in healthy people in terms of the presence of S. aureus. The relative rarity (2%-40%) of colonization by S. aureus on normal skin sites (Kluytmans et al. 1995) 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 (Leysen et al. 1993). Among various factors contributing to this high colonization of skin by *S. aureus* in AD include an altered epidermal barrier, increased bacterial adhesion, defective bacterial clearance and defective cutaneous innate immune response.

**An altered epidermal barrier**
The skin of patients with AD tends to be drier due to altered skin lipid content which causes cracking of the skin resulting in transepidermal water loss. The average pH of the skin has shown to be more alkaline, and sphingosine (amino alcohol which forms a primary part of sphingolipids, a class of cell membrane lipids) levels are decreased in both lesional and non lesional stratum corneum, the outermost layer of the skin (Rippke et al. 2004, Arikawa et al. 2002). This disruption of the 'normal' skin defenses against bacterial colonization may facilitate colonization with bacteria such as *S. aureus* (Baker. 2006).

**Increased bacterial adhesion**
Cytokines such as Interleukin-4 (IL-4) produced by Th-2 subtype of T helper cells in the skin of patients with AD, have shown to increase expression of fibronectin and fibrinogen, receptors that mediate the adhesion of *Staphylococcus aureus* to stratum corneum (Cho et al. 2001). Cytokines are non-antibody proteins secreted by inflammatory leukocytes and some non-leukocytic cells. They trigger inflammation and respond to infections. The cytokines include interleukins, lymphokines and cell signal molecules, such as tumor necrosis factor and interferons.

**Defective bacterial clearance**
Persistent *S. aureus* colonization is shown to be associated with higher total IgE levels specific to staphylococcal enterotoxin B (SEB) and other enterotoxins (Guzik et al. 2005, Breuer et al. 2000) because cytokines produced by Th-2 subtype of T helper cells favour development of IgE type antibodies. IgE type antibodies are not good at opsonization and complement activation, which are needed for microbial clearance.

**Defective cutaneous innate immune response**
The microbe-specific molecules are recognized by Pattern Recognition Receptors (PRRs), proteins expressed by cells of the immune system. Various types of PRRs include the large families of membrane-bound Toll-like
receptors (TLRs) and cytoplasmic NOD-like receptors. The molecules specific for the microbe that are recognized by a given PRR are called Pathogen-Associated Molecular Patterns (PAMPs). PAMPs include bacterial carbohydrates (lipopolysaccharide, mannose), bacterial flagellin, lipoteichoic acid from Gram-positive bacteria, peptidoglycan and nucleic acid variants normally associated with viruses.

Changes in the genes (genetic polymorphisms) that code these PRRs can result in impaired recognition of microbes or an altered or impaired innate immune response. Studies have found genetic polymorphisms in genes that code for TLRs and NOD like receptors in AD (Weidinger et al. 2005, Ahmad et al. 2004).

**Role of *Staphylococcus* superantigens**

*S. aureus* is able to secrete exotoxins with superantigenic properties. Studies have shown that the staphylococcal enterotoxins A-D (SEA-D) and the toxic shock syndrome toxin - 1 (TSST-1) are secreted by *Staphylococcus aureus* strains isolated from the skin of up to 65% of AD patients who are colonized with this microorganism (Llwelyn et al. 2002, Bunikowski et al. 2000, Bunikowski et al. 1999, Nomura et al. 1999, Akiyama et al. 1996).

Superantigens (SAg) are proteins with powerful immunomodulatory properties. Unlike conventional antigens superantigens do not require processing by antigen-presenting cells to activate T cells. Instead superantigens are presented to T cells by binding to nonpolymorphic regions of class II major histocompatibility complex (MHC) molecules or antigen-presenting cells. Their importance lies in their ability to activate many T cells, resulting in large amount of cytokine production.

Studies show that the amount of serum SAg-specific IgE is correlated with the severity of AD and is strongest when patients produce specific IgE against Staphylococcal enterotoxins originating from *S. aureus* on their skin surface (Bunikowski et al. 2000, Strange et al. 1996). Staphylococcal Enterotoxins B (SEB), when applied to intact normal skin or the non-lesional skin of patients with AD, can induce erythema and dermatitis and in some AD patients, a flare of the disease in the elbow flexure of the same arm to which the toxin was applied (Michie et al. 1996). Development of chronic eczematous dermatitis was seen in patients recovering from toxic shock syndrome caused by TSST-1, but not with patients recovering from Gram-negative sepsis (Michie et al. 1996).
In addition to T cells, superantigens can also mediate effects on other cell types such as eosinophils, Langerhans cells, macrophages and keratinocytes (Baker, 2006). During flares of AD, eosinophils are recruited to the skin by chemotactic attractants where they are activated and the products released by degranulation and cytolytic degeneration promote inflammation and tissue damage (Wedi et al. 2002). Superantigens can modulate the effector function of eosinophils by inhibiting eosinophil apoptosis, a programmed sequence of events leading to elimination of cell without releasing harmful substances into the surrounding area (Wedi et al. 2002). They also bind to Langerhans cells and macrophages and stimulate them to produce cytokines that up-regulate the expression of adhesion molecules on endothelial cells (Baker, 2006). Further, keratinocytes that have been induced to express MHC Class II molecules by stimulation with Interferon-γ (IFN-γ) can interact with superantigens resulting in the release of pro-inflammatory Tumor Necrosis Factor-α (TNF-α) (Ezepchuk et al. 1996). Activated keratinocytes enhance antigen presentation to T cells (Nickoloff et al. 1993). This has a major impact on AD, due to worsening of T cell mediated immune responses. The capability of superantigens to initiate, exacerbate and maintain inflammation associated with AD can be deduced from these findings.

**Clinical implications**

Clinical management of AD is aimed at prevention and treatment of flare ups and long term skin care which best suits the individual patient (Bieber. 2008). The cause of recurrent flare ups in AD is not well established. However, in most instances they are usually associated with *S. aureus* infection of the lesions. Therefore, apart from aggressive treatment of these acute episodes with the appropriate topical steroids, emollients, topical calcineurin inhibitors and dressings, treatment of infection with antibiotics which are effective against *S. aureus* is warranted (NICE 2007).

Treatment with a systemic antibiotic such as is usually recommended for a period of 2 weeks with Flucloxacillin or Erythromycin/Clarithromycin of the patient allergic to Flucloxacillin or the organism is resistant to it. Topical antibiotics may be used if the infection is localized. However, topical antibiotics should not be for more than 2 weeks because of the development of antibiotic resistance (NICE 2007). Currently, the long term use of antibiotics is not recommended as the benefit of such treatment has not been established.
Conclusion
Atopic dermatitis (AD) is a chronic relapsing, itchy inflammatory condition of the skin usually associated with other allergic diseases such as asthma and hay fever. It is commoner among children than among adults. The bacterial skin flora of patients with atopic dermatitis is strikingly different from that in healthy people in terms of the presence of *S. aureus*. An altered epidermal barrier, increased bacterial adhesion, defective bacterial clearance, and defective cutaneous innate immune response are among various factors contributing to this high colonization of skin by *S. aureus* strains with ability to secrete toxins, aggravates the disease by cellular activation to produce cytokines.

Reference


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