S. aureus and IgE-mediated diseases: pilot or copilot? A narrative review

Journal:	*Expert Review of Clinical Immunology*
Manuscript ID	ERM-2022-RT-0047.R1
Manuscript Type:	Review
Keywords:	Staphylococcus aureus, IgE, type 2 inflammation, omalizumab, chronic rhinosinusitis with nasal polyps, asthma, chronic spontaneous urticaria, atopic dermatitis

S. aureus and IgE-mediated diseases: pilot or copilot? A narrative review

Abstract

Introduction. *S. aureus* is a major opportunistic pathogen that has been implicated in the pathogenesis of several chronic inflammatory diseases including bronchial asthma, chronic rhinosinusitis with nasal polyps (CRSwNP), chronic spontaneous urticaria (CSU), and atopic dermatitis. *S. aureus* can induce the production of both polyclonal and specific IgE that can elicit an inflammatory cascade.

Areas covered. The link between the sensitization to *S. aureus* enterotoxins and the severity of several chronic inflammatory diseases is reviewed in detail, as well as its therapeutic implications.

Expert opinion. An anti-IgE strategy to inhibit *S. aureus* enterotoxins would be a valid approach to treat several endotypes of severe asthma, CRSwNP and CSU in which IgE against *S. aureus* enterotoxins should represent, not only a marker of severity of the diseases but also a target of a treatment.

Keywords: *Staphylococcus aureus*, IgE, type 2 inflammation, omalizumab, chronic rhinosinusitis with nasal polyps, asthma, chronic spontaneous urticaria, atopic dermatitis.

Article highlights:

- Colonization with *S. aureus* has been associated with bronchial asthma, chronic rhinosinusitis with nasal polyps (CRSwNP), chronic spontaneous urticaria (CSU), and atopic dermatitis.
- *S. aureus* can be an IgE-inducing pathogen and IgE against *S. aureus* enterotoxins can induce the production of both polyclonal and specific IgE that can elicit the inflammatory cascade.
- A link between sensitization to *S. aureus* enterotoxins and the severity of these diseases has been shown and an anti-IgE strategy appears to be a valid approach to treat the IgE-mediated endotypes of severe asthma, CRSwNP and CSU.
- The anti-IgE agent omalizumab is currently the only biological agent that specifically targets IgE approved for the treatment of severe asthma, CRSwNP and CSU.
- In CRSwNP and CSU, omalizumab can be prescribed regardless of the presence and nature of the allergic sensitization, while in severe asthma omalizumab can be prescribed only to patients sensitized to perennial allergens.
- There is a need to measure specific IgE to *S. aureus* enterotoxins in severe asthmatic patients because, in our opinion, *S. aureus* enterotoxins can be considered as perennial allergens.
- In conclusion, *S. aureus* in patients sensitized to staphylococcal enterotoxins should be considered as a driver of pathology and potential target for treatment.
- Further studies to better assess the role of *S. aureus* in severe asthma, CRSwNP, CSU and atopic dermatitis are warranted.

1.0 Introduction

Staphylococcus aureus is a major opportunistic pathogen that is highly prevalent in humans causing both invasive infections and toxin-mediated diseases [1]. *S. aureus* is associated with an increasing number of healthcare-related infections, especially infective endocarditis and device-related infections, as well as community-related skin and soft tissue infections [2]. In addition to the skin and intestine, the nostrils and throat are among the most common sites of colonization [3,4]. It is estimated that around one-fourth to one-fifth of the human population is persistently colonized with *S. aureus* [5], with another 10-15% as intermittent carriers [3,6]. A positive association has been found between colonization with *S. aureus* and several chronic airway diseases such as chronic rhinosinusitis with nasal polyps (CRSwNP), allergic rhinitis, bronchial asthma, and chronic spontaneous urticaria (CSU) [7,8]. Indeed, the sinus mucosa is colonized by *S. aureus* in around 70% of patients with CRSwNP [9,10] and in at least 50% of those with CSU [11].

Infection with *S. aureus* can lead to activation of a type 2 inflammatory response, involving eosinophils and their related cytokines, and several types of T cells (e.g., Th2 and T regulatory cells) and innate lymphoid cells (ILC) (e.g. type 2 ILC) have been firmly implicated in the host's responses to *S. aureus* and development of both asthma and CRSwNP [12-15]. In addition, *S. aureus* enterotoxins (SEs) can lead to increased production of IgE [16]. *S. aureus* can be considered an IgE-mediated pathogen since it is well established that serum IgE against SEs (polyclonal IgE and/or specific IgE) are increased in patients with several chronic airway diseases [10,17,18]. As a result, the correlation between high levels of IgE and T2 inflammation in CRSwNP and bronchial asthma may be relevant to the pathophysiology of these conditions.

Different pathologic mechanisms have been implicated in the *S. aureus* induced IgE production and T2 inflammation in both nasal CRSwNP and bronchial asthma as summarized in Figure 1. Firstly, *S. aureus* can produce enterotoxins, which are functionally-related bacterial proteins that share sequence homology [19]. Enterotoxins are pyrogenic and have been related to several human diseases including food poisoning and toxic shock syndrome [19]. Some of the most common SEs are SE type A (SEA) and type B (SEB) [19]. SEs can act as superantigens, crosslinking T cell receptor and major histocompatibility complex (MHC) class II molecules on antigen-presenting cells, which leads to production of polyclonal IgE and cytokine production in T cells [8,20,21]. In addition, *S. aureus* can induce the production of IgE that can activate basophils by binding as superantigens to the framework regions of IgE in the IgE–FcεRI complexes as well as in the conventional manner binding through complementarity-determining regions [22]. Moreover, a recent study, using the basophil activation test, demonstrated the ability of SEs to activate basophils in patients with severe asthma, confirming that *S. aureus* can act not only as a superantigen, but also as an allergen [23]. Secondly, most isolates of *S. aureus* also release serine protease–like proteins (Spls), a group of six proteins Spl A-F, which can activate a type 2 response by stimulating epithelial cells to produce IL-33 [24,25]. Lastly, several clinical isolates of *S. aureus* synthesize protein A, a bacterial superallergen, which interacts with IgE V_H3+ to activate basophils and mast cells to release proinflammatory mediators and cytokines [26,27]. Exacerbations of certain forms of bronchial asthma, CRSwNP, chronic urticaria and atopic dermatitis associated with *S. aureus* infection can be mediated through the above-mentioned mechanisms.

The aim of this review is to highlight the pathogenetic role of S. aureus in IgE-mediated endotypes of diseases such as the bronchial asthma, CRSwNP, chronic urticaria,

and atopic dermatitis, investigating the association between IgE overexpression and disease severity and exploring the potential therapeutic implications of anti-IgE therapies.

2.0 S. aureus and asthma

A number of investigations have examined the association between colonization with *S. aureus* and asthma [28]. Serum enterotoxin IgE positivity is higher in patients with asthma compared to healthy controls and has been found to be an independent risk factor for asthma [29]. A number of studies have shown that asthma is associated with SE, and a meta-analysis of 7 studies by Song et al. in 2013 reported that sensitization to SE has a significant relation with asthma (OR 2.95; 95% CI 2.28-3.82) [30]. In 2019, a meta-analysis concluded that there is a modest but significant association between nasal colonization with *S. aureus* and asthma (OR 1.19; 95% CI 1.06-1.34) [31].

The GA(2)LEN study examined the prevalence and association of serum SE-IgE positivity with asthma in the general population in Europe [32]. In the 2908 subjects enrolled, a positive serum SE-IgE result was seen in 29.3% of individuals with no significant geographic differences, and independently of sensitization to other common allergens. Serum SE-IgE positivity was more common in smokers and was associated with asthma in a concentration–dependent manner. This finding was confirmed in a recent longitudinal analysis of the Epidemiological Study of the Genetics and Environment of Asthma (EGEA) cohort where serum SE-IgE positivity was observed in 39% of controls without asthma, in 58% of those with mild asthma, and in 76% of patients with severe asthma [33]. SE-IgE sensitization was also associated with the severity of asthma when evaluated one or two decades later (adjusted OR 2.69; 95% CI 1.18-6.15). Lastly, a community-based population

study in Korea found that SE-IgE sensitization was independently linked with adult-onset asthma [34].

SE-IgE sensitization is predictive of asthma severity as shown in a study by Kowalski et al [35]. In that investigation, the serum levels of enterotoxin-specific IgE were 3-fold higher in individuals with severe asthma compared to those with milder asthma. In addition, SE-IgE sensitization was much more prevalent among asthmatic patients with frequent exacerbations compared to those with no asthma (adjusted OR 4.59; 95% CI 1.40-15.07) [33]. As observed in a cohort of 172 adults by Tanaka et al., sensitization to SE, and in particular to SEA but not SEB, was significantly associated with poor asthma control after adjusting for age, sex, and positivity for other aeroallergens (OR, 2.66; 95% CI 1.02-8.65) [36].

SE-IgE sensitization has also been related to late-onset asthma in the elderly; Song et al. compared 249 elderly patients with asthma to 98 non-asthmatic controls, finding significantly higher median serum SE-IgE levels in elderly patients with asthma compared to the control cohort [0.16 (interquartile range 0.04-0.53) vs. 0.10 (0.01-0.19), $P < 0.001$] [37]. The association between serum SE-IgE levels and asthma in these patients was further confirmed in a multivariate analysis (OR 7.47, 95% CI 1.86-30.03).

As reported by Bachert et al., in western countries, 85% of cases of CRSwNP have a type 2 eosinophilic inflammatory pattern of expression, while only 15% have inflammation that is prevalently neutrophilic [38]. The extent of type 2 inflammation also correlates with severity of disease and asthma comorbidity [39], and the association with *S. aureus*, through polyclonal IgE and SE, is particularly evident in the most severe forms of disease [38,39].

3.0 S. aureus and CRSwNP

Several studies have indicated that there is a relationship between S. *aureus* and CRSwNP. Starting in 2005, Seiberling et al. published an investigation of 42 patients undergoing surgery for chronic rhinosinusitis [40]. Surgical samples were analyzed for the presence of 5 staphylococcal toxins, and the presence of at least one toxin was detectable in 14 of 29 patients with CRSwNP. The most commonly detected toxins were SEB and toxic shock syndrome toxin type 1. Cui et al. confirmed these findings, showing that both the rate and levels of serum IgE to SEB were significantly higher in patients with CRSwNP vs. a control group [41]. Cheng et al. later reported that total serum IgE, as well as IgE against SEA and SEB, were elevated in both non-eosinophilic and eosinophilic CRSwNP compared to healthy controls [42]. Thus, the finding that specific IgE towards SEB are more prevalent in patients with CRSwNP suggests that SEB may play a role in the pathogenesis of CRSwNP.

Interestingly, SE-specific IgE expressions show geographic diversity among patients with CRS from Europe, Asia, and Oceania [43]. While these differences might be explained by environmental factors such as microbiota and air pollution, these findings also raise the possibility that there are different immunologic endotypes of CRSwNP. Independently of the reasons for the differences in individual profiles, these findings give further weight to the need to personalize therapy based on the specific endotype. In this regard, it has been suggested that even if the clinical manifestations of eosinophilic and non-eosinophilic CRSwNP are similar, these different forms may have different pathological drivers of disease, thus necessitating different therapeutic strategies that target distinct pathways [44].

Tomassen et al. carried out an analysis on 173 cases with CRS, and tissue samples were analyzed for the presence of different biomarkers. Using partition-based clustering, the

authors were able to identify 10 clusters, 4 of which had low or undetectable levels of IL-5, eosinophil cationic protein, and IgE and 6 with high levels of these biomarkers. Interestingly, in the group with high IL-5 levels the latter two clusters with the highest concentrations of IgE (about 1000 kU/L) also showed the highest proportion of patients with comorbid asthma (64% and 71%) and disease recurrence with all samples expressing IgE toward SEs [9].

In broad terms, SE, and in particular SEB, are believed to disrupt the integrity of the nasal epithelial barrier in CRSwNP through involvement of the toll-like receptor 2 (TLR2) as shown in a mouse model [45]. Additionally, SE genes have been detected in both CRSwNP and chronic rhinosinusitis without nasal polyps (CRSsNP) and Th2 differentiation has been correlated with disease extent, at least in non-asthmatic CRSwNP [46]. SE may thus promote Th2 responses and as such have a key role on the development of CRSwNP. Indeed, a number of cytokines derived from epithelial cells such as IL-25 and IL-33 can promote a Th2 response [47]. At present, while there is evidence to suggest a strong link between the role of SE in contributing to Th2 inflammatory responses, this area still warrants additional investigation. In this regard, a very recent study reported that sensitization to both mold and SE appears to be related to development of type 2 inflammation given that all type 2 inflammatory markers with the exception of eosinophils in sinus tissue were elevated in patients with CRS compared to healthy subjects [48]. In a study of 69 patient with CRS and 45 healthy controls, Dobretsov et al. noted that levels of S. aureus in the nasal cavity were higher in CRS, and further concluded that higher titers of colonization were associated with lesser levels of eosinophilic inflammation [49]. However, this possibility requires additional study in larger samples of patients and controls. Together with other serological data, SE-IgE can be considered as a sign of type 2 inflammation, with a more probable risk of CRSwNP

recurrence or asthma association in a strong type 2 inflammatory reaction; based on inflammatory patterns, including cytokines like IL-5 and SE-IgEs, it can be hypothesized that the different endotypes can also have predictive value in determining both asthma comorbidity and recurrence of disease [50]. In this regard, it is known that *S. aureus* induces eosinophil migration to the epithelium and form eosinophilic extracellular traps that further damage the airway epithelium [50].

As mentioned, the presence of specific serum IgE for *S. aureus* has been correlated not only with disease severity, but also with recurrence of disease following surgical treatment [38,39]. In nasal mucosa, *S. aureus* may find a favorable environment for colonization [10]. In vitro analysis has shown that in tissues incubated with *S. aureus*, a number of bacterial proteins are found including enterotoxins and serine-like proteases [51]. Moreover, *S. aureus* has been found in mast cells and its internalization is apparently promoted by SEB [52].

Lastly, while CRSsNP is traditionally thought of as a condition dominated by a type 1 immune response, recent evidence suggests that it is also a type 2 mediated disease as underlined in the European Position Paper on Rhinosinusitis and Nasal Polyps 2020 [53]. Moreover, in a study of 240 patients with CRSsNP, evidence for a type 2 inflammatory response was seen in nearly half of cases, with increased levels of IL-4, IL-5, serum IgE, and SE-specific IgE, along with significant eosinophilic inflammation [54]. Importantly, the observation that CRSsNP, and especially CRSwNP, and asthma are highly comorbid reinforces the hypothesis that these diseases share a common type 2 inflammatory pathophysiology [55]. In a study on 337 patients with moderate-to-severe CRSwNP, 49% were reported to have comorbid asthma [56].

4.0 S. aureus and CSU/atopic dermatitis

CSU is the most common subtype of urticaria, characterized by recurrent episodes of wheals caused by unknown triggers and lasting more than 6 weeks [57]. Several hypotheses have been forwarded regarding the pathogenesis of CSU, although autoimmune etiology is believed to be involved in around half of cases [58]. CSU is not considered as a traditional allergy as typical exoallergens are not involved in degranulation of mast cells. However, it is now widely accepted that IgE, via its high affinity receptor, plays a role in the pathogenesis of CSU [58]. In a study of 203 patients with CSU, Kessel et al. found a significant relation between total IgE levels and disease severity: 93% of patients with increased levels of IgE had moderate-to-severe CSU, which was significantly higher compared to patients with normal IgE levels [59]. Moreover, the activation of skin mast cells via IgE may be related to the signs and symptoms of urticaria [58].

S. aureus has been detected in swab specimens from the nasal cavity in patients with CSU; after antimicrobial treatment, 40% of patients had a partial or complete recovery from CSU [60]. This indicates that nasal carriage of *S. aureus* can indeed act as an etiological factor in CSU. Increased rates of elevated levels of serum IgE towards SEs have been described in CSU. Ye et al. detected an increased prevalence of serum specific IgE against SEA and SEB as well as toxic shock syndrome toxin TSST-1 in Korean patients with CSU [61]. More recently, Altrichter et al. assessed the prevalence and functional relevance of IgE to SEs in CSU [62]. These authors demonstrated that serum concentrations of IgE-SEB were significantly correlated with total IgE serum levels in CSU. Moreover, in CSU patients, levels of IgE-SEB have histamine-releasing effects, which are linked to both disease activity and its duration.

An early study showed that some bacterial antigens may be the target of IgE and that mast cells with antibacterial IgE receptor on their surface degranulate when exposed to IgE-specific bacterial antigens such as SEs [17]. Most clinical isolates of *S. aureus* can synthesize protein A, which has a classical site that binds to Fc gamma of IgG, and an alternative site that binds the Fab portion of 15-50% of human polyclonal IgG, IgM, IgA, and IgE [26,27]. Since protein A of *S. aureus* is a bacterial superantigen, this raises the possibility that exacerbations of CSU and atopic dermatitis associated with *S. aureus* infection might occur through this mechanism. *S. aureus* frequently colonizes skin in atopic dermatitis patients [63] and the ability of its enterotoxins to polyclonally activate T cells with the subsequent release of huge amounts of IgE and other immunoglobulin isotypes is well established. IgE directed against enterotoxins is a common finding in atopic dermatitis. Staphylococcus aureus might also influence the natural course of the disease. Some of its products down-regulate FcεRI expression on dendritic cells [64]. Taken together these findings suggest a relevant IgE mediated pathophysiological role of S. aureus both in CSU and atopic dermatitis.

5.0 Therapeutic implications of *S. aureus* involvement in IgE-mediated diseases

In 2013, Gevaert et al published a study demonstrating the efficacy of omalizumab in both atopic and non-atopic patients affected by CRSwNP and comorbid asthma, most of whom were positive to serum IgE specific to SEs. After 16 weeks, a significant reduction in total nasal endoscopic polyp score, confirmed by computed tomography of the paranasal sinuses, associated with an improvement of symptoms and asthma quality of life, was seen only in the omalizumab group [65].

Several studies have demonstrated the efficacy of omalizumab in severe non-atopic asthmatics, i.e. patients who, although their skin prick test were negative to the common panel of aeroallergens, had serum total IgE levels in the range of omalizumab prescribability. In this group of patients, Garcia et al. demonstrated that omalizumab, in comparison with placebo, led to a significant increase in FEV_1 % and determined a trend towards a reduction in asthma exacerbation rates. In addition, a multicenter registry study demonstrated the ability of omalizumab in reaching several clinical outcomes in a similar way in both non-atopic and atopic severe asthmatic patients, followed over 2 years [66]. A further study in symptomatic non-atopic asthmatics demonstrated that omalizumab, compared to placebo, determined a significant reduction of bronchial mucosal IgE and an improvement of lung function [67]. Lastly, a recent real-world post-hoc analysis of 80 symptomatic non-atopic asthma patients reported that following 1 year of treatment with omalizumab, fifty percent of patients had no daytime symptoms, more than half no longer required rescue medication and a remarkable disease control was achieved [68].

Very interestingly, the “Identify Project”, through the measurement of serum specific IgE against 35 perennial aeroallergens, demonstrated that 51.5% of severe asthmatic patients previously considered non atopic were sensitized to at least one of them and the two most common sensitizations were towards staphylococcal enterotoxins A and B. This result suggests that the percentage of allergic asthmatics may be underestimated, and that there is a need to a correct evaluation of allergic status, in particular against staphylococcal enterotoxins.

The efficacy of omalizumab has also been recently demonstrated in severe CRSwNP patients regardless of the atopic state. In particular, in two recent studies, POLYP 1 and

POLYP 2, omalizumab determined a significant change from baseline in Nasal Polyp Score and Nasal Congestion Score and other secondary endpoints, in comparison with placebo [69]. Based on these positive results, the EMA approved the therapeutic indication of omalizumab as an add-on therapy with intranasal corticosteroids for the treatment of adults with severe CRSwNP.

The efficacy and safety of omalizumab in CSU is largely recognized [70] and patients affected by CSU are already candidates to anti-IgE therapy regardless of the presence and nature of the allergic sensitization. To this regard, omalizumab may be beneficial in patients with increased levels of serum IgE towards SEs, as already described in CSU.

As stated previously, several studies have demonstrated a strong link between bronchial asthma, CRSwNP and CSU with SEs, particularly in patients with the most severe forms of the diseases. Searching for the presence of serum IgE against SEs in this subsets of patients could improve our understanding on the involvement of this pathogen in these disorders that frequently are concomitant, can share common pathogenetic mechanisms and can benefit from an anti-IgE treatment.

6.0 Conclusion

There is increasing evidence indicating that *S. aureus* may play a greater role in the pathogenesis of severe asthma, CRSwNP and CSU than previously thought. Through the release of its enterotoxins, *S. aureus* can induce both the production of polyclonal IgE and the synthesis of specific IgE that can elicit the inflammatory cascade. Based on these assumptions, an anti-IgE strategy could be a valid approach in these *S. aureus*-mediated

diseases. In this regard, omalizumab is currently the only biological agent available in clinical practice that specifically targets IgE and which is approved for treatment of severe allergic asthma, CSU, and CRSwNP [71]. Further studies evaluating the efficacy of omalizumab in these subsets of patients showing the presence of serum IgE against SEs are needed.

7.0 Expert opinion

Several endotypes of severe asthma, CRSwNP and CSU are characterized by the presence of sensitization toward the enterotoxins of *S. aureus*. Serum levels of IgE against SEs appear to be associated with poor outcomes of these diseases. In particular, as described herein, in severe asthma IgE to SEs correlated with the frequency of exacerbations, risk of hospitalization, and no symptom control [33,36]. In patients with CRSwNP the presence of IgE to *S. aureus* represents a risk factor for recurrence of disease and comorbidity with bronchial asthma [9]. SEs can also induce the activation of IgE-bearing cells as demonstrated in a recent flow-cytometric study in which the exposure of circulating basophils to SEs was able to activate them in about one-third of patients affected by severe asthma [23].

On the basis of these assumptions, we believe the detection of serum IgE against SEs should be carried out in all patients suffering from severe bronchial asthma, CRSwNP, and CSU as their presence can represent, not only a marker of severity of disease, but also a target of anti-IgE therapy. Gevaert et al. demonstrated the efficacy of omalizumab in patients suffering from bronchial asthma and CRSwNP sensitized to SEs [65]. Further studies are needed to validate these results not only in severe asthma and CRSwNP but also in CSU and atopic dermatitis. However, while in CSU and CRSwNP omalizumab can be prescribed on

the basis of serum IgE levels regardless the identification of a specific sensitivity to an aeroallergen, in severe asthma, it can be prescribed only in presence of a sensitization to a perennial allergen. Hence the need to measure specific IgE to SEs, particularly in patients with increased total serum IgE levels and not allergic to one of the most common perennial aeroallergens. Patients showing serum IgE against SEs and even colonized with *S. aureus*, are exposed to allergens that, in our opinion, can be considered as perennial and could benefit of an anti-IgE therapy. *S. aureus* can also induce the activation of a type 2 eosinophilic inflammation mediated by the release of allarmins, such as TSLP, and/or IL5 and these molecules could also be the targets of biological therapies [72].

In conclusion, we believe that in all patients suffering from severe forms of bronchial asthma, CSRwNP, and CSU with evidence of *S. aureus* involvement, as airways colonization and/or sensitization to its enterotoxins, it is essential to better define the role of this bacterium in the pathogenesis of these type 2 disorders and to evaluate different therapeutic strategies with the available biological drugs.

Declaration of interest

References

* = of interest, ** = of considerable interest

1. Lowy FD. Staphylococcus aureus infections. N Engl J Med. 1998 Aug 20;339(8):520-32.
2. Tong SY, Davis JS, Eichenberger E, et al. Staphylococcus aureus infections: epidemiology, pathophysiology, clinical manifestations, and management. Clin Microbiol Rev. 2015 Jul;28(3):603-61.
3. Sollid JU, Furberg AS, Hanssen AM, et al. Staphylococcus aureus: determinants of human carriage. Infect Genet Evol. 2014 Jan;21:531-41.
4. Wertheim HF, Melles DC, Vos MC, et al. The role of nasal carriage in Staphylococcus aureus infections. Lancet Infect Dis. 2005 Dec;5(12):751-62.
5. Verhoeven PO, Grattard F, Carricajo A, et al. An algorithm based on one or two nasal samples is accurate to identify persistent nasal carriers of Staphylococcus aureus. Clin Microbiol Infect. 2012 Jun;18(6):551-7.
6. Nouwen JL, Ott A, Kluytmans-Vandenbergh MF, et al. Predicting the Staphylococcus aureus nasal carrier state: derivation and validation of a "culture rule". Clin Infect Dis. 2004 Sep 15;39(6):806-11.
7. Nordengrun M, Michalik S, Volker U, et al. The quest for bacterial allergens. Int J Med Microbiol. 2018 Aug;308(6):738-750.
8. Teufelberger AR, Broker BM, Krysko DV, et al. Staphylococcus aureus Orchestrates Type 2 Airway Diseases. Trends Mol Med. 2019 Aug;25(8):696-707.
9. Tomassen P, Vandeplas G, Van Zele T, et al. Inflammatory endotypes of chronic rhinosinusitis based on cluster analysis of biomarkers. J Allergy Clin Immunol. 2016 May;137(5):1449-1456 e4.

**** Work demonstrating that distinct clusters have different inflammatory mechanisms that correlate with phenotype.**

10. Van Zele T, Gevaert P, Watelet JB, et al. Staphylococcus aureus colonization and IgE antibody formation to enterotoxins is increased in nasal polyposis. J Allergy Clin Immunol. 2004 Oct;114(4):981-3.

11. Ertam I, Biyikli SE, Yazkan FA, et al. The frequency of nasal carriage in chronic urticaria patients. J Eur Acad Dermatol Venereol. 2007 Jul;21(6):777-80.

12. Lane AP, Truong-Tran QA, Schleimer RP. Altered expression of genes associated with innate immunity and inflammation in recalcitrant rhinosinusitis with polyps. Am J Rhinol. 2006 Mar-Apr;20(2):138-44.

13. Ramanathan M, Jr., Lee WK, Spannhake EW, et al. Th2 cytokines associated with chronic rhinosinusitis with polyps down-regulate the antimicrobial immune function of human sinonasal epithelial cells. Am J Rhinol. 2008 Mar-Apr;22(2):115-21.

14. Suzaki H, Watanabe S, Pawankar R. Rhinosinusitis and asthma-microbiome and new perspectives. Curr Opin Allergy Clin Immunol. 2013 Feb;13(1):45-9.

15. Van Bruaene N, Perez-Novo CA, Basinski TM, et al. T-cell regulation in chronic paranasal sinus disease. J Allergy Clin Immunol. 2008 Jun;121(6):1435-41, 1441 e1-3.

16. Derycke L, Perez-Novo C, Van Crombruggen K, et al. Staphylococcus aureus and Chronic Airway Disease. World Allergy Organ J. 2010 Aug;3(8):223-8.

17. Bachert C, Gevaert P, Holtappels G, et al. Total and specific IgE in nasal polyps is related to local eosinophilic inflammation. J Allergy Clin Immunol. 2001 Apr;107(4):607-14.

18. Flora M, Perrotta F, Nicolai A, et al. Staphylococcus Aureus in chronic airway diseases: An overview. Respir Med. 2019 Aug;155:66-71.

***Good review for those desiring additional information.**

19. Pinchuk IV, Beswick EJ, Reyes VE. Staphylococcal enterotoxins. Toxins (Basel). 2010 Aug;2(8):2177-97.

20. Broker BM, Holtfreter S, Bekeredjian-Ding I. Immune control of Staphylococcus aureus - regulation and counter-regulation of the adaptive immune response. Int J Med Microbiol. 2014 Mar;304(2):204-14.

21. Krakauer T. Update on staphylococcal superantigen-induced signaling pathways and therapeutic interventions. Toxins (Basel). 2013 Sep 24;5(9):1629-54.

22. Chen JB, James LK, Davies AM, et al. Antibodies and superantibodies in patients with chronic rhinosinusitis with nasal polyps. J Allergy Clin Immunol. 2017 Apr;139(4):1195-1204 e11.

23. Flora M, Perna F, Abbadessa S, et al. Basophil activation test for Staphylococcus aureus enterotoxins in severe asthmatic patients. Clin Exp Allergy. 2021 Apr;51(4):536-545.

24. Stentzel S, Teufelberger A, Nordengrun M, et al. Staphylococcal serine protease-like proteins are pacemakers of allergic airway reactions to Staphylococcus aureus. J Allergy Clin Immunol. 2017 Feb;139(2):492-500 e8.

25. Teufelberger AR, Nordengrun M, Braun H, et al. The IL-33/ST2 axis is crucial in type 2 airway responses induced by Staphylococcus aureus-derived serine protease-like protein D. J Allergy Clin Immunol. 2018 Feb;141(2):549-559 e7.

26. Marone G, Rossi FW, Detoraki A, et al. Role of superallergens in allergic disorders. Chem Immunol Allergy. 2007;93:195-213.

27. Marone G, Spadaro G, Liccardo B, et al. Superallergens: a new mechanism of immunologic activation of human basophils and mast cells. Inflamm Res. 2006 Apr;55 Suppl 1:S25-7.

28. Bachert C, Humbert M, Hanania NA, et al. Staphylococcus aureus and its IgE-inducing enterotoxins in asthma: current knowledge. Eur Respir J. 2020 Apr;55(4).

29. Bachert C, van Steen K, Zhang N, et al. Specific IgE against Staphylococcus aureus enterotoxins: an independent risk factor for asthma. J Allergy Clin Immunol. 2012 Aug;130(2):376-81 e8.

30. Song WJ, Jo EJ, Lee JW, et al. Staphylococcal enterotoxin specific IgE and asthma: a systematic review and meta-analysis. Asia Pac Allergy. 2013 Apr;3(2):120-6.

31. Kim YC, Won HK, Lee JW, et al. Staphylococcus aureus Nasal Colonization and Asthma in Adults: Systematic Review and Meta-Analysis. J Allergy Clin Immunol Pract. 2019 Feb;7(2):606-615 e9.

****Meta-analysis demonstrating significant relationships between nasal S. aureus colonization and asthma.**

32. Tomassen P, Jarvis D, Newson R, et al. Staphylococcus aureus enterotoxin-specific IgE is associated with asthma in the general population: a GA(2)LEN study. Allergy. 2013 Oct;68(10):1289-97.

**** Pivotal study showing for the first time that SE-IgE is common in the general population.**

33. Sintobin I, Siroux V, Holtappels G, et al. Sensitisation to staphylococcal enterotoxins and asthma severity: a longitudinal study in the EGEA cohort. Eur Respir J. 2019 Sep;54(3).

34. Song WJ, Chang YS, Lim MK, et al. Staphylococcal enterotoxin sensitization in a community-based population: a potential role in adult-onset asthma. Clin Exp Allergy. 2014 Apr;44(4):553-62.

35. Kowalski ML, Cieslak M, Perez-Novo CA, et al. Clinical and immunological determinants of severe/refractory asthma (SRA): association with Staphylococcal superantigen-specific IgE antibodies. Allergy. 2011 Jan;66(1):32-8.

36. Tanaka A, Suzuki S, Ohta S, et al. Association between specific IgE to Staphylococcus aureus enterotoxins A and B and asthma control. Ann Allergy Asthma Immunol. 2015 Sep;115(3):191-197 e2.

37. Song WJ, Sintobin I, Sohn KH, et al. Staphylococcal enterotoxin IgE sensitization in late-onset severe eosinophilic asthma in the elderly. Clin Exp Allergy. 2016 Mar;46(3):411-21.

38. Bachert C, Gevaert P, Hellings P. Biotherapeutics in Chronic Rhinosinusitis with and without Nasal Polyps. J Allergy Clin Immunol Pract. 2017 Nov - Dec;5(6):1512-1516.

39. Bachert C, Zhang L, Gevaert P. Current and future treatment options for adult chronic rhinosinusitis: Focus on nasal polyposis. J Allergy Clin Immunol. 2015 Dec;136(6):1431-1440.

40. Seiberling KA, Conley DB, Tripathi A, et al. Superantigens and chronic rhinosinusitis: detection of staphylococcal exotoxins in nasal polyps. Laryngoscope. 2005 Sep;115(9):1580-5.

41. Cui XY, Miao JL, Lu HQ, et al. Serum levels of specific IgE to Staphylococcus aureus enterotoxins in patients with chronic rhinosinusitis. Exp Ther Med. 2015 Apr;9(4):1523-1527.

42. Cheng KJ, Wang SQ, Xu YY. Different roles of Staphylococcus aureus enterotoxin in different subtypes of nasal polyps. Exp Ther Med. 2017 Jan;13(1):321-326.

43. Wang X, Zhang N, Bo M, et al. Diversity of TH cytokine profiles in patients with chronic rhinosinusitis: A multicenter study in Europe, Asia, and Oceania. J Allergy Clin Immunol. 2016 Nov;138(5):1344-1353.

***Interesting study demonstrating that TH cytokine profiles have extreme geographic diversity.**

44. Cao PP, Zhang YN, Liao B, et al. Increased local IgE production induced by common aeroallergens and phenotypic alteration of mast cells in Chinese eosinophilic, but not non-eosinophilic, chronic rhinosinusitis with nasal polyps. Clin Exp Allergy. 2014;44(5):690-700.

45. Martens K, Seys SF, Alpizar YA, et al. Staphylococcus aureus enterotoxin B disrupts nasal epithelial barrier integrity. Clin Exp Allergy. 2020 Oct 14.

46. Rha MS, Kim SW, Chang DY, et al. Superantigen-related TH2 CD4(+) T cells in nonasthmatic chronic rhinosinusitis with nasal polyps. J Allergy Clin Immunol. 2020 May;145(5):1378-1388 e10.

47. Ryu G, Kim DW. Th2 inflammatory responses in the development of nasal polyps and chronic rhinosinusitis. Curr Opin Allergy Clin Immunol. 2020 Feb;20(1):1-8.

48. Kanemitsu Y, Fukumitsu K, Kurokawa R, et al. Moulds and Staphylococcus aureus enterotoxins are relevant allergens to affect Type 2 inflammation and clinical outcomes in chronic rhinosinusitis patients. ERJ Open Res. 2020 Oct;6(4).

49. Dobretsov K, Negm H, Ralli M, et al. The theory of a "staphylococcus superantigen" in chronic rhinosinusitis with nasal polyps: myth or reality? Eur Rev Med Pharmacol Sci. 2019 Mar;23(1 Suppl):48-54.

50. Bachert C, Zhang N, Hellings PW, et al. Endotype-driven care pathways in patients with chronic rhinosinusitis. J Allergy Clin Immunol. 2018 May;141(5):1543-1551.

51. Bachert C, Holtappels G, Merabishvili M, et al. Staphylococcus aureus controls interleukin-5 release in upper airway inflammation. J Proteomics. 2018 May 30;180:53-60.

52. Hayes SM, Biggs TC, Goldie SP, et al. Staphylococcus aureus internalization in mast cells in nasal polyps: Characterization of interactions and potential mechanisms. J Allergy Clin Immunol. 2020 Jan;145(1):147-159.

53. Fokkens WJ, Lund VJ, Hopkins C, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. Rhinology. 2020 Feb 20;58(Suppl S29):1-464.

**** Latest update for clinicians.**

54. Delemarre T, Holtappels G, De Ruyck N, et al. Type 2 inflammation in chronic rhinosinusitis without nasal polyps: Another relevant endotype. J Allergy Clin Immunol. 2020 Aug;146(2):337-343 e6.

55. Massoth L, Anderson C, McKinney KA. Asthma and Chronic Rhinosinusitis: Diagnosis and Medical Management. Med Sci (Basel). 2019 Mar 27;7(4).

56. Scott M, et al. Comorbidities, hypersensitivity and biomarkers in a real-world US nasal polyps population European Respiratory Journal Sep 2019, 54 (suppl 63) PA5066.

57. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA(2)LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Allergy. 2018 Jul;73(7):1393-1414.

58. Bracken SJ, Abraham S, MacLeod AS. Autoimmune Theories of Chronic Spontaneous Urticaria. Front Immunol. 2019;10:627.

59. Kessel A, Helou W, Bamberger E, et al. Elevated serum total IgE--a potential marker for severe chronic urticaria. Int Arch Allergy Immunol. 2010;153(3):288-93.

60. Sharma AD. Role of Nasal Carriage of Staphylococcus aureus in Chronic Urticaria. Indian J Dermatol. 2012 May;57(3):233-6.

61. Ye YM, Hur GY, Park HJ, et al. Association of specific IgE to staphylococcal superantigens with the phenotype of chronic urticaria. J Korean Med Sci. 2008 Oct;23(5):845-51.

62. Altrichter S, Hawro T, Liedtke M, et al. In chronic spontaneous urticaria, IgE against staphylococcal enterotoxins is common and functional. Allergy. 2018 Jul;73(7):1497-1504.

63. Ong PY, Leung DY. The infectious aspects of atopic dermatitis. Immunol Allergy Clin North Am. 2010 Aug;30(3):309-21.

64. Jinnestal CL, Belfrage E, Back O, et al. Skin barrier impairment correlates with cutaneous Staphylococcus aureus colonization and sensitization to skin-associated microbial antigens in adult patients with atopic dermatitis. Int J Dermatol. 2014 Jan;53(1):27-33.

65. Gevaert P, Calus L, Van Zele T, et al. Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. J Allergy Clin Immunol. 2013 Jan;131(1):110-6 e1.

66. de Llano LP, Vennera Mdel C, Alvarez FJ, et al. Effects of omalizumab in non-atopic asthma: results from a Spanish multicenter registry. J Asthma. 2013 Apr;50(3):296-301.

67. Pillai P, Chan YC, Wu SY, et al. Omalizumab reduces bronchial mucosal IgE and improves lung function in non-atopic asthma. Eur Respir J. 2016 Dec;48(6):1593-1601.

68. Campo P, Soto Campos G, Moreira A, et al. Real-life study in non-atopic severe asthma patients achieving disease control by omalizumab treatment. Allergy. 2021 Jun;76(6):1868-1872.

69. Gevaert P, Omachi TA, Corren J, et al. Efficacy and safety of omalizumab in nasal polyposis: 2 randomized phase 3 trials. J Allergy Clin Immunol. 2020 Sep;146(3):595-605.

70. Saini SS, Bindslev-Jensen C, Maurer M, et al. Efficacy and safety of omalizumab in patients with chronic idiopathic/spontaneous urticaria who remain symptomatic on H1 antihistamines: a randomized, placebo-controlled study. J Invest Dermatol. 2015 Jan;135(1):67-75.

71. Omalizumab, Summary of Product Characteristics.

72. Vu AT, Baba T, Chen X, et al. Staphylococcus aureus membrane and diacylated lipopeptide induce thymic stromal lymphopoietin in keratinocytes through the Toll-like receptor 2-Toll-like receptor 6 pathway. J Allergy Clin Immunol. 2010 Nov;126(5):985-93, 993 e1-3.

Figure legends

Figure 1. Inflammatory response mechanisms induced by *S. aureus* infection.

BCR: B-cell receptor; ILC: innate lymphoid cells; MHC: major histocompatibility complex; SEs: staphylococcal enterotoxins; SplD: serine protease–like protein D; TCR: T-cell receptor; TSLP: thymic stromal lymphopoietin;

S. aureus infection

Epithelium

SpID or SEs as conventional antigen

SEs (SEA - SEB)

Basophil

Protein A

Protein A - IgE V_H3^+

Th2-cell

IL-9

V_H3+IgE

FCεRI$^+$

SEs - IgE

Mast cell degranulation

IL-33 TSLP

ILC2

IL-13

M2 Macrophage

IL-4 IL-13

IL-5

IL-33

IL-33 TSLP

Dendritic cell

Antigenic peptide

Naïve T-cell

Th2-cell

IL-5

IL-4 IL-13

Eosinophils

B-cell

Plasma cell

Specific IgE

MHC-II

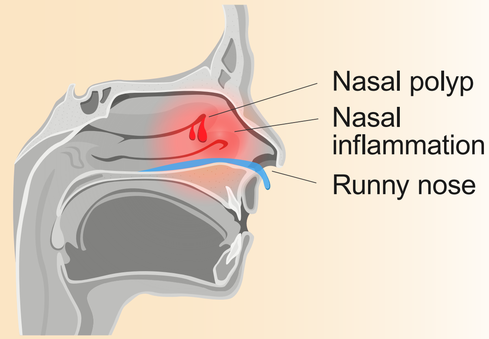
SEs

TCR

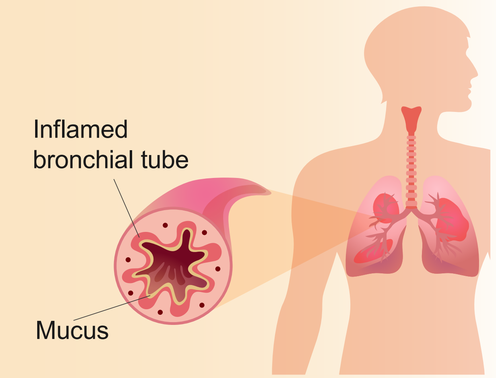
Naïve T-cell

Polyclonal T-cell activation and polysensitization

NASAL POLYPOSIS



ASTHMA



URTICARIA ATOPIC DERMATITIS