
Review article

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Role of staphylococcal superantigens in atopic dermatitis: from colonization to inflammation

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Objective: This review article has been prepared in order to enable the readers to understand the role of staphylococcal superantigens (SsAgs) in atopic dermatitis (AD).

Data sources: MEDLINE literature search was performed for obtaining references. Recent reviews, research articles, poster presentations, and letters (to the editor) were meticulously reviewed.

Results: (1) SsAgs contribute to the pathogenesis of cutaneous inflammation in AD with five potential mechanisms:

- Direct stimulation of antigen presenting cells (APCs) and keratinocytes
- Stimulation of T cell proliferation [superantigenic binding to T cell receptor (TCR)].
- Expansion of skin-homing cutaneous lymphocyte antigen (CLA) (+) T cells
- The role of superantigens as allergens
- Reduction of apoptosis

(2) Effectiveness of antibiotic therapy in AD patients without signs of bacterial infection is still under discussion. If signs of skin infection are present, antibiotic therapy (topical/oral) may help exacerbations of AD. Prolonged topical/oral antibiotic therapy, however, may cause development of antibiotic-resistant strains of *Staphylococcus aureus* (SA).

Conclusions: Atopic dermatitis is a genetically determined, chronically relapsing, inflammatory skin disease which has many aspects and a complex immunopathogenesis involving both immediate and cellular immune responses. While the pathogenic role of SsAgs may not be of primary importance, SsAgs appear to be one of the important triggering factors that contribute to the cutaneous inflammation in AD. We suggest that staphylococcal colonization does not always mean SsAg-mediated inflammation, and anti-staphylococcal treatment should be considered in cases with signs of bacterial infection.

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There is no little enemy.

—Benjamin Franklin

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INTRODUCTION

Atopic dermatitis (AD) is a genetically determined, chronic pruritic inflammatory cutaneous disease which is usually seen in association with asthma and allergic rhinoconjunctivitis. Onset of this disease occurs within the first year of life in 60% of cases, and within the first 5 years in 85%. Even if AD clears in about 40% of children, it affects

10% to 15% of the population at some point during childhood.^{1,2} Because it is lifelong and difficult to treat, AD causes significant interference with school, work, and social relationships, especially in moderate-to-severe cases.¹

From the allergy and immunology point of view, AD may be classified as “mixed” and “pure.” About 60% of cases have associated respiratory allergies, and this variant is called the “mixed-type of AD” which is distinct from the other main type; “pure AD.” In its pure form, there is no association with respiratory allergies. Pure AD, which constitutes approximately 40% of all cases, is divided into two subgroups: “extrinsic-type of pure AD” and “intrinsic-type of pure AD.” The extrinsic type, which forms about 70% of all pure AD cases, shows specific IgE responses and skin test reactivity against inhalants and foodstuffs; however, 20% to 40% of cases of pure AD without concomitant respiratory allergies (intrinsic-type of pure AD) have neither elevated IgE levels, nor a specific IgE sensitization. As a result, allergy management is suggested to be useful in the “mixed-type of AD” and “extrinsic-type of pure AD.”³

While AD is greatly influenced by environmental factors, it is generally regarded a genetic disease. The high concordance rate in twins, and obvious familial occurrence support the genetic theory.² Thestrup-Pedersen et al propose the hypothesis that AD results from a genetically determined ectodermal defect that disturbs T lymphocyte maturation.⁴

Atopic dermatitis has a complex immunobiology involving a combination

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of immediate and cellular immune responses. Inhalant and food allergens, microorganisms (staphylococci, pityrosporum spp.), hormonal factors (menstruation, pregnancy), stressful life events (emotional factors), climatic/seasonal factors (autumn and winter months), irritating substances (wool, detergents, or occupational substances), pollution, and lifestyle have been shown important provocation factors in AD.⁵ The reduction of infections in early childhood or reduced contact with antigens which cause cellular immune responses of type-1 cytokine pattern of T cells (ie, high IFN- γ and low IL-4, IL-5) is suggested to be associated with atopic diseases. The fact that the prevalence of childhood AD is higher in families with a more privileged lifestyle and higher paternal income supports this hypothesis.⁶

Several theories have been proposed in order to understand the pathogenesis and etiology of AD. Among those most widely studied ones are the allergic theory (inhalant and food allergens), the β -adrenergic blockade theory, δ -6 desaturase enzyme deficiency, neurogenic inflammation, and autoimmunity.^{2,5,7-10} Despite these theories, the etiology and pathogenesis of AD are not precisely understood. It is reasonable to suggest that the efficacy of all these pathogenic and/or provocative factors may be variable.

Serum IgE levels are elevated in almost 80% of patients with AD, and in most of them, there is a correlation between IgE levels and disease activity. Atopic dermatitis is characterized by local infiltration of monocytes and lymphocytes. Recent experimental studies support the hypothesis that activation and expansion of T-helper type 2 (Th2) lymphocytes and allergen sensitization have important roles in the pathophysiology of AD.^{1,2,5,8,11,12}

The fact that food and inhalant allergens play a triggering role in only a subset of AD patients led to new research aiming to reveal other pathogenetic and/or triggering factors. *Staphylococcus aureus* (SA) was isolated from the lesional skin of more than 90% of AD patients by Leyden et al for

the first time in 1974.¹³ In 1988, Lever and associates published their clinical trial revealing that patients treated with antibiotics plus corticosteroids had significantly greater improvement than patients treated with corticosteroids alone.¹⁴

Superantigens (sAgs) are a group of bacterial and viral proteins that were recognized by their ability to stimulate large numbers of different T-cell clones and cytokine secretion.^{15,16} White and associates first proposed the term "superantigen" to describe the bacterial toxins causing massive T-cell receptor (TCR) V β -restricted primary response in 1989.¹⁷

In the following sections, the relationship between AD and exacerbation mechanisms by staphylococcal superantigens (SsAgs) will be reviewed. Prior to this, the features of the TCR will be reviewed because it is the basic principle for understanding "conventional" and "superantigenic" binding.

T-CELL RECEPTOR: CONVENTIONAL VERSUS SUPERANTIGENIC BINDING AND PROPERTIES OF SUPERANTIGENS

The T-Cell Receptor

The T-cell receptor is composed of two peptide chains-either α/β or γ/δ -and three regions: extracellular, transmembrane, and cytoplasmic. The extracellular region has constant and variable regions. Most TCRs have α and β chains, and their variable regions (V α , J α and V β , D β , J β gene segments or "specificity providing" regions) form a pocket in which conventional antigens are presented to the T cells by class II major histocompatibility complex (MHC) molecules. The similarity between the structural configurations of TCR and Ig is very striking. Both of them have binding pockets for antigenic specificities and complementarity-determining regions (CDRs) that mediate the antigen-binding regions of the receptor.^{15,16,18-20} The most diverse area is CDR-3 which is located in the V-D-J joining regions of the TCR. This area plays an important role in the

recognition of conventional antigens presented within the binding pocket of an MHC molecule.¹⁸

Conventional Antigenic Binding (classical response)

In the classical immune response, the antigen is taken up by specialized antigen presenting cells, including B cells, monocytes/macrophages, and dendritic cells. Then, the antigen is extensively processed into relatively small peptides prior to presentation to CD4+ (helper) T cells. These molecules fit into the class II MHC peptide-binding groove. Later, the peptide-MHC complex is expressed on the surface of the antigen presenting cells (APCs), and the TCR (antigen-specific)-antigenic complex interaction begins. On activation, the T cells proliferate and secrete cytokines. Cytokine secretion means the potentiation of T-cell activation and stimulation of other immune mechanisms. Antigen presenting cells also provide accessory or costimulatory signals to the T cells to enhance activation. This is necessary for full T-cell activation.^{15,16,18-20}

Because genetically determined specificities are required, conventional binding is under strict control of the immune system. Conventional antigens require recognition of all gene segments (V α , J α , V β , D β , and J β) of the TCR. Activated T cells are those that are HLA identical and whose TCRs conform to the shape and charge pattern of the presented antigenic molecules. Thus, in the classical immunologic response, the amount of the activated T-cells is approximately 0.01% to 0.1% even after clonal expansion.^{15,18,19}

Superantigenic Binding

The binding process is much less complex in superantigenic binding. This process does not require processing by APCs. Superantigens (sAgs) bypass intracellular processing and bind directly to the MHC class II molecule on the surface of the APC outside the antigen binding groove. They serve as a bridge that connects the HLA complex (MHC class II molecule) of an

APC with a V β compatible TCR. Because the highly restrictive antigen recognition component of the TCR does not play a critical role in the superantigenic activation process, the immunologic response will be completely different. Superantigens cause T cells to behave like "antigenically stimulated cells."^{15,16,18-20} While conventional antigens require recognition of all five gene segments of the TCR, the recognition sequence for sAg is almost entirely dependent on V β only.

After cross-linking between APC and TCR V β , polyclonal T cell activation begins and both the CD4 and the CD8 subtypes are activated. It has been shown that there are at least 30 V β families (V β 1, V β 2, V β 3, etc. phenotypes) in humans. Each family represents numerous different T-cell clones. Different sAgs recognize different groups of V β designations, and each one has the ability of activating up to six TCR V β families, resulting in activation of approximately 20% of all T cells.^{15,16,18} Since a given type of V β molecule may be expressed frequently, infrequently, or not at all on that individual's T cells, it should be kept in mind that a particular sAg may stimulate many (30%), few (1%), or none.¹⁵

Properties of Superantigens: a Comparative Summary

There are four major differences between sAgs and conventional peptide antigens²¹:

- sAgs cause a strong primary response that is never seen with normal peptide antigens.
- Unlike the conventional antigens, the V β chain of the TCR is sufficient for recognition of a sAg.
- Even if all sAgs require MHC class-II proteins for presentation to T lymphocytes, the T cell response is not class-II restricted. Yet, in all other conventional peptide antigen-specific T-cell responses, MHC restriction is seen.
- sAgs associate with MHC class-II in unprocessed form. In contrast, conventional antigens are broken down into peptides before interaction.

BACTERIAL SUPERANTIGENS AND SKIN

The fact that it is sometimes difficult to separate the overlapping clinical features of (erythema, desquamation, and tenderness) of scarlet fever, toxic shock syndrome, Kawasaki syndrome, and staphylococcal-scalded skin syndrome reveals that the skin is a common site of manifestations of many toxin-induced diseases in humans.¹¹ Below are the staphylococcal and streptococcal superantigenic exotoxins which play important roles in the skin^{11,12}:

SA

- Staphylococcal enterotoxin A (SEA)
- Staphylococcal enterotoxin B (SEB)
- Staphylococcal enterotoxin C (SEC)
- Staphylococcal enterotoxin D (SED)
- Staphylococcal enterotoxin E (SEE)
- Toxic shock syndrome toxin-1 (TSST-1)
- Exfoliatin

Streptococcus pyogenes

- Staphylococcal pyrogenic exotoxin A (SPEA)
- Staphylococcal pyrogenic exotoxin B (SPEB)
- Staphylococcal pyrogenic exotoxin C (SPEC)

The following is a list of the skin diseases, and systemic diseases with characteristic cutaneous findings that are mediated or triggered by staphylococcal and streptococcal sAgs (known or possible)^{11,12,16,18-22}:

- Toxic shock syndrome (SsAg)
- Streptococcal toxic shock syndrome (streptococcal sAg)
- Scarlet fever (streptococcal sAg)
- Erysipelas (streptococcal sAg)
- Staphylococcal scalded skin syndrome (SsAg)
- Kawasaki disease (streptococcal and SsAg)
- Psoriasis (streptococcal and SsAg)
- Atopic dermatitis (SsAg)

There are also some other dermatologic diseases in which sAgs might be triggers. In none of them, however, is there a careful study of superantigen activation^{11,23-26}:

- Seborrheic dermatitis

- Nummular dermatitis
- Infectious eczematoid dermatitis
- AIDS-related skin diseases
 1. Eosinophilic folliculitis
 2. AIDS-associated seborrhea
 3. AIDS-associated psoriasis
 4. AIDS pruritus

ATOPIC DERMATITIS, STAPHYLOCOCCI, AND INFLAMMATION

Atopic Dermatitis and Skin Inflammation: a Brief Review

Atopic dermatitis is characterized by chronic skin inflammation. The presence and activation of multiple cell types have appeared on skin biopsy samples of AD lesions. Dysfunction of macrophages and T lymphocytes is thought to play the most important role in the pathogenesis of cutaneous lesions and the overproduction of IL-4 and IL-5. These two cytokines (IL-4 and IL-5) are likely responsible for the high IgE levels and eosinophilia characteristic of AD.²⁷ T cells in the acute skin lesions of AD patients demonstrate cytokine RNA patterns most consistent with a Th2 phenotype (elevated IL-3, IL-4, IL-5 and IL-13, but not IFN- γ). In some recent studies, however, a biphasic cytokine mRNA pattern was observed, with IL-2 and IL-4 mRNA elevation seen at 24 hours and increased expression of the Th1 cytokines seen at 48 hours.^{1,2,12,27,28}

Chronic AD skin lesions show predominance of macrophages and monocytes, which express high levels of GM-CSF and IL-10 mRNA in the mononuclear cell infiltrate. While the increased expression of GM-CSF contributes to enhanced eosinophil and monocyte survival, IL-10 diminishes IFN- γ production. Overexpression of these two cytokines and the inability to produce IFN- γ therefore, contribute to the increased IgE synthesis and sustained T cell activation, ie, the maintenance of the Th2 cytokine network.^{1,12}

Activated eosinophils are also found in significantly greater numbers in chronic compared with acute lesions. Eosinophil major basic protein, which may contribute to the pathogenesis of

AD not only through its cytotoxic properties but also its capacity to induce basophil and mast cell degranulation, has been shown in the dermis.²⁷

As a result, long-term antigen exposure (allergenic and/or superantigenic stimulation), keratinocyte injury caused by scratching, Th2 cell stimulation, allergen-specific IgE production, mast cell degranulation, eosinophil infiltration, and reduction of monocyte apoptosis play important roles in the chronic skin inflammation/cutaneous hyperreactivity observed in AD.^{1,12,27}

Atopic Dermatitis and Staphylococci: from Colonization to Inflammation

Staphylococci commonly found on human skin are collectively known as the 'coagulase-negative' staphylococci. While the most abundant ones are *S. epidermidis*, *S. haemolyticus*, and *S. hominis*, they are rarely involved in skin diseases. Although it is not an inhabitant of normal skin, SA is the only coagulase-positive staphylococcus which is commonly found in humans. Anterior nares (in more than 1/3 of the population), perineum (20%), axillae, and toeweb (5% to 10%) are the common carrier sites. In AD patients, this rate, including those on the skin surface, usually exceeds 90%.^{19,29} One of the most important and interesting points, which must be emphasized, is that neutral pH and other factors optimize TSST-1 production; therefore, SA is likely to produce lower levels of TSST-1 on the skin of patients with eczema than vaginal SA in toxic shock syndrome.³⁰

Staphylococcus aureus colonization has been well described and is regarded as one of the most important initiating and/or exacerbating factors in AD. More than half of the SA strains isolated from AD patients have been demonstrated to secrete superantigenic toxins SEA, SEB, and TSST-1.^{12,19} This study by Strange et al at the University of Copenhagen has provided very important scientific proofs to this approach: in order to determine whether the SEB can induce an inflammatory reaction when applied on the skin, SEB was applied with and with-

out occlusion on the volar aspect of the skin on the forearm of 10 healthy subjects without skin disease and also on six patients with AD of minimal activity and no eczema on the volar aspect on the skin of their forearm.

Staphylococcal enterotoxin B induced erythema and induration were observed in all subjects. Besides the induction of local inflammation following application of SEB to uninvolved normal appearing skin in all AD patients, the authors reported that three of them experienced a flare in their disease in the elbow flexure ipsilaterally to where the SEB patch was applied. They also observed a generalized flare, which remitted within 1 week in two of these three subjects.³¹

Similarly, Dr. Patrick M. Schlievert, working in the University of Minnesota Medical School, Department of Microbiology explained that he developed clinically documented AD lasting 3 to 4 months after accidentally splashing SEA on his face.²⁰

Michie and Davis reported that 14 patients out of 68 with previous TSS, who had no dermatitis or a history of atopy before the toxic shock episode, later developed long-standing dermatitis (AD?). Further, four of them had increases in IgE suggesting atopy.³²

In the literature on AD, we have not seen any other reports that regard SsAg as an "AD-initiating factor" in nonatopics. It is unknown to the authors whether Dr. Patrick M. Schlievert had AD before accidentally splashing SEA or not, it is unknown whether the findings observed in 14 survivors of TSS by Michie and Davis completely satisfy the diagnostic criteria of AD or not; and finally it is also unknown whether these 14 patients have still cutaneous findings (AD?) or not.

As a result, it is difficult to interpret the data outlined above. Since it has a genetically determined basis, and many aspects from pathogenetic and immunologic point of view, the opinion that SsAg might initiate AD in nonatopics seems highly unlikely in the light of the scientific data.

Contribution of SsAg to the Cutaneous Inflammation in AD: Potential Mechanisms

Five potential mechanisms by which SsAg may contribute to the pathogenesis of cutaneous inflammation in AD have been proposed:

- (1) Direct stimulation of APCs and keratinocytes
- (2) Stimulation of T cell proliferation (superantigenic binding to TCR)
- (3) Expansion of skin-homing CLA+ T cells
- (4) Superantigens as allergens
- (5) Reduction of apoptosis

It is clear that all these processes affect each other.^{1,2,5,11,19,33-40} SsAg, probably penetrating the injured skin barrier in patients with AD more easily than they do on intact skin barrier, may directly stimulate Langerhans cells (LCs), macrophages, dermal dendritic cells, or keratinocytes. Upon stimulation, TNF- α or IL-1 α is released from these cells and leukocyte infiltration is promoted.^{11,12,16,19,35} Ezepechuk et al has shown that SsAg produced in the skin of patients with AD and psoriasis might induce local inflammation ("direct proinflammatory effect") through the release of primary cytokines from the epidermal keratinocytes.³⁶

While keratinocytes lack MHC class II molecules in healthy epidermis, they are shown in vitro to potently activate T cells by expressing MHC class II molecules in the presence of sAg. T cell activation by "activated" keratinocytes, which express MHC II and therefore can function as "sAg-presenting cells," will lead to further inflammation and cytokine release, resulting in enhanced MHC class II expression on keratinocytes. It is clear that this "vicious circle" will continue as long as sAg are present.^{16,19,36}

T cell proliferation is the most important step in the sAg-mediated process. It is reasonable to suggest that sAg-induced skin inflammation is T cell dependent. Saloga et al have reported that epicutaneous application and the intracutaneous injection of small amounts of SEB cannot elicit an

inflammatory response in the skin of nude (T cell deficient) mice.⁴¹

Expansion of skin homing CLA+ T cells play a central role in the inflammatory response observed in AD.¹ CLA has been hypothesized to be a homing receptor involved in selective migration of T cells to the skin. In a study by Abernathy-Carver et al, it has been demonstrated that peripheral blood mononuclear cells from children with AD and IgE-mediated milk hypersensitivity stimulated in vitro with casein resulted in proliferation of T cells bearing the CLA, whereas no increase in CLA+ cells was seen in milk-allergic children with asthma or gastrointestinal allergies.⁴²

In 1995, Leung et al showed that there was a significant increase in the numbers of CLA+ T cell blasts, but not blasts bearing the mucosa-associated adhesion molecule $\alpha\epsilon\beta 7$ -integrin after in vitro stimulation of peripheral blood mononuclear cells with SsAgs. IL-12, which is specifically induced by sAgs, has been suggested to be the most important cytokine in the induction of the CLA on T cells.³⁴

On the basis of the induction of the CLA on T cells, the phases of immunologic events that cause inflammation are as follows^{1,34,43}:

1. Penetration of inflamed skin and stimulation of epidermal macrophages or LCs by SsAgs.
2. Local production of IL-1, TNF- α , and IL-12 by epidermal macrophages or LCs.
3. Induction of the expression of E-selectin on vascular epithelium.
4. Initial influx of CLA+ memory/effector cells.
5. Upregulation of the expression of CLA by IL-12 which is secreted by sAg-stimulated LCs migrating to skin-associated lymph nodes.
6. Amplification of the initial cutaneous inflammation and formation of more favorable conditions for staphylococcal skin colonization.

Another potential mechanism which contributes to the cutaneous inflammation in AD is "the role of sAgs as allergens." Studies on this concept

have been based on the following observations^{11,12,33}:

- In the pathogenesis of AD, antigen-driven activation of T cells and IgE producing B cells play an important role.
- sAgs are globular proteins of 24 to 30 kD.

Leung et al investigated the immune responses to SsAgs (SEA, SEB, and TSST-1). It was reported that 57% of patients with AD have circulating IgE against SEA, SEB, and TSST-1. In addition, basophils from these patients with IgE antitoxin showed significant degranulation when incubated in vitro with the specific toxin for which the IgE was specific. No degranulation was observed in basophils from normal controls or from AD patients without IgE antitoxin when exposed to superantigenic toxins.⁴⁴ These findings suggest the possibility that epicutaneous staphylococcal superantigenic toxins might induce specific IgE in AD patients, including mast cell degranulation in vivo. The SsAg penetrate the disrupted epidermal barrier and induce IgE-triggered histamine release, which promotes the "itch-scratch cycle" in AD patients.¹¹

Hofer et al determined for the first time the in vitro effects of TSST-1 enhanced IgE synthesis in peripheral blood mononuclear cells (PBMCs) from patients with AD. They showed that TSST-1 produced antagonistic effects on IgE synthesis by PBMCs from AD patients depending on the concentration used. The concentrations of TSST-1 needed to enhance IgE were found to be much lower than those required for maximal lymphocyte activation. In this study, it was determined that in the nanogram range, TSST-1 induced massive T cell proliferation associated with marked IFN γ production, and, as a result, an inhibition of IgE production in both AD and non-atopic PBMCs; in contrast, at lower concentrations, TSST-1 stimulated T cells to a lesser extent and enhanced IgE production via a polyclonal B cell activation. These findings indicate that stimulation of the humoral immune response by low level exposure to

TSST-1, in toxin amounts insufficient to cause toxic shock syndrome, may contribute to the increased IgE synthesis in AD.

The fact that the authors showed the inhibition of TSST-1 enhanced IgE synthesis by anti-HLA-DR and anti-leukocyte function-associated antigen-1 (LFA-1) monoclonal antibodies was one of the most important data obtained from this research. These findings indicate that TSST-1 stimulated IgE synthesis is a T-cell dependent process and needs the bridging of the TCR and the MHC class II molecules in order to activate B cells.³⁷

In two recent studies, a correlation has been found between serum IgE antibodies to the SA-derived sAgs and severity of AD. Bunikowski et al studied 20 children with AD who were sensitized to superantigens, and demonstrated that the degree of AD severity correlated with the presence of SEA and SEB-specific IgE antibodies than with total serum IgE levels. It was also suggested that severe dermatitis was significantly more often observed in SEA/SEB-sensitized children.⁴⁵

While no difference in severity between AD patients with or without exotoxin-producing SA were reported by Namura et al, anti-SEB IgE antibodies were more frequently detected in patients with severe AD than in patients with mild and moderate AD. The authors concluded that SsAgs may worsen AD through type I allergy.⁴⁶

Apoptosis, or programmed death of effector cells is one of the other basic immunologic processes in the control or resolution of tissue inflammation. It has been suggested that enhanced survival of inflammatory cells in inflamed cutaneous tissues may be a factor in the establishment of chronic inflammation in AD.¹

Interleukin-4, which is found to be increased in AD, enhances apoptosis of normal human monocytes after stimulation.¹ In a study by Bratton et al, however, it has been demonstrated that cultures of PBMCs from patients with AD had a lower incidence of spontaneous apoptosis and were unresponsive to IL-4 induced apoptosis, in

contrast to the responses of monocytes from normal donors. Their findings showed that the most probable cause of inhibition of apoptosis and unresponsiveness to IL-4 was the increased GM-CSF production by circulating monocytes of patients with AD.⁴⁷

The fact that increased levels of GM-CSF mRNA were demonstrated in the inflamed tissues of AD suggests a role of increased numbers of macrophages and eosinophils in the chronic AD lesions.¹ Recent research originating from these scientific findings indicate that SsAgs inhibit apoptosis and prolong survival of AD monocytes via the stimulation of GM-CSF production.^{12,40}

Despite many scientific studies supporting the causative or triggering function of SsAg in AD, there are also a few studies that do not completely support their pathogenic role. In a controlled study by Jappe et al, the SA carriage rate was 62.9% in 35 AD patients. Only 45% of the SA strains from AD patients were found to be capable of producing SsAgs (SEB, SEC, and TSST-1). The rate was 44% in healthy nasal carriers. In addition, the proposal that SA colonization is a stimulant for IgE production could not be confirmed in this research. On the basis of the results of their study, the authors suggested that the occurrence of SA in AD is not associated with a particular group of strains and superantigen formation is not an essential prerequisite in the pathogenesis of the AD.⁴⁸ Their study does not exclude a possible role of SsAg in the acceleration of AD. The authors share this opinion.

These suggestions have been challenged by Zollner and Kaufman. According to their approach, although the frequency of SsAg-producing SA may be similar in AD versus healthy controls, these observations do not exclude its importance in the disease process. The point is that the Jappe et al study does not take into account the importance of genetic predisposition. House dust mites, for example, do not cause allergic disease in healthy controls, but are important as triggers of

respiratory allergy in atopics. Similarly, gliadin, for example, is tolerated by large majority of individuals. Nevertheless, in the presence of a defined genetic background, ie, specific HLA class II DQ and DR alleles, gliadin causes celiac disease. Thus, IgE sensitization to SsAgs occurs only in AD but not in healthy controls. Jappe et al can only conclude that in the absence of the atopic background, bacterial sAgs are not sufficient to induce AD.⁴⁹

In another study, the expression of TCR $\nu\beta$ chain was studied by means of immunohistochemical technique. In 4 out of 14 AD patients, the tendencies of preferential expression of specific TCR $\nu\beta$ were found in lesional skin. As a result, it has been suggested that SsAgs and its corresponding T cell subsets may act as causative or pathogenic factors in a *subgroup* of AD.³⁸

It is therefore not unreasonable to assert that the role of SsAgs is limited in some AD cases.

ANTISTAPHYLOCOCCAL THERAPY IN AD

Staphylococcus aureus was isolated from the lesional skin of more than 90% of AD patients for the first time in 1974.¹³ An increased carrier state of SA has been demonstrated in not only involved, but also uninvolved areas of the skin of AD cases.⁵⁰⁻⁵² There are many reports suggesting that it is reasonable to try anti-staphylococcal antibiotic therapy in patients with AD.^{14,35,51,53,55}

In a double-blind, placebo-controlled study, Lever et al reported that a significant reduction in the staphylococcal colonization correlated with the diminution of clinical symptoms in nearly all 45 patients with AD after 14 days of topical mupirocin therapy. They also showed that the patients treated with antibiotics plus corticosteroids had significantly greater improvement than the patients treated with corticosteroids alone. Although recolonization occurred during the follow-up period, reduction of clinical severity was maintained.¹⁴

Dhar et al treated 50 subjects with AD, and other dermatoses with oral

cloxacillin or erythromycin, in a controlled study. *Staphylococcus aureus* density diminished after seven days, and cleared by 21 days. Reduction of SA density was associated with clinical improvement in 48 of 50 AD patients. It was striking that 43 of 50 patients still maintained clinical improvement six months after treatment.⁵¹

Use of antiseptics, such as chlorhexidin or triclosan combined with emollients, was also found to give successful results in the treatment of larger skin areas in AD patients who did not show clinical signs of active staphylococcal infection.^{56,57}

These studies stress the importance of anti-staphylococcal antibiotic/antiseptic therapy in AD patients who show colonization with SA, even if no signs suggestive of bacterial infection are apparent.

Results of a more recent study of Lewing et al do not support the view that antibiotic therapy is helpful in AD patients who do not have any signs suggestive of bacterial infection. Fifty children with AD between 1 to 16 years old who had no signs of bacterial infection (pustules, a purulent discharge, crusting combined with weeping, crusting alone, or sudden appearance of weeping) were treated with oral flucloxacillin or placebo, in a 4-week, randomized, double-blind study. The authors revealed that flucloxacillin did not improve the clinical symptoms of AD, and only temporarily diminished staphylococcal skin colonization. Further it was also reported that methicillin-resistant strains of SA were cultured from five patients during or after oral flucloxacillin therapy.⁵⁵

We have not administered anti-staphylococcal antibiotic therapy to AD patients without any signs of cutaneous infection. Nonetheless, our observations on five moderate-to-severe AD patients revealed that oral anti-staphylococcal antibiotic therapy rapidly improved cutaneous symptoms and diminished clinical severity of AD patients who show the clinical

signs of cutaneous staphylococcal infection (unpublished data).

Today, whether the presence of SA has effects on the clinical course of AD patients without the signs of staphylococcal infection remains unclear. In our opinion, antibiotic therapy generally should be given only to patients with signs of bacterial infection, because of the following criteria:

- (1) SsAgs are only one of the triggering factors in AD which is a multifactorial disease.
- (2) Staphylococcal colonization is a constant feature of AD.
- (3) Effectiveness of antibiotic therapy in AD without signs of bacterial infection is still under discussion. It is impossible to permanently eliminate cutaneous SA colonization with antibiotic therapy. Recolonization is inevitable.
- (4) Prolonged topical/oral antibiotic therapy may cause development of antibiotic-resistant strains of SA.

In AD exacerbations, oral administration of anti-staphylococcal drugs has been shown to be very effective. The drugs of choice are the penicillin-resistant penicillins, such as cloxacillin, and the oral cephalosporins. Topical mupirocin and fusidic acid have also been shown to inhibit staphylococci.^{14,35,55}

Phototherapy has an anti-staphylococcal effect. It should be kept in mind that a combination of anti-staphylococcal management and phototherapy might be a reasonable therapeutic approach for the treatment of AD which is triggered by SsAgs. It is effective in both acute (UVA-1 or systemic PUVA) and chronic (conventional UVA/UVB or 311nm UVB) stages of the disease.^{58,59}

CONCLUSION

Even if SsAgs are not of primary importance in the pathogenesis of AD, they are recognized as one of the important triggering factors that contribute to the process of skin inflammation and acute exacerbations observed in this disease.

Atopic dermatitis is a heterogenous chronic inflammatory disorder of genetic origin which has subgroups with

different pathophysiologic mechanisms. All of this data outlined above should be evaluated in the light of this basic approach.

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CME Examination

Identification No 000-001

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CME TEST Questions

1. Extrinsic-type of pure atopic dermatitis constitute approximately:
 - a. 10–15% of all cases of atopic dermatitis
 - b. 25–30% of all cases of atopic dermatitis
 - c. 35–40% of all cases of atopic dermatitis
 - d. 40–45% of all cases of atopic dermatitis
 - e. 50% of all cases of atopic dermatitis
2. Which of the following statements is false regarding atopic dermatitis?
 - a. At least 50% of all atopic dermatitis cases have been shown to be associated with respiratory allergies.
 - b. In general, there is a correlation between IgE levels and disease activity.
 - c. Acute skin lesions demonstrate cytokine RNA patterns most consistent with a Th1 phenotype.
 - d. Neurogenic inflammation may have a role in the pathogenesis.
 - e. Allergological management is possible in mixed-type of atopic dermatitis.
3. Conventional antigens require recognition of:
 - a. $V\alpha$ and $J\alpha$ gene segments of the TCR (T Cell Receptor).
 - b. $V\alpha$, $J\alpha$ and $V\beta$ gene segments of the TCR.
 - c. $V\alpha$, $J\alpha$, $V\beta$ and $D\beta$ gene segments of the TCR.
 - d. $V\beta$ and $D\beta$ gene segments of the TCR.
 - e. $V\alpha$, $J\alpha$, $V\beta$, $D\beta$ and $J\beta$ gene segments of the TCR.
4. In the classical immune response, the amount of the activated T cells is approximately:
 - a. 0.01% to 0.1%.
 - b. 0.1% to 1%.
 - c. 1% to 10%.
 - d. More than 10%.
 - e. None of them.
5. In the superantigenic binding process, the recognition sequence for superantigens is almost entirely depends on:
 - a. $V\alpha$ only.
 - b. $J\alpha$ only.
 - c. $J\beta$ only.
 - d. $D\beta$ only.
 - e. $V\beta$ only.
6. Which of the following diseases is not mediated or triggered by staphylococcal and/or streptococcal superantigens?
 - a. Kawasaki disease
 - b. Psoriasis
 - c. Toxic shock syndrome
 - d. Toxic epidermal necrolysis
 - e. Scarlet fever
7. Which of the following is a false statement?
 - a. Highly restrictive antigen recognition component of the TCR (T Cell Receptor) does not play
 - b. Superantigens bypass intracellular processing and bind directly to the MHC class I molecule on the surface of the APC (Antigen Presenting Cell) outside the antigen binding groove.
 - c. Superantigens may activate approximately 20% of all T cells.
 - d. Superantigens are not broken down into peptides before interaction.
 - e. Superantigens cause activation of both the CD4 and CD8 subtypes.
8. The potential mechanism/mechanisms by which SsAgs (staphylococcal superantigens) may contribute the pathogenesis of cutaneous inflammation in atopic dermatitis is/are:
 - a. Reduction of apoptosis
 - b. Expansion of CLA (Cutaneous Lymphocyte Antigen) (+) T cells
 - c. Direct stimulation of APCs (Antigen Presenting Cells) and keratinocytes
 - d. a and b
 - e. All of them
9. The most important cytokine in the induction of the CLA (Cutaneous Lymphocyte Antigen) on T cells is:
 - a. IL-5
 - b. IL-12
 - c. IL-4
 - d. IL-10
 - e. IFN- γ
10. Which cytokine enhances apoptosis of normal human monocytes after stimulation?
 - a. IL-4
 - b. IL-5
 - c. IL-10
 - d. IL-12
 - e. IFN- γ
11. Onset of atopic dermatitis is within first year of life in:
 - a. 30% of cases.
 - b. 40% of cases.
 - c. 50% of cases.
 - d. 60% of cases.
 - e. 70% of cases.
12. SsAgs (staphylococcal superantigens) inhibit apoptosis and prolong survival of AD monocytes via the stimulation of:
 - a. G-CSF production.
 - b. IL-4 production.
 - c. IL-5 production.
 - d. IL-12 production.
 - e. GM-CSF production.
13. Which of the following topical antibiotic/antibiotics may be used to inhibit Staphylococci?
 - a. Mupirocin
 - b. Bacitracin
 - c. Fusidic acid
 - d. a and b
 - e. a and c
14. Which of the following is a true statement?
 - a. Staphylococcal colonization is rarely seen in atopic dermatitis.
 - b. It is possible to permanently eliminate cutaneous staphylococcus aureus colonization with oral/topical antibiotics.
 - c. Prolonged antibiotic therapy may cause development of an-

- tibiotic-resistant strains of staphylococcus aureus.
- d. PUVA therapy is effective especially in chronic atopic dermatitis cases.
- e. Topical antibiotics have been shown not to inhibit staphylococci in atopic dermatitis.
15. Provocation factors in atopic dermatitis are:
- Inhalant and food allergens, hormonal factors, and climatic/seasonal factors.
 - Inhalant and food allergens, climatic/seasonal factors, emotional factors, and hormonal factors.
 - Inhalant and food allergens, climatic/seasonal factors, emotional factors, irritating substances, and hormonal factors.
 - Inhalant and food allergens, climatic/seasonal factors, emotional factors, irritating substances, hormonal factors, and pollution.
 - Inhalant and food allergens, climatic/seasonal factors, emotional factors, irritating substances, hormonal factors, pollution and lifestyle.
16. Which is/are the coagulase-positive staphylococcus/staphylococci commonly found in humans?
- S. aureus*
 - S. epidermidis*
 - S. haemolyticus*
 - S. hominis*
 - All of them
17. Allergological management is suggested to be useful in:
- Mixed-type of atopic dermatitis and pure atopic dermatitis.
 - Mixed-type of atopic dermatitis and pure-extrinsic atopic dermatitis.
 - Pure atopic dermatitis.
 - Mixed-type of atopic dermatitis and pure-intrinsic atopic dermatitis.
 - Pure-intrinsic atopic dermatitis.
18. Which of the following is a false statement about atopic dermatitis?
- Food and inhalant allergens play a triggering role in only a subset of AD.
 - Patients treated with antibiotics plus corticosteroids have significantly greater improvement than those treated with corticosteroids alone.
 - AD is characterized by local infiltration of monocytes and lymphocytes.
 - Reduction of monocyte apoptosis is one of the important factors in cutaneous inflammation.
 - Activated eosinophils are found in significantly greater numbers of acute compared with chronic lesions.
19. Which of the following is a true statement?
- Approximately 30% of staphylococcus aureus strains which are isolated from atopic dermatitis patients have been shown to secrete superantigenic toxins.
 - SsAgs (staphylococcal superantigens) may not directly stimulate LCs (Langerhans cells).
 - Keratinocytes have been shown in vitro to potently activate T cells by expressing MHC class II molecules in the presence of superantigens.
 - TSST-1 stimulated IgE synthesis is not a T cell-dependent process.
 - It is unreasonable to assert that the role of SsAgs (staphylococcal superantigens) is limited in some atopic dermatitis cases.
20. Antistaphylococcal therapy in AD includes:
- Oral/topical antibiotics
 - Topical corticosteroids
 - UVA and UVB
 - a and c
 - All of them

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| 1. e | 6. a | 11. d | 16. d |
| 2. d | 7. d | 12. a | 17. a |
| 3. d | 8. e | 13. b | 18. c |
| 4. d | 9. a | 14. a | 19. e |
| 5. e | 10. d | 15. e | 20. c |