

The role of sinus disease in asthma

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Purpose of review

Some time ago, a link between upper and lower respiratory disease was described, which gave rise to the concept of 'united airways disease'. This concept primarily refers to the well established link between allergic rhinitis and asthma, but it also covers a possible link between sinus disease and asthma (allergic or nonallergic) and other lower airway disease.

Recent findings

The current classification of chronic rhinosinusitis (CRS) includes disease without and with nasal polyps, which are considered subgroups of CRS. Different patterns of inflammatory and regulatory cytokines (involving distinguishable T-helper lymphocyte populations) and of remodelling markers, however, were recently described to differentiate nasal polyposis from CRS, yielding two discrete entities. These patterns resemble those of lower airway diseases, such as asthma and chronic obstructive pulmonary disease, and suggest a common aetiological/pathogenetic background. Whereas the link between nasal polyps and asthma is well established (indeed, asthma improves after medical or surgical treatment of sinus disease), that between CRS and lower airway disease is not well understood. Recently, *Staphylococcus aureus* enterotoxins, acting as superantigens, were identified as a possible link between nasal polyps and asthma, resulting in severe disease manifestations in both upper and lower airways.

Summary

The role played by sinus disease in asthma is only partially understood, largely because of deficits in the clinical classification and in basic knowledge of pathophysiological pathways. Recent research into upper airway and sinus inflammation and remodelling may reveal new perspectives and lead to a classification of sinus disease, which will facilitate appropriate clinical and epidemiological studies.

Keywords

asthma, chronic rhinosinusitis, nasal polyposis, *Staphylococcus aureus*

Abbreviations

COPD	chronic obstructive pulmonary disease
CRS	chronic rhinosinusitis
CT	computed tomography
ECP	eosinophil cationic protein
IFN	interferon
IL	interleukin
SAE	<i>Staphylococcus aureus</i> -derived enterotoxin
TGF	transforming growth factor
Th	T-helper
TNF	tumour necrosis factor

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Introduction

In ancient Greece, Galenus was the first physician to recognize the link between the nose and lung. The link between upper and lower airways is now well established and has led to the concept of 'allergic rhinitis and its impact on asthma' (ARIA) [1]. A body of literature demonstrates the link between allergic rhinitis and asthma; as many as 50% of patients with allergic rhinitis have asthma, and up to 80% of asthma patients appear to suffer also from allergic rhinitis [2–4]. Allergic and non-allergic rhinitis are independent risk factors for development of asthma [5], and hypotheses have been developed to explain the link between allergic rhinitis and asthma. Today, most recent data are in favour of a systemic pathway, involving bloodstream and bone marrow.

Furthermore, comorbidity has also been described between sinus disease and lower airway disease, mostly asthma. Classification based on clinical symptoms, however, is difficult, and even small clinical studies mostly lack clear definitions and proper diagnostic approaches. The present review analyzes the link between sinus disease and asthma, and identifies deficits.

Clinical definition of sinus diseases

According to the European position paper on rhinosinusitis and nasal polyps [6•], rhinosinusitis (including nasal polyps) is clinically defined as an inflammation of the nose and the paranasal sinuses characterized by two or more symptoms including nasal blockage, anterior or postnasal drip, facial pain or pressure, and reduction in or loss of smell. Furthermore, together with the symptoms, there must be endoscopic signs or changes identifiable using computed tomography (CT). Endoscopic signs include presence of polyps, mucopurulent discharge from the middle meatus or oedematous, and mucosal obstruction primarily in the middle meatus. The CT changes are

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mucosal swelling or fluid levels within the ostiomeatal complex or sinuses. Severity of sinus disease can be scored using endoscopy or CT. The endoscopic staging system for polyps gives scores from 0 to 4, depending on the location of polyps with respect to the middle turbinate [7]. The CT staging system modified after Lund-Mackay scores the opacification of the sinus cavities. Detailed scoring will contribute to more precisely defined disease entities, mainly in relation to subgroups of patients with comorbid disease, such as young adults with mild asthma and allergic rhinitis, and adults with severe nasal polyposis and late onset, difficult-to-treat asthma.

For epidemiological studies, however, diagnostic tools are limited to symptoms. In this context, acute rhinosinusitis is defined as sudden onset of two or more of the symptoms mentioned above, with symptoms lasting less than 12 weeks. Chronic rhinosinusitis with or without nasal polyps is defined on the basis of symptoms only, such as nasal obstruction with facial pain or pressure, discoloured discharge, or reduction in or loss of smell. Furthermore, according to the European position paper [6^{**}], the severity of disease can be divided into mild or moderate/severe, based on a visual analogue scale.

Pathophysiology of sinus disease

The nose and the paranasal sinuses are a complex system of air-filled cavities at the entrance to the upper airways. The nose has several highly specific functions, including air conditioning, air filtering and warming inspired air, and may mount an immunologic response to allergens, pollutants and other particles in order to protect the lower airways. The nasal cavity and the adjacent paranasal sinuses have pseudo-stratified epithelium with columnar, ciliated cells resting on a basement membrane. In the submucosa, vessels, glands and nerves are present, and the lamina propria also contains variable amounts of inflammatory cells such as lymphocytes, macrophages, mast cells, dendritic cells, monocytes, eosinophils, neutrophils and basophils [8^{*}].

Rhinosinusitis

In chronic rhinosinusitis (CRS) the mucosa is characterized by goblet cell hyperplasia, limited subepithelial oedema, cell infiltration and presence of fibrosis. A number of factors may contribute to the development of CRS [6^{**},9], including mucociliary impairment [10], bacterial or viral infection [11], allergy [12], swelling of the mucosa for other reasons, and obstruction caused by anatomical variations in the nasal cavity or paranasal sinuses [13]. In CRS a number of inflammatory cells, such as mast cells, lymphocytes and macrophages, are increased [14]. Consequently, levels of some proinflammatory mediators, cytokines and growth factors are also increased in patients with rhinosinusitis compared with individuals without. In

tissue homogenates of acute rhinosinusitis, interleukin (IL)-8 level is significantly increased in comparison with control levels [15], and in CRS tissue there is IL-8 gene expression [16] along with increased IL-8 protein in nasal secretions compared with controls [17,18]. Furthermore, IL-3 is increased in CRS tissue homogenates relative to inferior turbinate samples [15]. Analysis of lavage fluid from patients with CRS reveals high concentrations of histamine, cysteinyl leukotriene and prostaglandin D₂, which are similar to levels obtained after challenge with antigen in patients with allergic rhinitis [19]. These high concentrations may indicate mast cell and basophil stimulation, and they may contribute to the persistent inflammation present in sinusitis. Furthermore, in CRS tissue the expression of transforming growth factor (TGF)- β_1 at RNA and protein levels is significantly greater than that in nasal polyp tissue. Immunohistochemical analysis demonstrates abundant TGF- β_1 staining of the extracellular matrix, which is related to fibrosis [20]. Inflammation and fibrosis of the ostiomeatal complex are believed to be pivotal in CRS, which could give justification to use of the term 'chronic obstructive sinus disease' rather than chronic rhinosinusitis.

Nasal polyposis

Nasal polyps appear as grape-like structures in the upper nasal cavity and are found in the middle nasal meatus or arise from the middle turbinates. Common features in bilateral polyps are pseudocyst formations, a thickened basement membrane, loose connective tissue with a reduced number of vessels and glands, and almost no neural structures. The epithelium is mostly respiratory pseudo-stratified epithelium with ciliated and goblet cells [21].

In patients from Western countries more than 70% of polyps exhibit abundant eosinophils, and these are localized around the vessels, glands and directly beneath the mucosal epithelium [22]. Furthermore, increased concentrations of IL-5 and eotaxin are found within the tissue, inducing eosinophil chemotaxis, migration, activation and prolonged survival [21,23,24]. Regulation of eosinophils in polyps is partially understood; in-vitro treatment of eosinophil infiltrated polyp tissue with neutralizing anti-IL-5 monoclonal antibody resulted in eosinophil apoptosis and decreased tissue eosinophilia [25]. IL-5 is the predominant cytokine in nasal polyposis, reflecting activation and prolonged survival of eosinophils [23], and the highest concentrations of IL-5 are found in polyps from patients with nonallergic asthma and aspirin intolerance [26]. TGF- β_1 is found in low levels in tissue homogenates from patients with nasal polyposis. TGF- β_1 is a fibrogenic growth factor that stimulates extracellular matrix formation and chemotaxis of fibroblasts but inhibits the synthesis of IL-5 [27]. An explanation for pseudocyst formation in nasal polyposis could be the lack of

TGF- β_1 , and overexpression of metalloproteinase-9 and metalloproteinase-7 without the upregulation of the tissue inhibitor of matrix metalloproteinase 1, which may account for the tissue destruction [28*].

In CRS with nasal polyps the eosinophil infiltration is strikingly increased relative to CRS without nasal polyps [29]. Not only is the eosinophil infiltration different between these two entities but also several other inflammatory mediators can differentiate CRS from nasal polyposis. First, nasal polyposis can be differentiated from CRS on the basis of markers of eosinophilic inflammation such as IL-5, eosinophil cationic protein (ECP) and eotaxin, as well as IgE. Second, CRS can be differentiated from nasal polyposis on the basis of levels of interferon (IFN)- γ , TGF- β_1 , myeloperoxidase and tumour necrosis factor (TNF)- α (Table 1). These markers highlight a T-helper (Th)1 compared with Th2 pattern. CRS is characterized by a Th1 response (IFN- γ), with T-regulatory (TGF- β_1) and fibrogenic potential, whereas nasal polyposis is associated with a Th2-pattern (IL-5), inducing vigorous amounts of eosinophils and IgE formation. Increased ECP concentration is a marker of eosinophil activation, and eotaxin (a CC-type chemokine), levels of which are increased, cooperates with IL-5 to recruit and activate eosinophils. Thus, based on cytokine and mediator profiles, CRS without polyps and nasal polyposis can be differentiated as distinct disease entities, opposing the view that CRS and nasal polyposis are in fact the same disease. In the future this differentiation may have considerable impact on the classification of chronic sinus disease, as well as on epidemiological, pathophysiological and therapeutic research [30].

Asthma and chronic obstructive pulmonary disease

Asthma is a chronic inflammatory disorder of the airways and may cause recurrent episodes of wheezing, breathlessness, tightness of the chest and coughing. These episodes are usually associated with widespread but variable airflow obstruction, which is often reversible either spontaneously or with treatment. In contrast, chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response in the

lungs to noxious particles or gases [31]. Both asthma and COPD are airway inflammatory diseases, but they have distinct characteristics. In order of importance, eosinophils, mast cells and CD4⁺ T lymphocytes are the most prominent inflammatory cells in asthma, whereas neutrophils, macrophages and CD8⁺ T cells are prominent in COPD [32]. Consistent with the Th2-dominated tissue inflammatory response in asthma, increased levels of IL-4, IL-5, IL-9 and IL-13 have been identified [33]. In COPD, activated inflammatory cells release a variety of other mediators, mainly IL-8, TNF- α , IFN- γ and leukotriene B₄ [31].

Using cytokine markers, similar patterns have been described in higher and lower airway inflammatory diseases. Of interest, CRS and COPD have a similar cytokine pattern, and nasal polyposis and asthma exhibit striking similarities.

Relationship between sinus disease and asthma

The relationship between sinus disease and asthma may be demonstrated by several means. First, they may be related on an epidemiological basis. Second, demonstration of improvement in asthma after medical or surgical treatment of rhinosinusitis supports such a relationship. Furthermore, some hypotheses have been proposed that could explain this relationship.

Epidemiology

In a study comparing patients with mild-to-moderate asthma with corticosteroid dependent asthmatic patients [34], about 70% of all participants reported symptoms of rhinosinusitis. The total symptom score, however, was significantly higher in patients with severe steroid dependent asthma than in those with mild-to-moderate asthma. In this study the entire corticosteroid dependent (severe asthmatic) group had abnormal CT scans, as compared with about 90% of the mild-to-moderate asthmatic group. Another study [35], however, demonstrated CT scan abnormalities in about 84% of the severely asthmatic patients, and extensive sinus disease was identified in 24% of those patients. Of asthmatic children, 44–70% exhibit clinical, endoscopic, or radiological findings of sinusitis [36–38]. In a group of 25 adult patients with CRS who had failed to respond to medical treatment, 24% had asthma and 36% had small airway disease [39*].

In asthma, 7% of patients have nasal polyposis [40]. The proportion is higher in patients with nonatopic asthma (13%) than in those with atopic asthma (5%) [41]. Late-onset asthma is associated with development of nasal polyposis in 10–15% [40]. In patients with nasal polyposis, approximately 30% have asthma [42] and 15% have aspirin-intolerance [43]. In approximately 69% of

Table 1. Markers differentiating nasal polyposis from chronic rhinosinusitis

	ECP	IgE	IL-5	Eotaxin	TGF- β_1	TNF- α	MPO	IFN- γ
NP	×	×	×	×				
CRS					×	×	×	×

CRS, chronic rhinosinusitis; ECP, eosinophil cationic protein; IFN, interferon; IL, interleukin; MPO, myeloperoxidase; NP, nasal polyposis; TGF, transforming growth factor; TNF, tumour necrosis factor.

patients with both asthma and nasal polyposis, asthma is the first disease to develop, and nasal polyposis takes between 9 and 13 years to be diagnosed. In only 10% of patients with both asthma and nasal polyposis do both diseases develop simultaneously, and in the remaining patients polyps develop first followed 2–12 years later by asthma [44]. In nasal polyposis the male : female ratio is 2 : 1. Women with nasal polyposis, however, are 1.6 times more likely to be asthmatic and 2.7 times more likely to have allergic rhinitis than are men [45].

Patients with asthma, nasal polyposis and aspirin sensitivity are usually nonatopic and the prevalence increases in those older than 40 years. When parents have asthma, nasal polyposis and aspirin sensitivity, their children more commonly have nasal polyposis and rhinosinusitis than do control children [46]. Of 500 patients with aspirin-induced asthma, almost 80% had symptoms of rhinosinusitis such as nasal blockage and rhinorrhoea. Abnormalities in the paranasal sinuses were detected in 75% of these patients. The combination of air-fluid levels, mucosal thickening and opacification was a characteristic finding in the paranasal sinuses. Nasal polyposis was diagnosed in 62% of aspirin-sensitive patients [47].

Epidemiological data on sinusitis and lower airway disease, however, must be evaluated with caution because they are mostly based on symptoms only and do not include nasal endoscopic or CT findings. Thus, the diagnosis of or differentiation between CRS and nasal polyposis is impossible, or at least unreliable, affecting any data on the link between these diseases and lower airway comorbidity. Efforts should be made to generate more reliable data, perhaps even including biomarker screening in mucosal tissue, as discussed above.

Medical and surgical management

One way to approach a possible causal relationship between rhinosinusitis and asthma is to demonstrate improvement in asthma after medical or surgical treatment of rhinosinusitis [48^{*}]. Some older studies concluded that there is a correlation between treatment of rhinosinusitis and improvement in asthma. In one study [49,50], 79% of children with asthma and rhinosinusitis were able to discontinue taking their bronchodilators after receiving antibiotic treatment for their rhinosinusitis. Moreover, pulmonary function tests normalized in 67% of those patients. In addition, improvement in asthma symptoms has been reported [50]. A large group of asthmatic children, both allergic and nonallergic, with rhinosinusitis, exhibited a Th2 polarization at the rhinosinusal level [51]. Treatment for rhinosinusitis in this group with antibiotics and a topical steroid spray plus a short course of oral corticosteroids appears to induce a decrease in IL-4 and an increase in IFN- γ levels [52].

In 18 asthmatic children, a recent study demonstrated an improvement in severity of asthma and respiratory functioning, together with reduced levels of inflammatory cells and a change from a Th2 cytokine profile to a Th1 profile [53]. In another study [54], patients with opacified maxillary sinuses at entry and normal sinus X-rays after 30 days of treatment exhibited a decrease in their sensitivity to metacholine, indicating improvement in their bronchial hyperresponsiveness.

Furthermore, studies have demonstrated the effect of sinus surgery on asthma. After endoscopic sinus surgery in patients with asthma and concomitant rhinosinusitis, there was an improvement in asthma symptoms and reductions in total dosage of steroids and in the number of days of steroid use in the first year after surgery [55]. Moreover there was an improvement in respiratory functions, including increased peak expiratory flow measurements [56] and a significant decrease in bronchial hyperreactivity [57], after sinus surgery. According to questionnaires, after functional endoscopic sinus surgery about 70% of patients had less frequent asthma and 65% had less severe asthma, along with a 75% reduction in hospitalizations and an 81% reduction in acute care visits during the year after the surgery [58]. It appears that treatment for rhinosinusitis has a beneficial effect on asthma. It is likely, however, that medical treatment used after surgery, such as oral antibiotics and oral or topical steroids, also have direct pulmonary effects [59].

Hypotheses explaining the link

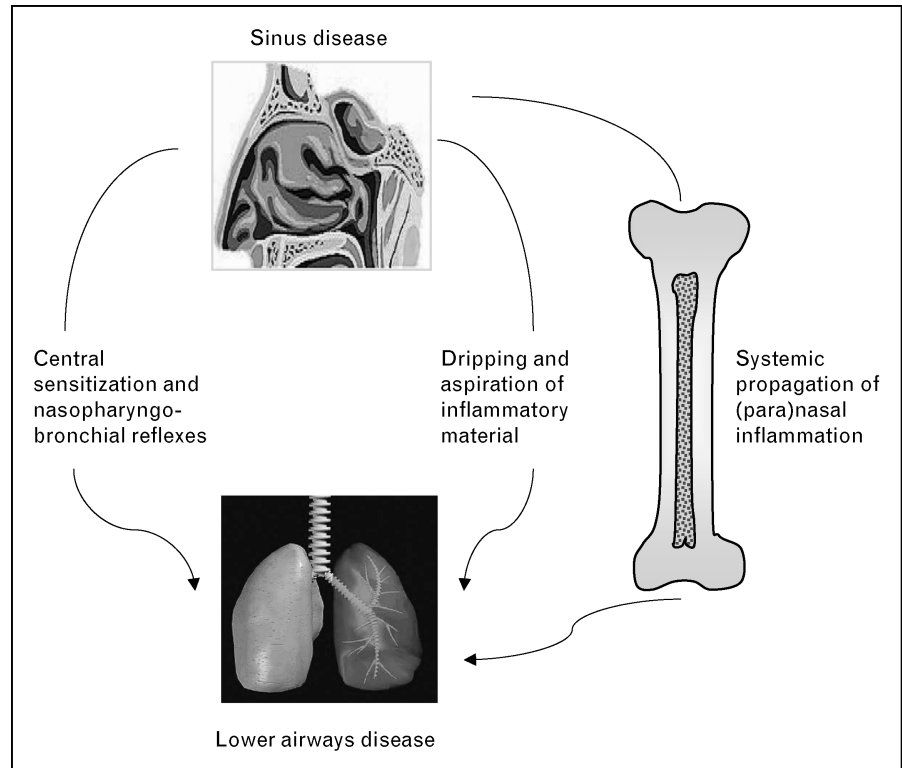
Many pathogenic hypotheses have been proposed to explain the link between sinus disease and asthma (Fig. 1).

It has been suggested that airway hyperresponsiveness in sinusitis may be caused by the activation of a pharyngobronchial reflex. A postulated neuroanatomical pathway that connects the paranasal sinuses to the lungs consists of receptors in the nose, pharynx and sinuses, which give rise to fibres that form a part of the trigeminal nerve. The trigeminal nerve connects with the dorsal vagal nucleus, which sends parasympathetic fibres via the vagus nerve to the bronchi [60^{*}]. In patients with chronic rhinosinusitis the pharyngeal mucosa is damaged, manifesting as epithelial thinning, and there is an increase in pharyngeal nerve fibre density [61]. The pharyngobronchial reflexes may be triggered by drainage of inflammatory mediators and material from infected sinuses into the pharynx.

Another theory to explain the association between sinus disease and asthma pertains to silent dripping of material containing mediators from the nose and aspiration into the bronchial tree. After placing radionuclides into the maxillary sinuses of patients with sinusitis and asthma,

Figure 1 Link between sinus disease and lower airways disease

Summarized are hypotheses explaining the link between sinus disease and lower airways disease.



however, the radionuclide was visible over a 24-hour period in the maxillary sinuses, the nasopharynx, the oesophagus and the lower gastrointestinal tract, but it was impossible to demonstrate any form of pulmonary aspiration [62]. In contrast to this report, pulmonary aspiration of radionuclide-labelled nasal secretions during sleep has been described [63], but there was no difference in aspirated amounts between the asthma/chronic sinusitis group and the control group.

The concept with the best supporting evidence involves the blood circulation and the bone marrow and its responses. Sinus diseases involve production of inflammatory mediators, eosinophil precursors, T-helper lymphocytes and cytokines, which may lead to increased generation of eosinophils, mast cells and basophils in the bone marrow and to subsequent recruitment of cells and mediators into the lungs. In patients with allergic rhinitis, segmental bronchial provocation and nasal provocation induced allergic inflammation in both the nasal and bronchial mucosa. In addition, allergen provocation resulted in an increase in circulating inflammatory cells and mediators [64]. Allergic provocation and release of inflammatory mediators (e.g. IL-5 and eotaxin) from inflammatory sites activate a systemic response that may provoke inflammatory cell production by the bone

marrow. Progenitors may then migrate to the airways and may differentiate into an eosinophilic phenotype [65,66]. The systemic allergic response is characterized by increased expression of adhesion molecules, such as vascular cell adhesion molecule-1 and E-selectin, on nasal and bronchial endothelium, which facilitates migration of inflammatory cells into the tissue [67].

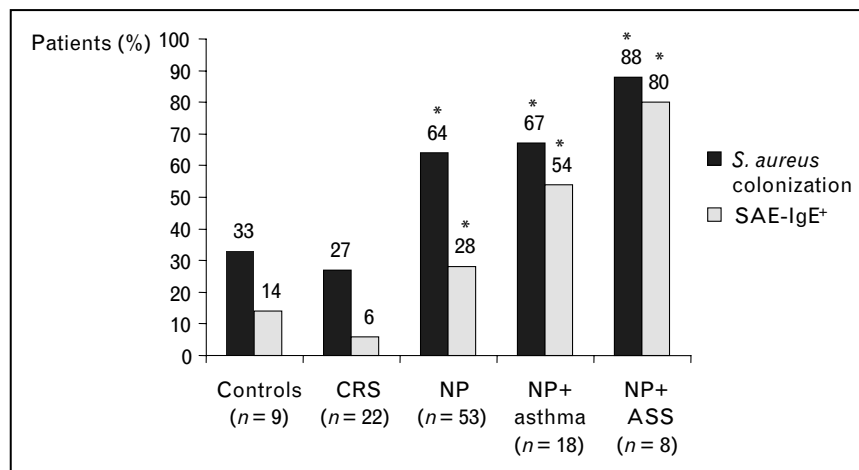
***Staphylococcus aureus* superantigens as disease modifiers**

The cause of bilateral eosinophilic polyps is still largely unknown. A definite association with nonallergic late-onset asthma and with aspirin sensitivity exists, forming the so-called Samter triad [68]. Not all patients with nasal polyposis, however, have aspirin sensitivity and 4% of the general population have nasal polyposis [69], whereas in patients with asthma the prevalence of nasal polyposis is 7–15%, and in patients with aspirin sensitivity prevalence rates of 36–60% have been reported [40,43].

Staphylococcus aureus-derived enterotoxins (SAEs) have been related to the eosinophilic inflammation in nasal polyposis [70]. In the middle meatus of patients with nasal polyposis, as compared with control individuals or patients with CRS without nasal polyposis, there is a

Figure 2 *Staphylococcus aureus* colonization and IgE antibodies to *S. aureus* enterotoxin mix in mucosal tissue

* $P < 0.05$ compared with chronic rhinosinusitis (CRS). ASS, aspirin sensitivity; NP, nasal polyposis; SAE, *S. aureus* enterotoxin. Adapted with permission from [71**].



greater rate of colonization with *S. aureus* [71**]. About 70% of *S. aureus* isolates can form SAEs, which may act as superantigens with potent immunostimulatory properties and which can heavily modify inflammation and induce polyclonal lymphocyte activation and secondary immunoglobulin synthesis.

Specific IgE antibodies, which have been identified as markers of a local immune reaction to classic SAEs (enterotoxins A or B), were found in 50–90% of patients with nasal polyposis [70,71**]. The presence of those IgE antibodies is related to the severity of local disease and comorbidities such as asthma (Fig. 2). Nasal polyposis tissue samples with specific IgE antibodies to SAEs do exhibit high levels of total tissue IgE and a more pronounced eosinophilic inflammation, with higher concentrations of ECP, IL-5 and eotaxin, compared with SAE IgE negative samples [70]. In serum from patients with asthma, IgE antibodies to SAE mix (SAEs A, C and toxic shock syndrome toxin 1) are more often found in patients with severe asthma than in those with mild asthma or control patients [72]. Furthermore, aspirin sensitivity in patients with asthma and nasal polyps is associated with increased concentrations of IgE antibodies to SAEs in polyp tissue [73*,74]. If aspirin sensitivity and asthma accompany nasal polyp disease, then the *S. aureus* colonization rate is as high as 87.5% and IgE antibodies are found in 80% of cases [71**]. Staphylococcal enterotoxins could act as disease modifiers in both upper and lower airway disease, and induce lower airway involvement in sinus disease.

Conclusion

The role of sinus disease in asthma is only partly understood, largely because of deficits in the clinical

classification and in basic knowledge of pathophysiological pathways. The current classification of CRS includes disease without and with nasal polyps, which are considered subgroups of CRS. Different patterns of inflammatory and regulatory cytokines, involving distinguishable T-helper lymphocyte populations, and of remodelling markers, however, have recently been described to differentiate nasal polyposis from CRS as two different entities. First, nasal polyposis can be differentiated from CRS on the basis of markers of eosinophilic inflammation such as IL-5, ECP and eotaxin, as well as IgE. Second, CRS can be differentiated from nasal polyposis on the basis of IFN- γ , TGF- β_1 , myeloperoxidase and TNF- α levels. These patterns resemble those of lower airway diseases, such as asthma and COPD, and suggest a common aetiological/pathogenetic background. In the future, characterization of patients with upper airway diseases on the basis of clinical parameters, infectious agents, inflammatory mechanisms and remodelling processes will permit differentiation of chronic rhinosinusitis into smaller disease entities and will elucidate the link with lower airway diseases.

Whereas the link between nasal polyps and asthma is largely established, that between CRS and lower airway disease is poorly understood. Recently, *S. aureus* enterotoxins, acting as superantigens, were identified as a possible link between nasal polyps and asthma, especially in severe disease manifestations in both upper and lower airways.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 72).

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