

Role of Superantigens in Allergic Inflammation: Their Relationship to Allergic Rhinitis, Chronic Rhinosinusitis, Asthma, and Atopic Dermatitis

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Abstract

Objectives: Our intention was to review all material published to date regarding superantigens (SAGs) and allergy from an otorhinolaryngological viewpoint to understand this association more clearly.

Methods: We identified all materials published mentioning both SAG and allergic rhinitis (AR), chronic sinusitis, asthma, and atopic dermatitis (AD) that are indexed on PubMed, Google, or the ProQuest Central databases.

Results: *Staphylococcus aureus* is a significant bacterial pathogen in humans and has the ability to produce enterotoxins with superantigenic features. The inflammatory response in allergy seen in both B cell and T cell may be attributed to SAGs. Sufferers of both allergic asthma with rhinitis and AR alone produce serological evidence of immunoglobulin E formation to SAGs produced by *S. aureus*. Perennial AR sufferers carry *S. aureus* more frequently and the presence of the organism within the nasal cavity may exacerbate perennial AR. SAG produced by *S. aureus* potentially worsens the asthmatic inflammatory response within the airway and may lead to the airways becoming hyperresponsive, as well as possibly activating T cells if asthmatic control is poor. Staphylococcal SAGs potentially increase the risk of developing chronic rhinosinusitis with nasal polyposis, additionally being a marker for more severe disease. If SAGs bring about chronic inflammatory responses in the nose and sinuses, then T cells excreting interferon-gamma may be a crucial mediator. In allergic dermatitis, *S. aureus* could be a key player in exacerbation of the condition. Even in younger pediatric patients with allergic dermatitis, allergic hypersensitivity to SAGs is frequent and may be a factor explaining how severe the condition becomes.

Conclusion: Just as SAGs are known to feature in many allergic conditions, they play their part in AR, chronic rhinosinusitis, asthma, and AD. Further research is required before the relationship between SAGs and allergy can be adequately explained.

Keywords

superantigens, allergy, allergic rhinitis, asthma, atopic dermatitis, chronic rhinosinusitis, *Staphylococcus aureus*, T-cell superantigens, B-cell superantigens

Introduction

Numerous studies of epidemiology, pathophysiology, and clinical features have demonstrated that allergic rhinitis (AR) and asthma tend to co-occur. Despite the fact that asthma affects the lower, and AR the upper, respiratory tract, the mucosae of the nose and bronchi share many features. Indeed, it is common for the bronchi to be hyperactive in nonspecific fashion even in cases of simple AR. The hypothesis that AR and asthma are the manifestations of a unitary disease affecting the entire airway draws support from the similar profiles of immunological

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involvement (both cellular and molecular) found in AR and asthma.¹ Between 85% and 95% of asthma sufferers also show features of AR,² while among those with AR, asthmatic co-occurrence is 20% to 50%.³ These observations have lead many researchers to postulate that treating AR may stop the development of asthma.

Staphylococcus aureus is a major bacteriological human pathogenic organism with the ability to synthesize coagulases, multiple highly efficacious toxins (including those of an exfoliative or epidermolytic kind), toxic shock syndrome toxin-1 (TSST-1), and enterotoxins types A, B, C through U.⁴ It is a normal inhabitant of the nasal and pharyngeal mucosae. Researchers suspect the organism of featuring in the genesis of allergic inflammatory disorders including rhinitis and atopic dermatitis (AD), while the fact that superantigens (SAGs) are important in chronic rhinosinusitis (CRS) and nasal polyp formation has been proven through research.^{5–7}

SAGs, first described by White et al.,⁸ are a distinct set of antigens produced by bacteria that can be differentiated from the usual protein or peptide antigens produced by microorganisms. They possess the ability to produce 10 000 times greater lymphocytic recruitment than occurs through the mediation of major histocompatibility complex (MHC) molecules, simultaneously potently inducing T-cell mitogenesis, even at concentrations at which conventional antigens have minimal effect (0.1 pg/mL). They can occasion shock, fever, and may be lethal in effect.⁹

How SAGs function and what their molecular structures consist of have attracted much research. In studies of allergy (as seen in asthma and AR), immunoglobulin E (IgE) to particular SAGs has been demonstrated to be present at high levels.^{4,10} Our aim was to elucidate what is known about the etiological role of SAGs in AR, allergic asthma, and sinusitis and to discover future directions for research in this field.

Methods

We identified all materials published mentioning both SAG and AR, chronic sinusitis, asthma, and AD that are indexed on PubMed, Google, or the ProQuest Central databases using the combined search terms “superantigens, allergic rhinitis,” “superantigens, asthma,” “superantigens, chronic rhinosinusitis” or “chronic sinusitis, atopic dermatitis.” The following were included: clinical trials, case-control studies, experimental studies, and reviews, while papers not centrally touching on these topics were excluded from our review. The papers were graded depending on what evidential level they achieved.¹¹

For the search combination “superantigens, allergic rhinitis,” 34 papers were retrieved, of which 12 lacked the centrality criteria. Of those remaining, 17 were reviews, 5 described research (from which 2 were at

level 4 [well-designed case-control studies], 1 was at level 5 [systematic review], and 2 were at level 6 [concerning single cases and had an experimental methodology]).

For the search combination “superantigens, asthma,” 114 papers were retrieved, of which 92 lacked the centrality criteria. Of those remaining, 9 were reviews and 13 described research (from which 3 were at level 4 [well-designed case-control studies] and 10 were at level 6 [concerning single cases]). One of the papers at level 6 was experimental in methodology.

For the search combination “superantigens, chronic rhinosinusitis,” 73 papers were retrieved, of which 28 lacked the centrality criteria. Of those remaining, 28 were reviews and 18 described research (from which 9 were at level 4 [well-designed case-control studies], 1 was at level 5 [systematic review], and 8 were at level 6 [concerning single cases]).

For the search combination “superantigens, atopic dermatitis,” 196 papers were retrieved, of which 140 lacked the centrality criteria. Of those remaining, 24 were reviews and 32 described research (from which 1 was at level 2 [evidence coming from a well-designed randomized controlled trial or several], 9 were at level 4 [a case-control study of good design], 1 was at level 5 [systematic review], and 21 were at level 6 [concerning a single case]).

Superantigens

Definition

SAGs have a relatively low molecular mass of between 19 000 and 30 000 Da and are extracellular proteins of an unusual type.¹² They remain active even despite being boiled for 1 hour, proteolytic attack (eg, trypsin), pepsin, or gastric hydrochloric acid. TSST-1 remaining on Petri dishes for more than 12 months, with consequent drying out, still has demonstrable activity.^{12–14} T-cell receptors (TCRs) are involved in the recognition of SAGs, with the variable beta (V β) chain playing a key role, and D β , J β , V α , and J α also featuring. MHC class II molecules can, in addition, provide SAG presentation, with the difference, however, that they bind to the amino acid residues beyond the usual peptide-binding domain^{9,15} (see Figure 1).¹⁶ SAGs that bind in this way produce a powerful stimulatory effect. In the early stage, this involves cytokine synthesis and excretion by T cells, leading to proliferation, other cytokine synthesis and cytotoxic reactions mediated by, for example, tumor necrosis factor-alpha (TNF- α), interferon-gamma (INF- γ), and interleukin-beta (IL-1 β), prompting a severe immunological response to occur,^{9,15,17–20} (see Figure 2).²¹

White et al.⁸ were able to isolate enterotoxin from cases where food poisoning had occurred secondary to

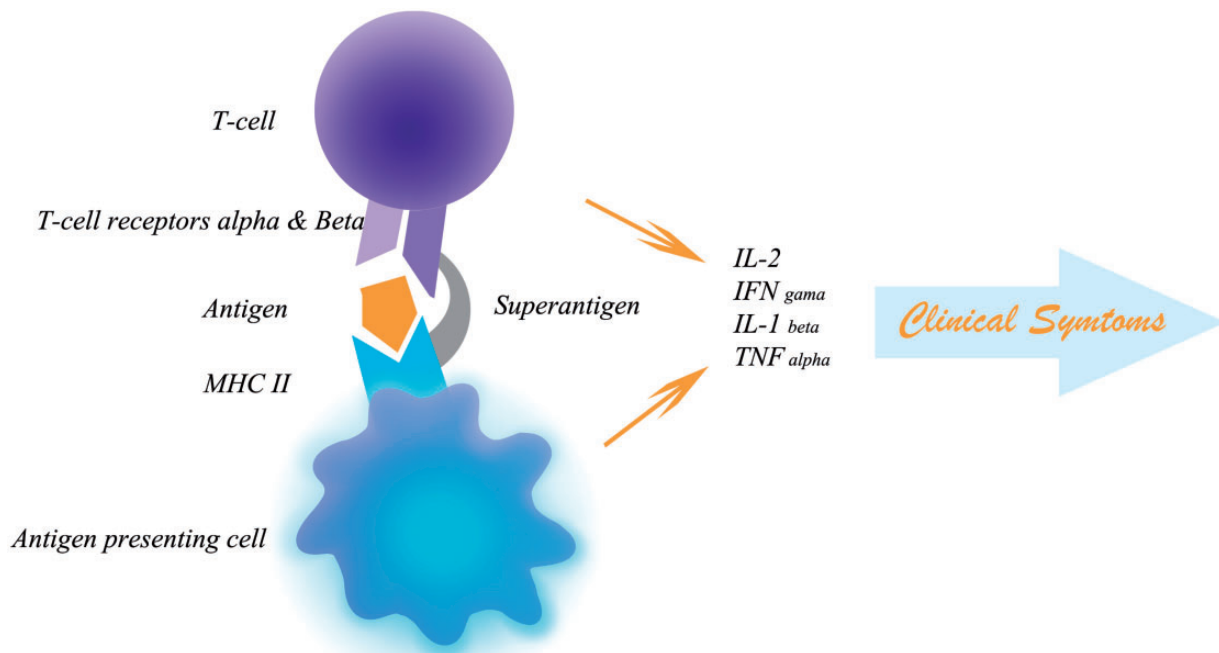


Figure 1. Superantigenic mechanism of action. Adapted from Lin and Peterson.¹⁶ IFN, interferon; IL, interleukin; MHC, major histocompatibility complex; TNF- α , tumor necrosis factor-alpha.

S. aureus. Such enterotoxins were discovered to cause CD4+ and CD8+ T-lymphocytes to release large volumes of inflammatory cytokines. Marrack et al. coined the term “superantigen” to indicate the additional potency of T-cell recruitment that was occurring. In the classical scenario, MHC class II molecules cause activation of CD4+ T-lymphocytes, while MHC class I molecules on antigen-presenting cells (APCs) are responsible for CD8+ activation. SAGs do not fit this classical scenario, as they can activate both T-cell subtypes via MHC class II molecules alone.²² Indeed, SAGs promote mitogenesis of T cells to a greater extent than any other known molecules. Bacterial SAGs, moreover, can interfere with normal antigenic responses significantly.²³

Staphylococcus aureus and Streptococci belonging to group A possess high pathogenicity for humans, a situation which can likely be attributed to their causing disease in several different ways at once. They present multiple cell surfaces and possess virulence factors of numerous kinds, including SAGs. Both *S. aureus* and Streptococci from group A produce a variety of SAGs that are distinguishable serologically.^{12–14}

Staphylococcus aureus is a major human pathogen, producing coagulases, a variety of powerful toxins such as exfoliative (epidermolytic) toxins (ExT-A and ExT-B), TSST-1, and enterotoxins (SEA, SEB, SEC, SED, SEE, SEG, SEH, SEI, SEJ, SEK, SEL, and SEM). The list does not include “SEF” since TSST-1 was initially characterized in error as “enterotoxin F.”²⁴ SAGs from *S. aureus*

feature in toxic shock syndrome, both menstrual and non-menstrual types, soft tissue infections, purpura fulminans and numerous rheumatoid diseases, Kawasaki disease, AD, and CRS.^{25,26}

Streptococci are bulky, gram-positive, coagulase-negative bacterial organisms of multiple types, some of which are commensals. In 1924, Dick and Dick²⁷ were able to isolate a toxin from a bacterial culture in a case of scarlatina, which was initially named Streptococcal pyrogenic exotoxin (SPE) (erythrogenic toxin/Dick toxin) and subsequently (in 1983) “Scarlet fever toxin” (aka SPE A). A variety of subsequent forms of the toxin were identified (including, but not limited to, SPE B, SPE C, SPE F, SPE H, SPE I, SSA, and SMEZ).²⁸ Such SAGs are generally produced by *Streptococcus pyogenes* (group A beta-hemolytic) but may also come from *Streptococcus dysgalactiae* or *Streptococcus equi* (belonging to groups C and G, respectively).²⁹ The action of SAGs on macrophages and T-helper (TH) cells results in disproportionate release of inflammatory cytokines. The ensuing pyrexia, exanthems, T-cell proliferation, and B-cell inhibition lead to further vulnerability to a number of diseases, for example, scarlatina, erysipelas, Toxic shock syndrome $\pm$ necrotizing fasciitis/myositis, guttate psoriasis, acute rheumatic fever, and acute glomerulonephritis.^{26,30}

Pathophysiology

The definition of SAGs is that they are molecules with binding activity to activated T-cells possessing MHC II

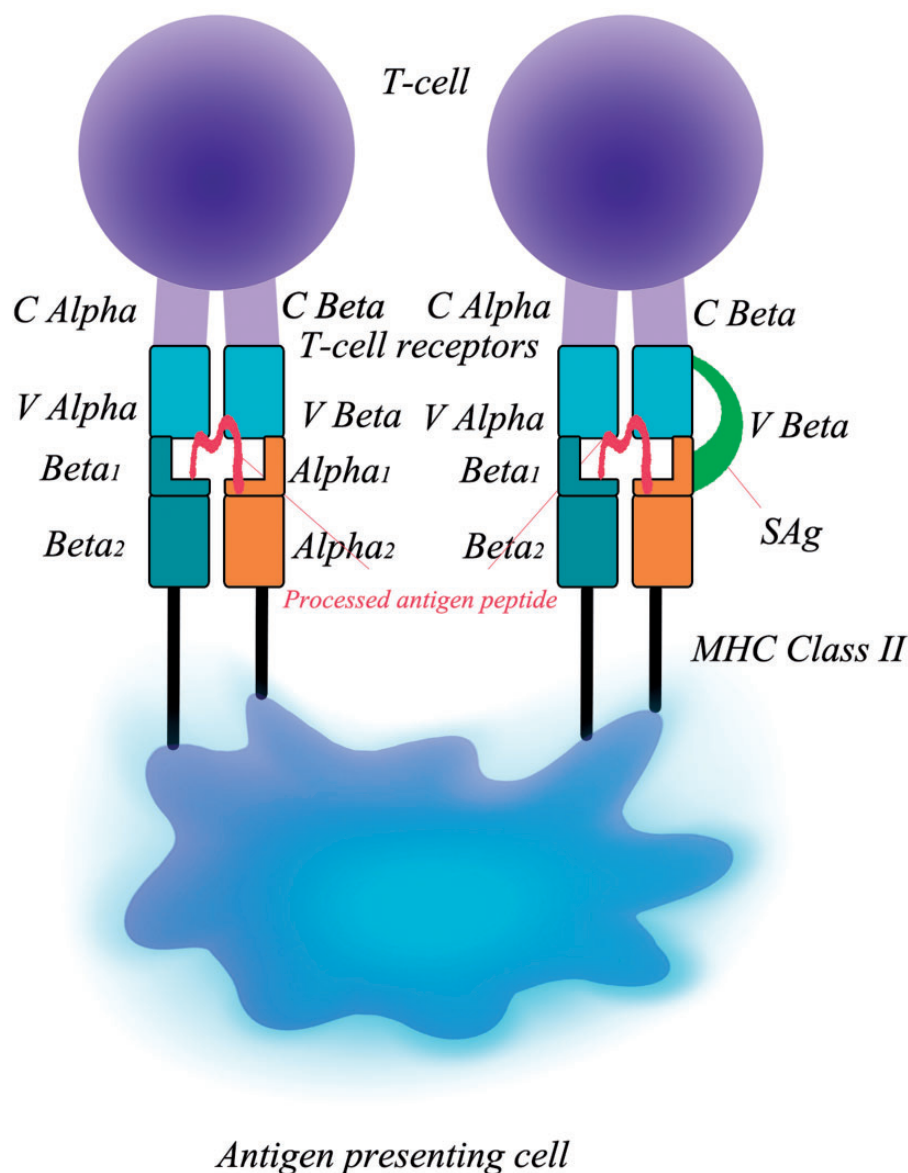


Figure 2. How SAg binds to the MHC class II molecule outside the usual antigen presentation site and the V β chain of the T-cell receptor. Adapted from Tuffs et al.²¹ MHC, major histocompatibility complex; SAg, superantigens; V α , variable alpha; V β , variable beta.

receptors as well as the V β portion of the TCR. In the living animal, SAgS interact with a number of different cell lineages that possess MHC class II receptors or the V β portion of the TCR. SAgS may be presented to T-lymphocytes by monocytes, macrophages, B-lymphocytes, and dendritic cells.³¹ To summarize, the interchange between APCs and T-lymphocytes occurs via MHC class II receptors and the TCR and leads to cytokine release and T-cell recruitment.

When SAgS are bound to APCs (eg, B-lymphocytes or macrophages), cellular alterations occur. Circulating monocytes release greater amounts of TNF- α and IL-1. Separately, B-lymphocytes undergo proliferation. Binding of SAg to MHC class II receptors leads to

B-lymphocytes and monocytes more easily adhering to other cells.

In concert with these effects, SAgS activate T cells in a disproportionately acute manner, resulting in cytokine release (IL-2, IFN- γ , and TNF) on a massive scale, an effect observable both in vitro and in vivo. A key feature of the T-cell response is that T-cell responses to SAgS fall after the initial 24 hours, while the remaining T cells proliferate some 2 to 3 days after exposure.³² Immunity against *S. aureus* and the Streptococci is believed to arise through the toxins being neutralized by immunoglobulin and complement action and the bacteria themselves being destroyed by chemotactically mediated phagocytosis. The inhibition of

immunoglobulin responses by SAGs is owed, at least to a degree, to IFN- γ overproduction by CD4+ T cells.^{33,34} Massive quantities of TNF arising from cells of the immune system exposed to SAGs result in inhibition of the migration of phagocytes to where the infection is located.^{26,35}

SAGs have an association with autoimmune disorders, as they promote the activation of T cells of an autoreactive type that possess particular V β portions. Autoimmunity can arise by T-lymphocyte activation or B-cell and T-cell interacting, both effects that SAGs can bring about. If there is a suitable genetic and environmental predisposition, the effect becomes progressive. A valuable piece of evidence comes from the way SAGs (mycoplasma arthritis-derived mitogen [MAM]) produced by *Mycoplasma arthritis* can cause arthritis in rodents. MAM activates T-lymphocytes directly as well as activating B-lymphocytes through T cells, initiating arthritis.³⁶

In humans, SAGs may promote disease in numerous ways. Toxic effects are seen with systemic shock or food poisoning directly. A pathogen may be potentiated by SAGs. SAGs can also trigger T- and B-cell activity as seen in autoimmune disorders.^{32,37}

SAGs and Allergic Inflammation

SAGs can induce T-cell mitogenesis at far lower concentrations than other immunogenic molecules known to date. Substances produced by *Staphylococci*, *Streptococci*, *Pseudomonas aeruginosa*, and *M. arthritis* are classified as SAGs. A key differentiating feature from other immunogens is the way they can be displayed on the MHC class II molecules of APCs without the need for intracellular preprocessing, prior to presentation to CD4+ or CD8+ T-lymphocytes. TCRs situated superficially on T-lymphocytes combine via linkage of the V β -chain portion of the receptor. CD4+ T-lymphocytes thereby become powerfully activated and stimulated to produce a range of cytokines.³⁸⁻⁴⁰

Following the discovery of SAGs, their role in various illnesses has been a subject of great interest. While they were found in the context of investigating food poisoning by *S. aureus*, it is now believed that they feature in many disorders involving chronic inflammation, such as asthma, eczema, and chronic sinusitis.⁴¹ SAGs have an allergenic role in that they both activate T-lymphocytes and cause immunoglobulin E specific to toxin to be released. These facts point to SAGs increasing symptomatology within allergic disorders.⁴²

SAGs in AR

The most evidence for SAGs comes from studies of *S. aureus*. These SAGs can provoke an inflammatory

reaction within the respiratory tract and demonstrably potentiate the response to inhaled allergens.⁴³⁻⁴⁵ SAG derived from *S. aureus* lengthens the time for which eosinophils survive and increases their activation through cytokine release. In vitro studies confirm that TH1- and TH2-cell mitogenesis induced by SEB is increased further by eosinophilic involvement.⁴⁶ This supports the notion that eosinophils, in addition to their part in promoting allergic inflammatory responses, also potentiate T-cell activation brought about by SAG, particularly where *S. aureus* is carried intranasally.⁴¹

Around 25% of people carry *S. aureus* intranasally and around 20% of pathogenic infections with Staphylococci arise from organisms already present on the individual.⁴⁷ Studies confirm that individuals with perennial AR have higher rates of *S. aureus* carriage intranasally.⁴⁸ Rossi and Monasterolo⁶ found IgE specific to SEA, SEB, SEC, SED, and TSST-1 was elevated serologically, as was eosinophil cationic protein in cases of chronic AR $\pm$ allergic asthma. Total IgE and IgE specific to house dust mite is also expected to be elevated significantly in such patients.^{49,50} Individuals with chronic AR who also demonstrated *S. aureus* carriage had a ratio of nasal IL-13 to IFN- γ that was elevated compared to those with chronic AR but no staphylococcal carriage.⁵⁰ Taken as a whole, this evidence reveals that SAGs present due to chronic carriage worsen inflammation linked to immunoglobulin E and eosinophils.

Table 1 lists studies that are concerned with SAGs and AR.

SAGs in Asthma and Chronic Obstructive Pulmonary Disease

Asthma is a persistent disorder involving inflammation of the respiratory tract which manifests as wheeze, shortage of breath, and coughing episodes. By contrast, chronic obstructive pulmonary disease (COPD) features irreversible restriction of the airways. Bachert et al.⁵ report on a number of studies indicating that SAGs are prominent in the disease mechanisms of upper and lower respiratory disorders through worsening eosinophilic inflammation and the production of IgE.

The key immune cellular components of asthma are eosinophils, mast cells, and CD4+ T cells. However, in COPD, it is neutrophils, macrophages, and CD8+ T cells that are most prominent.⁵⁴ IL-4, IL-5, IL-9, and IL-13 are all raised in asthmatics as a result of the CD4+ predominance.⁵⁵ IL-8, TNF- α , IFN- γ , and leukotriene B4 are preeminent in COPD as a result of CD8+ predominance.⁵⁶ Notably, CRS and COPD share many features in common with asthma and sinusitis with nasal polyp formation in terms of cytokine response.

Table 1. SAGs and AR.

Study	Level of Evidence ^a	Conclusion
Liu et al. ⁴	4	IgE specific to <i>Staphylococcus aureus</i> SAGs can be found in cases of allergic asthma with rhinitis and AR alone.
Moon et al. ⁵¹	6 Experimental	Cytokine production (IL-1 β , IL-4, IL-6, and IFN- γ) is higher in nonmutant mice exposed to SEB than in mice from the AR (OVA) group.
Pastacaldi et al. ¹⁰	5	Results confirmatory for SAGs playing a part potentially in respiratory disorders of allergic type.
Shiomori et al. ⁴⁸	4	Patients with chronic AR carry <i>S. aureus</i> more frequently, and this carriage may worsen the illness.
Yang et al. ⁵²	6 Experimental	Mice had sensitivity induced by a combination of SWF and OVA (leading in the latter case to a maximum titer of specific IgE of 1:64). Sinus washout fluid from a case of sinusitis positive for SEB, when administered to the gut led to the colon allowing greater passage of large proteins into the mucosa.
Fakhri et al. ⁵³	6 Experimental	First, tissue was harvested from the inferior conchae of the nose from individuals who were either nonallergic or allergic to ragweed. SAG in both cases then induced more production of GRbeta.

Abbreviations: AR, allergic rhinitis; GRbeta, glucocorticoid receptor beta; IFN, interferon; IgE, immunoglobulin E; IL, interleukin; OVA, ovalbumin; SAGs, superantigens; SEB, staphylococcus-derived enterotoxin B; SWF, sinus wash fluid.

^aLevel IV: Evidence from well-designed case-control or cohort studies; Level V: Evidence from systematic reviews of descriptive and qualitative studies (meta-synthesis); Level VI: Evidence from a single descriptive or qualitative study.¹¹

Within humans, that SAGs have direct effects on lower respiratory disorders is becoming increasingly evident. Some research has found a significant elevation in IgE specific to SAGs in those with severe asthma than in healthy controls. The level of total IgE detected serologically and the degree of eosinophilic inflammation were found to be positively correlated.⁵⁷

Hauk et al. examined levels of V β from bronchoalveolar lavage taken from cases of asthma where control was poor. V β was overexpressed in CD8+ T cells, indicative of their being activated by staphylococcal enterotoxins.⁵⁸ The study reveals that SAGs of unknown type stimulate T cells in such asthma cases.

Hellings et al.⁴³ investigated how *S. aureus* enterotoxin (SEB) functions using a rat model and nasal and bronchial aspiration. The bronchi were infiltrated with an eosinophilic inflammatory exudate and the bronchial tissue expressed messenger RNA for IL-4, IL-5, IFN- γ , IL-12, p40, eotaxin-1, and transforming growth factor- β , thereby showing that SEB has a part in this model of human asthma.

Sixty-two percent of cases of severe asthma had serology that revealed IgE to specific staphylococcal SAGs, that is, SEA, SEC, and TSST-1. For mild asthma and nonasthmatic controls, the figures were 41% and 13%, respectively.⁴ There is a correlation between the grade of asthma and possessing specific IgE to particular SAGs.⁵⁹ A different study replicated the result in COPD cases, revealing raised levels of SEA, SEC, and TSST-1.⁶⁰ Table 2 lists the studies related to SAGs and asthma.

SAGs in Chronic Sinusitis

CRS is frequently encountered by otorhinolaryngologists, being subdivided into CRS with nasal polyp (CRSwNP) formation and CRS without polyposis. Acute rhinosinusitis may occur following particular environmental conditions in individuals with predisposing genetic tendencies and can morph into the chronic form (CRS). A large number of factors may be involved etiologically in CRS, among which researchers now add SAGs derived from *S. aureus* which has colonized the nasal lining, especially in cases where polyps occur. Numerous researchers agree that for cases of nonpolyptotic CRS, the rate of *S. aureus* colonization is 27.3%, while for CRSwNP, it is 63.6%.⁷² Exotoxins derived from *S. aureus* can function like SAGs in the nasal lining in CRS cases. Immunoglobulin E specific to the exotoxins promotes allergic inflammation, and this, in turn, causes polyps to form within the nose.⁷³ *Staphylococcus aureus* thereby plays an active role in CRS through the enhanced IgE response within the nose and the formation of polyps.⁷⁴

Numerous studies have been undertaken to comprehend how exactly *S. aureus* works within CRSwNP. In cases of CRSwNP, it is usual for colonization with *S. aureus* and for serological evidence of IgE specific to staphylococcal SAGs to be at higher levels than in healthy controls, showing the organism has an effect on etiology of the disease and on how severe it becomes.⁷⁵ Just how this occurs, though, remains unknown. Thunberg et al.⁷⁶ observed that cases of CRSwNP have heavier *S. aureus* carriage than where

Table 2. SAg and Asthma.

Study	Level of Evidence ^a	Conclusion
Filho et al. ⁶¹	6	In a cohort of patients, the detection rate for SEA, SEB, SEC, and TSST was 43.7%. An association between SAg and how severe asthma is was not statistically significant.
Kerzel et al. ⁶²	6	There is a range of specific IgE expression by pediatric cases of allergy. Preschool individuals who suffered from eczema had their IgE transcripts compared with childhood asthmatic sufferers: the transcripts had lower levels of mutation, less restricted to particular clones, and do not suggest particular antigens. The results support the idea that SAg activates a maturation and selection response in IgE expression in cases of eczema.
Tomassessn et al. ⁶³	6	IgE specific to <i>Staphylococcus aureus</i> enterotoxin is frequently seen in European general populations. The risk factors are not the same as those for developing IgE to airborne allergens. This research was the first to show that enterotoxin-specific IgE has a significant and independent association with asthma in unselected populations.
Losol et al. ⁵⁹	4	SEA can provoke a specific and generalized IgE response that is multiplied by the polymorphic (A to G) section of the IL-5 promoter at position 746. This may then mediate a response in which adults with asthma have hyperresponsive airways.
Krysko et al. ⁶⁴	6 Experimental	The authors permit deeper understanding of how SAg influences the way airways react in the case of allergy. The elements of asthma that happen due to OVA and SEB (eosinophilic infiltration of the bronchi, goblet cell multiplication, specific IgE to OVA and dendritic cell proliferation) do not depend upon IL-1R. Nonetheless, without IL-1R CD4+ cells do not gather nor do TH2 cells secrete cytokine.
Bachert et al. ⁶⁵	4	How severe asthma is can be predicted from the presence of IgE against <i>S. aureus</i> enterotoxin but not from the presence of IgE to inhaled antigens. The authors suggest that circulating IgE to enterotoxin can be interpreted as showing <i>S. aureus</i> SAg are intrinsic to the pathogenesis of severe asthma.
Kowalski et al. ⁶⁶	6	The average level of IgE to enterotoxin in severe asthmatics is 3 times higher than in nonsevere asthmatic ($P=.01$). IgE to enterotoxin has a significant association with markers of low respiratory functionality (decreased FEV ₁ , FEV ₁ /FVC, and MEF 25/75) plus with airways being more easily dilated following albuterol administration.
Pérez Novo et al. ⁶⁷	6	If patients have asthma with nasal polyposis, SEB activates the inflammatory response of both TH1 and TH2 cells, whether or not hypersensitivity to aspirin coexists. Foxp3, if present in low levels, as seen in asthmatics with nasal polyposis, may be instrumental in the response, as may upregulated TNFRS18-L in monocytes and the precursors of the dendritic cell.
Lee et al. ⁶⁸	4	Authors suggest SAg from <i>S. aureus</i> in asthmatics may add to inflammation within the airways and their tendency to become hyperresponsive.
Liu et al. ⁶⁹	6	Authors suggest SEB SAg within the sinuses may be an essential component of the lower airways developing hypersensitivity.
Suh et al. ⁷⁰	6	Nasal polyp tissue was homogenized and ECP levels checked. These were greater in asthmatic patients intolerant to asthma than ECP levels in those who tolerated the drug ($P<.02$). Tryptase, IL-5, and sIL-2R levels did not differ. IgE as a whole, and IgE targeting both SEA and SEB existed in some samples from both groups of patients. <i>Staphylococcus aureus</i> SAg may be provoking eosinophilic infiltration in nasal polyps, an effect enhanced in those asthmatics without aspirin sensitivity.
Smart and Kemp ⁷¹	6	Peripheral blood circulating mononucleocytes were stimulated polyclonally (<i>S. aureus</i> SAg, SEB, and 2 inhaled antigens, house dust mite and rye grass pollen, plus a food allergen, OVA) in 2 groups: 36 child cases of allergies (asthma, eczema, and hay fever) and 35 healthy controls.
Hauk et al. ⁵⁸	6	Where asthma is insufficiently controlled, SAg may cause activation of T-lymphocytes.

Abbreviations: ECP, eosinophil cationic protein; FEV, forced expiratory volume; FVC, forced vital capacity; IgE, immunoglobulin E; IL, interleukin; MEF, maximum expiratory flow; OVA, ovalbumin; SAg, superantigens; SEA, staphylococcus-derived enterotoxin A; SEB, staphylococcus-derived enterotoxin B; SEC, staphylococcus-derived enterotoxin C; TH, T-helper; TSST, toxic shock syndrome toxin.

^aLevel IV: Evidence from well-designed case-control or cohort studies; Level VI: Evidence from a single descriptive or qualitative study.¹¹

Table 3. SAgS and CRS.

Study	Level of Evidence ^a	Conclusion
Cheng et al. ⁸²	4	CRSwNP may be promoted by topical allergy, separately from <i>Staphylococcus aureus</i> -derived enterotoxin SAgS, which, however, may have importance in understanding how the condition does develop.
Chen et al. ⁸³	6	<i>Staphylococcus aureus</i> enterotoxins, SEA, SED, and SEE, were radioactively labeled and used to locate one-by-one B-lymphocytes with specific antibodies using a fluorescence-activated cellular sorting technique. The cells were derived from nasal polyps of cases of aspirin-exacerbated respiratory disease. Basophils can become activated in 2 ways: as usual, through antigen binding to CDRs; but also in superantigenic fashion by binding to the framework region of anti-SEE IgE, thus producing complexes of IgE targeting SEE and FcεRI.
Mruwat et al. ⁸⁴	6	Discusses what part PLA2 plays in respiratory diseases. Argues for blockade of secretion of PLA2 as a way to treat CRS among other airway diseases.
Clark et al. ⁸⁵	6	Research observes that cases of AFRS have higher carriage rates of <i>S. aureus</i> than other types of CRSwNP. Comments on role of <i>S. aureus</i> in modifying CRSwNP.
Fakhri et al. ⁸⁶	6	SAgS prevent explanted tissue from the nose of allergy sufferers from responding to steroids by increasing levels of the glucocorticoid receptor beta. Concludes that the overexpression occurs locally in association with IL-2 and IL-4 messenger RNA translation.
Ou et al. ⁷⁵	5	SAgS from <i>S. aureus</i> may contribute to the risk of CRSwNP and influence how severe it becomes.
Foreman et al. ⁸⁷	4	Newly emerging evidence points toward biofilms produced by <i>S. aureus</i> biasing the immune reaction to a TH2-orchestrated response not dependent on SAgS.
Cho et al. ⁸⁸	4	If SAgS provoke a persistent inflammatory response in the nose and sinuses (ie, CRSwNP), then T-cell production of IFN-γ is significant.
el-Fiky et al. ⁸⁹	4	Calls for a deeper appreciation of SAgS and how they provoke CRS as essential to identify methods of mitigating their effects and treating the disease adequately.
Wang et al. ⁹⁰	4	Cases with evidence of SAg contact had high levels of T-lymphocytes with Vβ expressed. Those with positivity for SEB had especially marked levels of Vβ 3, 14, 15, 17, and 20. Those with positivity for TSST-I had especially marked levels of Vβ 2 and 6.1 to 6.3. Rates were compared with specimens showing no SAg contact.
Wang et al. ⁹¹	4	<i>Staphylococcus aureus</i> -derived SAgS are linked with the expression of T-cell receptor Vβ subtypes in nasal polyps. CRSwNP may be linked pathogenetically to SAgS.
Fan et al. ⁹²	4	<i>Staphylococcus aureus</i> could only be grown from 3 specimens of secretion from the middle meatus, one of which was a case of nasal polyposis, the other 2 CRS. Three groups examined had no statistically significant differences for specific IgE to staphylococcal enterotoxin (detected by fluorescence), tissue IgE, or ECP. Thus further research would be needed to prove SAg involvement in nasal polyp formation.
Douglas et al. ⁹³	4	SEB from <i>S. aureus</i> stimulates circulating lymphocytes to provide an inflammatory response. Fungal extracts may work in synergy with SEB.
Wang et al. ⁹⁴	6	CRSwNP cases correlate with <i>S. aureus</i> SAgS. SAgS may be involved in the etiology of CRSwNP.
Damm et al. ⁹⁵	6	Cell culture of the nasal epithelium shows immunological responses to staphylococcal enterotoxins, providing additional evidence for the “SAg hypothesis” of CRS.
Tripathi et al. ⁹⁶	6	In 7 of the 12 cases (58.3%) of nasal polyps, SAgS were found to produce an effect locally. If IgE specific to enterotoxin is found serologically, Vβ expansion is found to be positively correlated.
Seiberling et al. ⁸⁰	4	Twenty-nine cases of CRSwNP were tested for enterotoxin SAgS, 14 of which were positive. SEB and TSST-I were the most frequent SAgS found.
Tripathi et al. ⁹⁷	6	Cases of CRSwNP have higher levels of IgE specific to toxins from Streptococci or <i>S. aureus</i> than expected, a fact suggestive of a role of such SAgS in the formation of CRSwNP.
Bernstein et al. ⁸¹	6	SAgS (enterotoxins) might be activating lymphocytes and thereby causing release of inflammatory cytokines that enhance the activity of the 3 cell types most often found in nasal polyps, that is, lymphocytes, eosinophils, and macrophages.

Abbreviations: AFRS, allergic fungal rhinosinusitis; CDR, complementarity-determining region; CRS, chronic rhinosinusitis; CRSwNP, CRS with nasal polyposis; ECP, eosinophil cationic protein; IFN, interferon; IgE, immunoglobulin E; IL, interleukin; PLA2, phospholipase A2; SAgS, superantigens; SEA, staphylococcus-derived enterotoxin A; SEB, staphylococcus-derived enterotoxin B; SED, staphylococcus-derived enterotoxin D; SEE, staphylococcus-derived enterotoxin E; TH, T-helper; TSST, toxic shock syndrome toxin; Vβ, variable beta.

^aLevel IV: Evidence from well-designed case-control or cohort studies; Level V: Evidence from systematic reviews of descriptive and qualitative studies (meta-synthesis); Level VI: Evidence from a single descriptive or qualitative study.¹¹

Table 4. SAgS and AD.

Study	Level of Evidence ^a	Conclusion
Lin et al. ¹⁰⁴	6	Although they are phenotypically T cells of regulatory type, T-lymphocytes that express CD4 and Foxp3 and home to the skin act like TH2 cells to effect responses following <i>Staphylococcus aureus</i> SAg contact, and this may exacerbate allergic inflammation in the skin.
Shin et al. ¹⁰⁵	6	It is hypothesized that a localized IgE-mediated immune response to <i>S. aureus</i> SAgS, particularly SEA, helps explain why allergic inflammatory processes are persistent in the adenoids of children with allergy.
Semic-Jusufagic et al. ¹⁰⁶	6	Compares serological IgE profiles of healthy children with those suffering from AD and wheezing. More severe disease correlates with higher sensitization to SE toxins.
Nissen et al. ¹⁰⁷	4	Enterotoxins from Staphylococci may have specific allergenic functions and lead to the production of IgE that worsens cutaneous inflammation in a subset of eczema sufferers.
de Wit et al. ¹⁰⁸	5	Compared to healthy controls, eczema patients exhibit specific IgE-mediated responses to Staphylococcal SAgS with raised frequency, which helps confirm a role for <i>S. aureus</i> in the development of eczema.
Nowrouzian et al. ¹⁰⁹	6	Specific <i>S. aureus</i> strains, with a particular genetic mix for SAgS and adhesin, when they colonize the gut, are associated with lower levels of AD. In infants, these strains may stimulate immune responses and cause the immune system to mature.
Orfali et al. ¹¹⁰	4	Evidence points to the contributory function of IgG4 and IgE immunoglobulins, production of which is provoked by <i>S. aureus</i> SAgS, in the development of eczema.
Rojo et al. ¹¹¹	4	How severe eczema is may depend on the bacterial genetics of <i>S. aureus</i> for more than just SAgS. SasG and scn may be pertinent. These genes affect when eczema develops and how severe it becomes.
Nada et al. ¹¹²	6	Staphylococci may be significant in worsening cases of eczema. Preventing skin affected by allergy from being colonized by <i>S. aureus</i> may be the prime way to prevent SAg-related immunological responses occurring.
Kozman et al. ¹¹³	6	SAg from Staphylococci is insufficient in itself to explain the heightened cutaneous inflammation seen in cases of childhood eczema that have <i>S. aureus</i> infection.
Ong et al. ¹¹⁴	6	Among young children with mild-to-moderate eczema, older age correlates with IgE hypersensitization to microbes, including <i>S. aureus</i> SAgS.
Leung et al. ¹¹⁵	2	For a group of cases which lacked sensitivity clinically to CS, how severe eczema was correlated significantly and positively with <i>S. aureus</i> exposure.
Ong et al. ¹¹⁶	6	It is frequent to observe allergic sensitivity to <i>S. aureus</i> SAgS in sufferers of mild-to-moderate eczema, even where the patient is a young child. This hypersensitivity may be linked to how severe the eczema becomes.
Schlievert et al. ¹¹⁷	6	There appears to be a selection process favoring <i>S. aureus</i> strains that produce more SAgS, as seen in their overrepresentation among isolates from cases of eczema that are steroid resistant compared with control groups. SAgS may give the bacteria a selective advantage in colonization.
Fukushima et al. ¹¹⁸	6	PBMCs from cases of severe eczema are less sensitive to FK506, and the corresponding plasma anti-TSST-I IgE levels are raised versus those from mild eczema cases. One reason for PBMCs to be less sensitive to FK506 is SAg. Individualized treatment would involve consideration of both sensitivity to the drug and serological evaluation of anti-TSST-I IgE.
Kim et al. ¹¹⁹	6	Keratin-producing skin cells from eczematous areas have a seemingly different response to Staphylococcal SAgS. The overproduction of inflammatory cytokines may be part of how eczema develops.
Ou et al. ¹²⁰	6	While Treg cell numbers are raised significantly in eczema sufferers, the Treg cells retain their usual immunosuppressive function. Nonetheless, after contact with SAgS, this function is lost. This may be evidence for a previously unknown way SAgS increase the activation of T-lymphocytes in cases of eczema.
Lin et al. ¹²¹	4	Inhibiting naturally occurring IL-4 caused CD4+ T-lymphocytes that respond to SEB to undergo apoptosis. This finding may point to new understanding of how Staphylococcal SAgS produce chronic and more severe inflammation of the skin in eczema.
Nomura et al. ¹²²	6	The reason inflammation is so severe in advanced eczema was reasoned to be allergic inflammation acting alongside colonizing <i>S. aureus</i> capable of producing SAg. Analysis of the cytokine response revealed a TH2-mediated reaction.

(continued)

Table 4. Continued

Study	Level of Evidence ^a	Conclusion
Matsui et al. ¹²³	6	It is the absolute number of <i>S. aureus</i> organisms present that determines whether eczema develops rather than simply whether these organisms produce SAg.
Lin et al. ¹²⁴	4	Posits a role for SEA and SEB in persistent inflammation and worsening of eczema via an IgE-orchestrated inflammatory response.
Zollner et al. ¹²⁵	4	It is proposed that <i>S. aureus</i> strains producing SAg have a positive association with more severe eczema. However, as SAg is not found just in eczema cases, and not all eczema cases have SAg, there may be extra factors influencing the pathogenesis.
Bunikowski et al. ¹²⁶	6	Exotoxins from <i>S. aureus</i> can influence how severe eczema is and how T cells infiltrate the dermis.
Campbell and Kemp ¹²⁷	4	How the immune system in AD responds to SEB affects colonization and thus how exposure to SAg occurs. Eczema is not due to a failure to produce anti- <i>S. aureus</i> immunoglobulins.
Strickland et al. ¹²⁸	6	T-lymphocytes that had homed to skin, presumably in response to SAg had their TCR B variable genes cloned and sequenced. This was done for 3 cases. The sequencing showed polyclonality, consistent with response to SAg. SAg influences pathogenesis by raising the numbers of memory T-lymphocytes, which can home to eczematous areas and undergo activation.
Bunikowski et al. ¹²⁹	6	Becoming sensitized to Staphylococcal SAg may influence disease progression. IgE to SEA/SEB is a marker of disease severity and may have value in characterizing cases involving severe eczema in children.
Torres et al. ¹³⁰	6	In active cases of eczema, skin-homing T cells in the circulation have a raised number of cells with TCR V β regions specific to <i>S. aureus</i> . Thus, <i>S. aureus</i> SAg may cause increased CLA+ T-cell numbers, or at least trigger their circulating.
Campbell and Kemp ¹³¹	6	If patients have impairments in producing IFN- γ in response to <i>S. aureus</i> , they may be unable to eradicate <i>S. aureus</i> from the skin. The ongoing presence of the bacterium would then promote inflammation via persistent activation of T cells and the secretion of inflammatory signals.
Yudate et al. ¹³²	4	That enterotoxins from <i>S. aureus</i> function as SAg are suggested by the following effects: circulating T cells proliferate oligoclonally, each clone responds readily, and V β segments are restricted in expression after SEA exposure.
Tanaka et al. ¹³³	4	Circulating white blood cells from 21 cases of eczema and 14 healthy individuals were cultured together with ideal levels of <i>Candida albicans</i> antigen and SEA/SEB. The reduced proliferation of the white cells was especially apparent in cases of a raised RAST score for <i>C. albicans</i> antigen. These findings support the notion that patients with eczema specifically do not respond to <i>C. albicans</i> antigen.
Hofer et al. ¹³⁴	6	SAg from <i>S. aureus</i> can, even at levels at which minimal IFN- γ is produced, promote the formation of IgE by PBMCs in patients with eczema. Staphylococcal enterotoxins may be boosting IgE levels in eczema.
Lester et al. ¹³⁵	6	TSST-I, the model SAg, utilizes various ways to control the production of IgE in eczematous (rather than normal, healthy) individuals. Anti-IFN- α can reverse the effect of TSST-I, which is to suppress the production of IgE in PBMCs from eczematous individuals. However, anti-IFN- γ cannot do so. This leads to the conclusion that TH1 cells are defective in eczema and monocytes are acting in a more active role.

Abbreviations: AD, atopic dermatitis; CLA, cutaneous lymphocyte antigen; CS, chronic sinusitis; IFN, interferon; IgE, immunoglobulin E; IgG, immunoglobulin G; IL, interleukin; PPMC, peripheral blood mononuclear cell; RAST, radioallergosorbent test; SAg, superantigen; SE, staphylococcal enterotoxin; SEA, staphylococcus-derived enterotoxin A; SEB, staphylococcus-derived enterotoxin B; TCR, T-cell receptor; TH, T-helper; TSST, toxic shock syndrome toxin; V β , variable beta.

^aLevel II: Evidence obtained from at least one well-designed randomized controlled trial (RCT) (eg, large multisite RCT); Level IV: Evidence from well-designed case-control or cohort studies; Level V: Evidence from systematic reviews of descriptive and qualitative studies (meta-synthesis); Level VI: Evidence from a single descriptive or qualitative study.¹¹

symptoms of CRSwNP are absent, both in the nose and the maxillary sinus. But multiple studies^{77,78} have asserted that the *S. aureus* found in healthy carriers and symptomatic CRSwNP cases does not differ in either genetic makeup or in the potency of the SAg

produced by the organism. Kern et al.⁷⁸ argue that SAg do not initiate CRSwNP, but just affect how the disease develops, as the molecular mechanisms in the disease are not specific to *S. aureus*. A number of factors relating to the host, rather than the bacterium may

remain to be discovered, and this area is in need of exploration.

One hypothesis is that *S. aureus*, when it colonizes the host, provokes localized eosinophilic inflammatory responses and thus speeds up the process of polyposis.⁷⁹ Seiberling et al.⁸⁰ found an association between CRSwNP and the presence of staphylococcal exotoxin plus raised eosinophil counts. Bernstein et al.⁸¹ assert that it is injury to the side wall of the nose caused by *S. aureus* toxicity that leads to vast increases in eosinophils, macrophages, and lymphocytes, which are the cell populations frequently observed in multiple polyp formation. Table 3 lists those studies that relate to SAGs and chronic sinusitis.

SAGs and AD

AD is a common dermatological disorder of childhood that involves long-term cutaneous inflammation that is pruritic in nature. Other allergic disorders may present with eczema as their first symptom.^{98,99} Over half of the eczema sufferers go on to become asthmatic, and around three-quarters will have hay fever subsequently.¹⁰⁰

A finding of significance in allergic dermatitis is that IgE levels are raised. As over 90% of eczema patients are colonized by *S. aureus* and IgE against *S. aureus* SAGs has been identified in such a group, the suggestion that staphylococcal exotoxin may be etiological has been made¹⁰¹ and much research on this hypothesis has subsequently been undertaken.

The level of detected IgE to *S. aureus* SAGs correlates strongly with how severe eczema becomes.^{102,103} Cutaneous inflammation leads to greater levels of colonizing *S. aureus*, and SAGs have an activating effect on TH2 cells plus macrophages, thus worsening the inflammation.¹⁰³ Table 4 lists research related to SAGs and AD.

Conclusion

Hay fever, CRS, asthma, and eczema are associated strongly from an epidemiological perspective, but what the common factor is remains a matter of great interest. SAGs are believed to feature in both upper and lower respiratory tract illnesses. *Staphylococcus aureus* is among the most frequent pathogenic bacterial organisms to afflict human beings, and it can produce enterotoxins with superantigenic features. SAGs themselves are unusual molecules of low molecular weight that lack glycosylation. Their involvement in many different allergic disorders, including hay fever, CRS, asthma, and eczema, has now been established.

Serological investigations show that IgE specifically directed against *S. aureus* SAGs are found in cases of allergic asthma with rhinitis and AR on its own. Perennial hay fever results in greater carriage of

S. aureus, which in turn may worsen the hay fever where the bacterium is present in the nose. Associated SAGs feasibly influence inflammatory response within the airways and make the bronchi become hyperresponsive. T cells may become active in asthmatics with poor disease control through SAGs. The risk of developing CRSwNP rises if SAGs are present, and they also influence how severe the disease becomes. Where inflammatory responses in the nose and sinuses have been brought about by SAGs, T cells secreting IFN- γ may be central to the process. In eczema, too, *S. aureus* might well function to worsen the disease. Becoming allergically hyperresponsive to *S. aureus* SAGs occurs frequently, even in the youngest patients with mild-to-moderate eczema. This hyperresponsivity may, in turn, influence how severe the disease becomes. Preventing colonization of affected skin areas by *S. aureus* is thus a key to damping down cutaneous inflammation triggered by allergic responses to SAGs. New studies need to be undertaken to understand more fully the role of SAGs in allergies.

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Authors' Contributions

Nuray Bayar Muluk involved in the planning of the literature survey, writing of the manuscript, and submission. Fazilet Altın involved in the planning of the literature survey and editing the language. Cemal Cingi involved in the planning of the literature survey.

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