

Rhinosinusitis and Asthma: A Link for Asthma Severity

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Abstract The term *rhinosinusitis* describes an inflammation of the mucosal lining of the nose and sinuses; however, recent evidence points to the need to differentiate patients with chronic rhinosinusitis without nasal polyps from those with nasal polyps. Asthma comorbidity is especially common in nasal polyp disease and may be associated with aspirin-exacerbated respiratory disease. Of interest, asthma comorbidity is uncommon in some parts of the world but common in others. A further analysis of the inflammatory patterns also revealed that nasal polyps do not represent one single entity; interleukin (IL)-5–positive nasal polyps can be differentiated from IL-5–negative forms by different inflammatory patterns (predominance of eosinophils vs neutrophils). *Staphylococcus aureus* superantigens frequently colonize IL-5–positive nasal polyps and may amplify the eosinophilic inflammation, induce a polyclonal local IgE formation, and increase the risk of asthma comorbidity. Recent findings in severe asthma patients confirm the role of superantigens in lower airway disease.

Keywords Chronic rhinosinusitis · Nasal polyps · Asthma · Interleukin-5 · IgE · ECP · *Staphylococcus aureus* enterotoxins · Superantigens

Introduction

The common airway concept, also referred to as *united airways*, has been widely accepted as a clinical phenomenon and is used primarily to demonstrate that allergic rhinitis is often complicated by asthma [1]. However, the topic needs to be approached with a much wider view and with much deeper insight at the same time. Whereas allergic rhinitis and its impact on asthma have been studied to some extent, the role of the paranasal sinuses in lower airway disease manifestations is largely obscure. Whereas the pathophysiologic link between allergic upper and lower airway disease seems partially understood, such understanding mostly lacks consideration of nonallergic sinus disease and its possible relationship with asthma or chronic obstructive pulmonary disease manifestations. There is a great lack of epidemiologic, clinical, pathophysiologic, and therapeutic knowledge and of understanding of the link between upper and lower airway disease outside the allergic rhinitis/asthma connection. However, such understanding seems mandatory for appropriate diagnostic and therapeutic management.

A condition *sine qua non* for the recognition of meaningful pathophysiologic links between airway diseases is the possibility to clearly depict disease phenotypes; this has been especially problematic for sinusitis or, even better, *rhinosinusitis*, as this term has been used to describe a basket of different disease entities [2]. The clinical tools in rhinology (eg, rhinomanometry, nasal endoscopy, smell tests, and CT scanning) are well-suited to describe the extent of the disease rather than the etiology or prognostic consequences and thus do not allow differentiating sinus disease appropriately. Furthermore, the recent discussion on eosinophilic versus neutrophilic airway disease points to the

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fact that clinical parameters alone may not be sufficient and may need to be complemented by biological parameters.

Sinus disease and lower airway comorbidity often present as clinically severe disease manifestations, such as nasal polyps, aspirin-exacerbated respiratory disease (AERD), and late-onset severe intrinsic asthma. Asthmatic patients with nasal polyposis and aspirin intolerance have the highest rates of exacerbation and hospital admissions [3]. Recent evidence points to a possible role for *Staphylococcus aureus* enterotoxins (SAEs), which may act as superantigens by amplifying airway inflammation and possibly inducing persistent severe disease. This hypothesis may be the key to unraveling the link between sinuses and lung and to understanding severe persistent airway disease.

What Clinical Evidence is There for a Link Between Rhinosinusitis and Asthma?

In patients with allergic rhinitis, the common atopic background may account for the increased risk of developing asthma; however, rhinitis is also a risk factor for asthma in nonatopic patients [4, 5]. In fact, nonatopic patients may develop the most severe forms of upper and lower airway disease. AERD develops according to a pattern characterized by a sequence of symptoms, with persistent rhinitis appearing at a mean age of 29.7 ± 12.5 years, then asthma, aspirin intolerance, and finally nasal polyposis. In half of these patients, asthma is severe and steroid dependent [6]. Nasal polyps are consistently associated with increasing severity of asthma. Sinonasal involvement, as evaluated by clinical symptoms and CT scan imaging, was significantly greater in patients with severe steroid-dependent asthma than in those with mild to moderate asthma [7]. In another study, CT scans showed abnormalities in 84% of patients with severe asthma [8]. A significant positive correlation was noted between CT scores and eosinophils in peripheral blood and induced sputum. The results of this study showed a direct relationship between sinonasal mucosa thickness and bronchial inflammation in severe asthma, particularly in patients with adult-onset disease. However, until recently, no etiologic explanation for this link had been proposed [9].

Chronic Rhinosinusitis: More Than One Disease

Chronic rhinosinusitis (CRS) is a heterogeneous group of chronic sinus diseases consisting of different disease entities. Neglecting small disease entities within sinus diseases, CRS without nasal polyps (CRSsNP) may be differentiated from CRS with nasal polyps (CRSwNP) [2]. Although it is difficult to differentiate CRS subgroups based on symptoms alone, those clinical signs may help to

separate CRSsNP from CRSwNP patients (Table 1) [10]. CRSwNP patients have a higher total symptom score and typically suffer from loss of smell and nasal obstruction, whereas headaches are less common compared with CRSsNP patients. The ear, nose, and throat specialist will be able to increase the accuracy of diagnosis by nasal rigid endoscopy and CT scan of the sinuses; however, such instruments are not accessible for epidemiologic studies. Further investigation of the pathomechanisms of CRS and the introduction of appropriate disease markers have recently facilitated and expanded disease classification. Evaluation of inflammatory cell profiles (in essence eosinophils vs neutrophils); the differentiation of T-helper (Th) cells, including, Th1, Th2, Th17, and regulatory T-cell (Treg) subtypes; the number of plasma cells; and the characterization of remodeling processes such as fibrosis or edema formation all provide tools to identify distinct disease entities within the group of chronic sinus diseases [11, 12].

Recent evidence from studies comparing CRS in Asia and Europe revealed that remodeling patterns are reasonably conserved and may serve as excellent tools to differentiate CRS subgroups [13], whereas inflammatory cell patterns may vary considerably between ethnic groups and even within a disease subgroup. Whether this variation is due to genetic or environmental differences remains unclear and needs to be studied. Due to the consistency of remodeling patterns, we propose using those markers for an innovative approach to CRS disease classification.

In a recent study in CRS [14] of the expression of transforming growth factor (TGF)- β isoforms, their receptors, the consecutive intracellular signaling, and the deposition of collagen as final readout, we unraveled a clearly different regulation of remodeling in CRS with and without nasal polyps. TGF- β 1 and TGF- β 2 protein concentrations, TGF- β receptor (R) I and RIII mRNA expression, the number of activated pSmad 2-positive cells, and the total collagen amount were significantly higher in CRSsNP patients compared with controls. In contrast, in CRSwNP patients, TGF- β 1 protein concentration, TGF- β RII and RIII mRNA expression, the number of activated pSmad 2-positive cells, and the total collagen deposition were significantly lower compared with controls. These findings indicate enhanced TGF- β signaling in CRSsNP and reduced TGF- β signaling in CRSwNP patients, compatible with the remodeling patterns observed in the disease subgroups: a lack of collagen formation in CRSwNP and excessive collagen production with thickening of collagen fibers in the extracellular matrix in CRSsNP patients. In essence, we were able to characterize TGF- β as a key switch between CRSsNP and CRSwNP.

The same remodeling patterns were confirmed in China [15]. Again, TGF- β was upregulated in CRSsNP patients, in line with an increased deposition of collagen. The study

Table 1 Patient characteristics and symptom scores

	Controls	Chronic sinusitis patients	Nasal polyposis patients
Included participants, <i>N</i>	9	8	10
Age, <i>y</i> (range)	33.8 (18–57)	36.2 (22–70)	35.6 (21–70)
Female/male	3/6	3/5	2/8
Asthma in history	0/9	0/8	4/10
Positive skin prick test	2/9	3/8	4/10
Aspirin intolerance	0/9	0/8	1/10
Smoking	0/9	2/8	1/10
Duration of disease, <i>y</i> (range)	6.8 (1–21)	4.2 (0.1–10.3)	6.7 (1.2–16.8)
Mean CT score (Lund-Mackay score) (range)	0 (0–1)	6 (2–11)	17 (7–24)
Mean polyp score (Davos) (range)	0	0	5.1 (2–6)
Mean total symptom score (range)	4 (3–5)	6.1 (4–10)	10.4 (4–14)
Mean nasal congestion score (range)	3 (2–3)	1 (0–3)	3 (2–3)
Mean sneezing score (range)	0	0.1 (0–1)	0.2 (0–2)
Mean rhinorrhea score (range)	0.3 (0–2)	1.6 (0–3)	1.6 (0–3)
Mean loss of smell score (range)	0	0	2.3 (0–3)
Mean postnasal drip score (range)	0	1.4 (0–2)	1.3 (0–3)
Mean headache score (range)	0.9 (0–2)	2.5 (1–3)	1.6 (0–3)

(Data from Van Zele et al. [10])

extended previous findings by studying matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) in CRSwNP and CRSsNP patients. Although there were no significant differences between the concentrations of MMP-7 and MMP-9 in CRSwNP and CRSsNP patients, these were significantly increased compared with controls. Of interest, CRSwNP patients showed significantly lower concentrations of TIMP-1 and TIMP-4 compared with CRSsNP patients, reflecting a deficit of naturally occurring MMP antagonists in nasal polyps, which allows for extracellular matrix destruction. These findings are in line with those published previously for European patients [16].

TGF- β not only plays a crucial role in the control of extracellular matrix formation but also is a key factor for the generation of Tregs. Two main populations of Tregs have been defined: the naturally occurring Tregs (nTregs), characterized by the CD41CD251 forkhead box P3 (FoxP3) phenotype, and the induced Tregs (iTregs), generated from naive T cells in the periphery. It is hypothesized that nTregs can migrate to sites of inflammation at mucosal surfaces and inhibit Th2 and Th1 cells via cell–cell contact [17]. iTregs suppress immune function via secretion of predominantly interleukin (IL)-10 and TGF- β [12]. Although FoxP3 was initially thought to be a specific marker for nTregs and could not be activated in peripheral T cells, recent studies demonstrated the induction of FoxP3 in iTregs [18], positioning this transcription factor as a marker for both nTregs and iTregs. Both Tregs depend on TGF- β for their induction and activation.

We aimed to study the direct tissue expression of transcription factors for Tregs and T-effector cells in relation to the cytokine expression patterns in the different rhinosinusitis subgroups [19]. The article demonstrated for the first time decreased FoxP3 expression, accompanied by the downregulation of TGF- β 1 protein and the upregulation of T-bet and GATA-3 expression—transcription factors for Th1 and Th2 effector cells—in CRSwNP tissue compared with controls and CRSsNP patients. The deficit in Tregs in nasal polyps thus could be related to the low expression of TGF- β and the increased activity of Th cells, a phenomenon that may be related to persistent airway disease. In contrast, CRSsNP patients demonstrate no deficit in Tregs and a much less severe inflammatory mucosal reaction. In an earlier study, it was shown that CRSsNP was characterized by a Th1 polarization with high levels of interferon- γ , whereas nasal polyps showed a Th2 polarization with high IL-5 protein concentrations, an increase in plasma cells, and high levels of IgE in Caucasian patients [10].

The preferentially eosinophilic appearance of nasal polyps was a dogma for decades that was also nurtured by the clinical understanding that polyps do respond to corticosteroid treatment, as they are characterized by abundant tissue eosinophils. However, reports from Asia were contradicting this dogma and claiming that nasal polyps also can be neutrophilic and may be treated with macrolide antibiotics [20]. We therefore sought to investigate the association of inflammatory cell predominance with T-effector cell patterns in Belgian and Chinese patients

with nasal polyps and in controls [21•]. Although the two CRSwNP groups were comparable in terms of symptoms, CT scan, and nasal endoscopy results, asthma comorbidity was significantly higher in Belgian patients. Polyp tissues from Caucasian CRSwNP patients were characterized by eosinophilic inflammation, expressed as a eosinophil cationic protein (ECP)/myeloperoxidase (MPO) ratio greater than 1, whereas samples from Asian patients were biased toward a neutrophilic inflammation. Both CRSwNP groups demonstrated a significant upregulation of the T-cell activation marker—soluble IL-2 receptor- α and a significant downregulation of FoxP3 expression and TGF- β 1 protein content compared with their respective control groups. However, whereas Belgian patients displayed a significant increase in Th2 cytokines and eosinophil-related markers compared with controls and with Asian patients, the latter showed a Th1/Th17 cell pattern as compared with control tissue.

Very recent data suggest that more than 80% of Caucasian polyps express IL-5 protein, and more than 50% are eosinophilic (ECP/MPO ratio > 1), whereas in the Chinese group, less than 20% express IL-5 protein and less than 10% are eosinophilic [22•]. Some polyp samples expressed several T-effector cell cytokines in parallel, including IL-5, interferon- γ , and IL-17, and demonstrated a mixed eosinophilic/neutrophilic activation pattern, whereas others did not express any of the key T-cell cytokines. Thus, specifically in CRSwNP, analysis of the specific inflammatory pattern may be necessary to adequately phenotype individual patients with respect to prognosis and treatment.

Role of *S. aureus* Superantigens in Mucosal Immunology

From animal models, it is clear that SAEs can aggravate airway inflammation in sensitized mice [23, 24]. Both nasal and bronchial *S. aureus* enterotoxin B (SEB) application enhanced the allergen-induced bronchial inflammation and increased the eosinophilic airway inflammation in ovalbumin (OVA)-sensitized mice; the aggravation of experimental asthma correlated with the expression of Th2 cytokines in the bronchi, and Th2 cytokines and OVA-specific and total IgE in serum. These data illustrate the potential of nasal and bronchial SEB to aggravate features of allergic asthma in a murine model. These observations were recently extended by studies on the potential of SEB to facilitate sensitization [25]. In fact, concomitant endonasal application of OVA and SEB resulted in OVA-specific IgE production in the mice, which normally develop tolerance when exposed to endonasal OVA alone. This effect was likely due to augmentation of dendritic cell migration and maturation, as well as the allergen-specific T-cell proliferation upon

concomitant OVA and SEB application. These data suggest that SEB may not only aggravate but also may facilitate airway inflammation.

In studies of the colonization rate of the middle nasal meatus, which forms the key region at the entrance to the sinuses, we found modest figures for controls and CRSwNP patients, whereas colonization in all groups of CRSwNP patients was twice as high (64%; $P < 0.05$ vs CRS) [26]. Of interest, those rates were 67% and 87% for polyp patients with asthma and aspirin sensitivity ($P < 0.05$ vs CRS for both), respectively. The prevalence of IgE antibodies to SAEs in tissue homogenates paralleled colonization rates at a somewhat lower level. The likelihood of finding IgE to SAEs in mucosal tissue in nasal polyp patients with concomitant asthma was seven times higher (OR, 7.78; 95% CI, 1.52–39.75) compared with nonasthmatic polyp patients. SAE-IgE positivity was linked to increased levels of ECP and IgE, suggesting a strong proinflammatory and IgE-inducing effect of SAEs in nasal tissue.

In a dose-dependent fashion, SEB induces chemokine release from epithelial cells and also may enhance the survival of granulocytes, exerting a direct proinflammatory effect on human nasal epithelial cells [27]. *S. aureus* may not only colonize the mucosae but may reside intramucosally or may form biofilms; current studies focus on the possible role of biofilms in the persistence of *S. aureus*, serving as a reservoir for saprophytic germs, which may invade the mucosa [28]. Our group recently discovered intramucosal *S. aureus*, especially in polyps from AERD patients, which can even reside intracellularly [29]. However, the formation of SAE-IgE rather than the presence of *S. aureus* in or on the mucosa determined the typical amplification of the Th2-related inflammation.

Among the most important activities of SAEs is the induction of IgE formation [30, 31]. Such activation of B cells and their transformation into plasma cells can be shown in nasal polyp tissue [32]. Naive B-cell and plasma cell counts were significantly higher in polyp tissue compared with control tissue, and IgA, IgG, and IgE concentrations were significantly higher in tissue homogenates—but not in serum—of patients with polyps compared with controls. In polyps with SAE-IgE, significantly higher concentrations of IgG and IgE, and also a significantly higher fraction of IgG₄ were demonstrated. These findings support a local production of immunoglobulins, including IgE, in nasal polyps in response to the chronic microbial trigger. Further studies need to demonstrate the local switch to IgE synthesis and the functional role of polyclonal IgE in the mucosa.

Finally, the polyclonal activation of T cells, preferentially Th2 cells, severely amplifies the preexisting mucosal inflammation. We used an ex vivo human mucosal model to study the effects of *S. aureus*-derived enterotoxin B, protein A, and lipoteichoic acid in nasal polyp and control

inferior turbinate tissue [33•]. Protein A stimulation resulted in a significant increase in histamine, leukotrienes, and prostaglandin D₂, indicating mast cell activation. Enterotoxin B stimulation over a period of 24 h induced a significant increase in proinflammatory and Th2 cytokines, including IL-4, IL-5, and IL-13 in both groups, and also induced the release of IL-2, which activates further T-effector cells. The expression of Th2 cytokines was more rigidly increased than the expression of regulatory cytokines in polyp tissue; this shift skews the T-cell pattern even more in the Th2 direction and at the same time disfavors Treg activity, contributing to the persistently and predominantly Th2-biased inflammation in polyp disease.

Evidence for Clinical Relevance: The Superantigen Link Between Nasal Polyps and Asthma

In a recent sinusitis cohort study within the Global Allergy and Asthma European Network (GA2LEN) consortium, which evaluated more than 600 CRS samples from 9 academic centers in Europe, we analyzed the distribution of lower airway disease in the different CRS groups. Asthma was present in 45% of all CRSwNP patients and significantly more frequently than in controls or CRSsNP patients. In parallel, the prevalence of AERD was 8.2% in the CRSwNP group and significantly higher than in controls or CRSsNP patients. In contrast, the prevalence of chronic obstructive pulmonary disease was highest in CRSsNP patients (3.6%). An analysis of nasal tissue and secretions of the mediators significantly increased in the asthmatic versus nonasthmatic patients identified total IgE and ECP as the most prominent markers (unpublished data).

This latter finding was in line with a previous observation that IgE antibodies to *S. aureus* enterotoxin A, *S. aureus* enterotoxin C, and toxic shock syndrome toxin-1 were found significantly more often in serum from asthmatic patients compared with controls, especially when comparing severe asthmatic patients with controls (62% vs 13%; $P=0.01$) [34]. Severe asthma was defined here by the need for regular, high-dose, inhaled corticosteroid therapy and persistently impaired lung function despite this treatment. These findings suggested a relationship between the presence of IgE antibodies to SAEs in serum and the severity of asthma.

In an attempt to identify the mediators associated with comorbid asthma in patients with CRSwNP, we analyzed the type of inflammation, T-cell cytokines, and IgE antibodies to SAEs in a group of Belgian patients with polyps who underwent sinus surgery [22•]. A total of 34% of those patients suffered from asthma, and more than 85% of the asthmatic patients used long-term inhalant and/or oral corticosteroid therapy. A total of 54% of the polyp samples showed an eosinophilic inflammation, characterized by an

ECP/MPO ratio greater than 1; the mean ECP/MPO ratio was 3.45 ± 5.99 (SD) for this Belgian patient group. The presence of SAE-IgE in the nasal tissue (37.3%), which was linked to the Th2 phenotype, was associated with significantly increased total IgE and ECP protein concentrations, obviously amplifying the Th2-biased inflammation.

A classification tree was developed for the parameter “comorbid asthma” to identify determinants within the categorical and continuous data. For the categorical data, the expression of SAE-IgE in the polyp tissue homogenates predicted asthma with an OR of 5.8 (95% CI, 1.8–29.6); for the continuous data, total IgE greater than 1442 kU/L and ECP greater than 17,100 $\mu\text{g/L}$ in homogenate samples with total IgE greater than 245 kU/L predicted asthma (OR, 8 [95% CI, 1.3–256] and 13 [95% CI, 2.21–305], respectively). These findings suggest an amplification of a primary Th2-biased eosinophilic inflammation by SAEs acting as superantigens and significantly increasing total IgE formation and ECP protein levels as the link to asthma comorbidity in nasal polyp patients.

To test this hypothesis in an independent cohort, we studied a group of 90 Chinese patients with CRSwNP; from previous studies [20, 21•], we expected asthma comorbidity to be low in this population and the inflammatory pattern to be different from that of Caucasian patients. Indeed, the ECP/MPO ratio was 0.2863 ± 0.5315 (SD) for the Chinese population, resembling neutrophilic polyps, and asthma comorbidity was as low as 8% [22•]. However, SAE-IgE in tissue homogenates (17.2% of patients) again was associated with significantly increased total IgE and ECP tissue concentrations. As demonstrated for the Belgian patients, SAE-IgE positivity, the expression of IL-5 protein, and a total IgE greater than 790 kU/L in samples with IL-5 greater than 194 pg/mL significantly predicted comorbid asthma (OR, 17–96).

These findings confirmed that asthma comorbidity specifically occurs in patients with Th2-biased eosinophilic nasal polyps. SAEs amplify the eosinophilic inflammation and IgE formation and thereby increase the risk of asthma comorbidity. Increased total IgE concentrations (> 100 kU/L) and, in some patients, SAE-IgE antibodies measurable in the serum in connection with increased ECP concentrations may reflect this link and are suitable for monitoring the course of disease (Fig. 1).

It is tempting to speculate that the same pathomechanisms may also apply for late-onset asthma, a disease with an inflammatory pattern and timing very similar to those of nasal polyp disease and frequently associated with nasal polyps and AERD. In a recent study including 109 patients with severe refractory asthma and 101 patients with nonsevere asthma observed for at least 12 months, specific IgE to SAEs and total IgE and ECP concentrations were measured in the serum [35]. A significant risk for severe

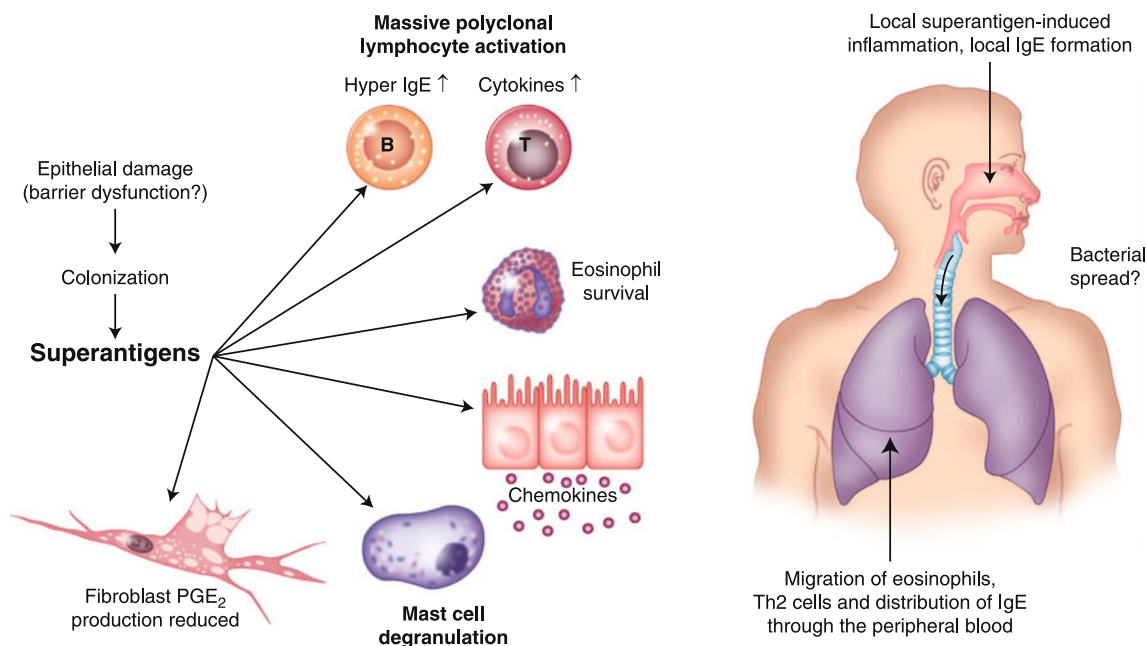


Fig. 1 Effects of superantigens on structural and inflammatory cell populations. Asthma comorbidity could be the consequence of bacterial spread to the lower airway mucosa or a systemic distribution of inflammatory cells via the blood. PG—prostaglandin

asthma was associated with known factors such as female gender (OR, 2.04), history of wheezing in childhood (OR, 2.47), presence of hypersensitivity to aspirin (OR, 1.96), and body mass index (OR, 3.08). Of interest, the mean level of enterotoxin-specific IgE was threefold higher in patients with severe asthma compared with patients with nonsevere asthma ($P=0.01$). The presence of specific IgE to enterotoxins carried a significant risk for patients to have serum total IgE levels greater than 100 kU/L (OR, 7.84), and concentrations of SAE-IgE antibodies were significantly associated with low respiratory function parameters (forced expiratory volume in 1 s [FEV₁], FEV₁/forced vital capacity, and maximum expiratory flow 25/75) and increased airway reversibility in response to albuterol. These findings strongly suggest that specific immune responses to enterotoxins are associated with clinical and immunologic parameters of asthma severity and suggest a role for staphylococcal enterotoxins also in the pathogenesis of intrinsic asthma [36].

New Therapeutic Approaches: From Antibiotics to Anti-IgE

The recommended treatment for nasal polyps consists of topical corticosteroids—spray or drops—and possibly oral corticosteroids, especially in severe disease, before surgery is indicated. Inhaled and oral corticosteroids also are indicated for asthma, especially in steroid-dependent and severe forms, including AERD, as they strongly inhibit Th2

cytokine release. However, some studies have also indicated that long-term use of antibiotics may be beneficial in CRSwNP [2]. The involvement of *S. aureus* would, of course, add to the rationale for the use of antibiotics, as it has been shown in other diseases with the impact of *S. aureus* superantigens (eg, atopic dermatitis) previously. A recent double-blind, placebo-controlled, multicenter trial study investigated the effect of doxycycline, 100 mg once daily, for 20 days on symptoms and objective clinical and biological parameters in CRSwNP [37]. Doxycycline significantly decreased nasal polyp size for 12 weeks compared with placebo and significantly reduced eosinophilic and neutrophilic inflammation markers as well as neutrophil-derived MMP-9 levels in nasal secretions. Doxycycline suppressed bacterial growth, including biofilm formation of *S. aureus*, in another study using local application [38]. Appropriate studies in comorbid asthma are lacking thus far.

Staphylococcal superantigens produced locally in the airways lead to class switching of local B cells, which results in polyclonal IgE production in the airways, including specific IgE against inhalant allergens and the superantigen itself. Polyclonal IgE leads to sensitization of mast cells, which can be chronically activated by inhalant allergens, but also unspecific triggers. This may also contribute to a reduced responsiveness toward corticosteroids, resulting in more severe asthma. Although it is currently not indicated for nonatopic severe asthma, we suggest that omalizumab counteracts these interactions by reducing serum levels of free IgE [39]. This approach may be beneficial for patients with severe polyp and asthma

disease irrespective of skin test or serum-specific IgE results, even in aspirin-sensitive patients. Omalizumab therefore may serve as a proof-of-concept study for the impact of *S. aureus*-induced polyclonal IgE on severe airway disease.

Conclusions

CRS is an umbrella term for sinus diseases distinct in remodeling and inflammation patterns. Within the group of CRSwNP, patients with Th2-biased inflammation are susceptible to the effects of *S. aureus* superantigens, which modify the eosinophil-dominated inflammation and induce local polyclonal IgE formation. This subgroup of nasal polyp patients are at risk of developing comorbid, often severe asthma. New therapeutic approaches need to be tailored for this specific subgroup of “united airway” patients.

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References

Papers of particular interest, published recently, have been highlighted as:

- Of importance

1. Bousquet J, van Cauwenberge P, Khaltaev N, et al.: Management of allergic rhinitis and its impact on asthma (ARIA). *J Allergy Clin Immunol* 2001, 108:S147–S334.
2. Fokkens W, Lund V, Mullol J, et al.: European position paper on rhinosinusitis and nasal polyps. *Rhinology* 2007, 20:1–136.
3. Ceylan E, Gencer M, San I: Nasal polyps and the severity of asthma. *Respirology* 2007, 12:272–276.
4. Guerra S, Sherrill DL, Martinez FD: Rhinitis as an independent risk factor for adult-onset asthma. *J Allergy Clin Immunol* 2002, 109:419–425.
5. Hens G, Hellings P: Sinonasal pathology in nonallergic asthma and COPD: ‘united airway disease’ beyond the scope of allergy. *Allergy* 2008, 63:261–267.
6. Szczeklik A, Nizankowska E, Duplaga M: Natural history of aspirin-induced asthma. AIANE Investigators. European Network on Aspirin-Induced Asthma. *Eur Respir J* 2000, 16:432–436.
7. Bresciani M, Paradis L, Des RA, et al.: Rhinosinusitis in severe asthma. *J Allergy Clin Immunol* 2001, 107:73–80.
8. ten Brinke A, Grootendorst DC, Schmidt JT, et al.: Chronic sinusitis in severe asthma is related to sputum eosinophilia. *J Allergy Clin Immunol* 2002, 109:621–626.
9. Bachert C, Gevaert P, Howarth P, et al.: IgE to *Staphylococcus aureus* enterotoxins in serum is related to severity of asthma. *J Allergy Clin Immunol* 2003, 111:1131–1132.
10. Van Zele T, Claeys S, Gevaert P, et al.: Differentiation of chronic sinus diseases by measurement of inflammatory mediators. *Allergy* 2006, 61:1280–1289.
11. Huvenne W, van Bruaene N, Zhang N, et al.: Chronic rhinosinusitis with and without nasal polyps: what is the difference? *Curr Allergy Asthma Rep* 2009, 9:213–220.
12. Bachert C, Van Bruaene N, Toskala E, et al.: Important research questions in allergy and related diseases: chronic rhinosinusitis and nasal polyposis: a GA2LEN paper. *Allergy* 2009, 64:520–533.
13. Zhang N, Liu S, Lin P, et al.: Remodeling and inflammation in Chinese vs. white patients with chronic rhinosinusitis. *J Allergy Clin Immunol* 2010 Jan 8 (Epub ahead of print).
14. Van Bruaene N, Derycke L, Perez-Novo CA, et al.: TGF-beta signaling and collagen disposition in chronic rhinosinusitis. *J Allergy Clin Immunol* 2009, 124:253–259.
15. Li X, Meng J, Liu F, et al.: Expression of transforming growth factor-beta, matrix metalloproteinases and tissue inhibitors of matrix metalloproteinases in Chinese chronic rhinosinusitis patients with and without nasal polyps. *J Allergy Clin Immunol* 2010 (in press).
16. Watelet JB, Bachert C, Claeys C, van Cauwenberge P: Matrix metalloproteinases MMP-7, MMP-9 and their tissue inhibitor TIMP-1: expression in chronic sinusitis versus nasal polyposis. *Allergy* 2004, 59:54–60.
17. Umetsu DT, DeKruyff RH: The regulation of allergy and asthma. *Immunol Rev* 2006, 212:238–255.
18. Walker MR, Carson BD, Nepom GT, et al.: De novo generation of antigen-specific CD41CD251 regulatory T cells from human CD41. *Proc Natl Acad Sci U S A* 2005, 102:4103–4108.
19. Van Bruaene N, Perez-Novo C, Basinski T, et al.: T cell regulation in chronic paranasal sinus disease. *J Allergy Clin Immunol* 2008, 121:1435–1441.
20. Zhang N, Holtappels G, Claeys C, et al.: Pattern of inflammation and impact of *Staphylococcus aureus* enterotoxins in nasal polyposis from South of China. *Am J Rhinol* 2006, 20:445–450.
21. • Zhang N, Van Zele T, Perez-Novo C, et al.: Different types of T effector cells orchestrate mucosal inflammation in chronic sinus disease. *J Allergy Clin Immunol* 2008, 122:961–968. *This article describes for the first time the difference in cytokine patterns between polyps from Asian and Caucasian patients and also demonstrates the common features. Conclusions can be derived on the link of inflammation to remodeling and on the role of predominant T cells in the eosinophilic versus neutrophilic inflammation.*
22. • Bachert C, Zhang N, Holtappels G, et al.: Presence of IL-5 protein and IgE-antibodies to staphylococcal enterotoxins in nasal polyps is associated with co-morbid asthma. *J Allergy Clin Immunol* 2010 (manuscript submitted). *This article analyzes the factors linking nasal polyps to asthma comorbidity: the presence of superantigen-specific IgE antibodies, high titers of IgE and ECP (which increase due to the impact of superantigens), and the presence of IL-5 protein (Th2 bias).*
23. Hellings PW, Hens G, Meyts I, et al.: Aggravation of bronchial eosinophilia in mice by nasal and bronchial exposure to *Staphylococcus aureus* enterotoxin B. *Clin Exp Allergy* 2006, 36:1063–1071.
24. Herz U, Rückert R, Wollenhaupt K, et al.: Airway exposure to bacterial superantigen (SEB) induces lymphocyte-dependent airway inflammation associated with increased airway responsiveness—a model for non-allergic asthma. *Eur J Immunol* 1999, 29:1021–1031.
25. Huvenne W, Callebaut I, Plantinga M, et al.: *Staphylococcus aureus* enterotoxin B facilitates allergic sensitization in experimental asthma. *Clin Exp Allergy* 2010 (in press).
26. van Zele T, Gevaert P, Claeys G, et al.: *Staphylococcus aureus* colonization and IgE antibody formation to enterotoxins is increased in nasal polyposis. *J Allergy Clin Immunol* 2004, 114:981–983.

27. Huvenne W, Callebaut I, Reekmans K, et al.: Staphylococcus aureus enterotoxin B augments granulocyte migration and survival via airway epithelial cell activation. *Allergy* 2010 Feb 4 (Epub ahead of print).
28. Foreman A, Psaltis AJ, Tan LW, Wormald PJ: Characterization of bacterial and fungal biofilms in chronic rhinosinusitis. *Am J Rhinol Allergy* 2009, 23:556–561.
29. Corriveau MN, Zhang N, Holtappels G, et al.: Detection of Staphylococcus aureus in nasal tissue with peptide nucleic acid-fluorescence in situ hybridization. *Am J Rhinol Allergy* 2009, 23:461–465.
30. Hofer MF, Lester MR, Schlievert PM, Leung DY: Upregulation of IgE synthesis by staphylococcal toxic shock syndrome toxin-1 in peripheral blood mononuclear cells from patients with atopic dermatitis. *Clin Exp Allergy* 1995, 25:1218–1227.
31. Hofer MF, Harbeck RJ, Schlievert PM, Leung DY: Staphylococcal toxins augment specific IgE responses by atopic patients exposed to allergen. *J Invest Dermatol* 1999, 112:171–176.
32. Van Zele T, Gevaert P, Holtappels G, et al.: Local immunoglobulin production in nasal polyposis is modulated by superantigens. *Clin Exp Allergy* 2007, 37:1840–1847.
33. Patou J, Van Zele T, Gevaert P, et al.: Staphylococcus aureus enterotoxin B, protein A and lipoteichoic acid stimulations in nasal polyps. *J Allergy Clin Immunol* 2008, 121:110–115. *In this publication, the direct effects of staphylococcal superantigens and other proteins on human nasal turbinate and polyp tissue T cells were investigated. The article also provides evidence that tissues react differently to SAEs depending on their inflammatory background.*
34. Bachert C, Gevaert P, Howarth P, et al.: IgE to Staphylococcus aureus enterotoxins in serum is related to severity of asthma. *J Allergy Clin Immunol* 2003, 111:1131–1132.
35. Kowalski ML, Cieślak M, Pérez-Novo CA, et al.: Clinical and immunological determinants of severe/refractory asthma (SRA): association with staphylococcal superantigen-specific IgE antibodies. *Allergy* 2010 (in press).
36. Barnes PJ: Intrinsic asthma: not so different from allergic asthma but driven by superantigens? *Clin Exp Allergy* 2009, 39:1145–1151.
37. Van Zele T, Gevaert P, Holtappels G, et al.: Oral steroids and doxycycline in nasal polyps: a 3-month double blind, randomized, placebo-controlled trial. *J Allergy Clin Immunol* 2010 (in press).
38. Huvenne W, Zhang N, Tijmsa E, et al.: A pilot study using doxycycline-releasing stents to ameliorate postoperative healing quality after sinus surgery. *Wound Repair Regen* 2008, 16:757–767.
39. Verbruggen K, Van Cauwenberge P, Bachert C: Anti-IgE for the treatment of allergic rhinitis—and eventually nasal polyps? *Int Arch Allergy Immunol* 2009, 148:87–98.