

Chronic Rhinosinusitis With and Without Nasal Polyps: What Is the Difference?

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Chronic rhinosinusitis is a heterogeneous group of chronic sinus diseases that may consist of clearly different disease entities. Further investigation of the pathomechanisms of chronic rhinosinusitis and the introduction of appropriate disease markers have recently facilitated disease classification. Evaluation of inflammatory cell profiles, the differentiation of T-effector cells, characterization of remodeling processes such as fibrosis or edema formation, and innate or adaptive immunity products such as Toll-like receptors and immunoglobulins all provide tools to identify distinct disease entities within the group of chronic sinus diseases. This disease differentiation will not only increase our knowledge of the pathophysiology of sinusitis but may lead to new diagnostic and therapeutic strategies specifically targeted and adapted to the diagnosed disease entity.

Introduction

Rhinosinusitis is a considerable and increasing health problem that places a large financial burden on society [1–3]. Its high prevalence has recently spurred increased interest in the pathophysiology of different forms of the disease in an effort to develop better treatment modalities. Because sinusitis usually coexists with rhinitis and isolated sinusitis is rare, the more correct term to use now is *rhinosinusitis*.

Rhinosinusitis is a group of disorders defined as inflammation of the nose and paranasal sinuses and characterized by nasal blockage/obstruction/congestion, nasal discharge, facial pain/pressure, and/or reduction in or loss of smell. The diagnosis is based on these symptoms and their duration, clinical findings, nasal endoscopy, and CT scan. Acute rhinosinusitis—defined as rhinosinusitis lasting less than 12 weeks, with complete resolution of symptoms—is of viral origin in most cases but rarely may be caused by bacterial infections. In these cases, the disease is generally more severe and may lead to complications. It remains speculative whether recurrent acute rhinosinusitis is a prerequisite for the development of chronic rhinosinusitis (CRS)—defined as rhinosinusitis lasting longer than 12 weeks, without complete resolution of symptoms—and may result in persistent obstruction of the ostiomeatal complex [4–6].

CRS, an ill-defined group of sinus diseases used as an umbrella to cover different disease entities, is estimated to affect 15.5% of the US population [7]. CRS with nasal polyps (CRSwNP) may be difficult to differentiate from CRS without nasal polyps (CRSSNP) without the use of nasal endoscopy. Therefore, the two groups are often grouped together as one disease by nonspecialists. However, it is unclear why polyps develop in some patients and not in others. Moreover, nasal polyps (CRSwNP) have a strong tendency to recur after sinus surgery, even when aeration is improved. This reflects a distinct property of those mucosae compared with the mucosae in CRSSNP patients [8].

In specific conditions such as cystic fibrosis (CF) and allergic fungal sinusitis, polyp formation can be differentiated into disease entities based on genetic defects (in CF) and specific IgE immune responses to fungi (in allergic fungal sinusitis) [9,10]. Moreover, development of appropriate disease markers has recently opened new possibilities and facilitated disease classification. These markers may be manifold: inflammatory cells and their products, T-cell differentiation markers, markers of the remodeling processes,

or markers derived from innate or adaptive immunity products. This disease differentiation may help to ameliorate the management of sinusitis by introducing new diagnostic and therapeutic strategies specifically targeted and adapted to the diagnosed disease entity.

A clear epidemiologic and clinical association has been demonstrated between upper and lower airway diseases such as allergic rhinitis and asthma [11], leading to the “united airways” concept. Interestingly, this concept holds true beyond the scope of allergic asthma, as patients with allergic and nonallergic asthma and chronic obstructive pulmonary disease show increased nasal symptoms and more nasal inflammation [12]. Moreover, up to 70% of patients with CRSwNP suffer from asthma, and there is evidence of bronchial hyperreactivity in CRSwNP patients without a history of asthma, particularly non-atopic patients [13]. The link of upper and lower airways is again reflected by the fact that medical or surgical treatment of nasal polyposis may have an impact on the control of asthma in those individuals. Until now, the link between upper airway disease and comorbid lower airway pathology had not been fully understood, possibly due to the ill-defined upper airway disease entities.

Prevalence and Pathophysiology

Prevalence

When reviewing the literature, it becomes clear that the estimation of CRS prevalence remains speculative because of the heterogeneity of this group of disorders and the diagnostic uncertainties. As mentioned previously, CRS has an estimated prevalence of 15.5% in the United States, ranking it second among all chronic conditions. This high prevalence was confirmed by another survey suggesting that 16% of the adult US population has CRS [14]. In a Canadian study, prevalence was shown to increase with age, with a mean of 2.7% in people 20 to 29 years old and 6.6% in those 50 to 59 years old. After the age of 60, prevalence levels of CRS leveled off to 4.7% [15]. In Belgium, Gordts et al. [16] reported that 6% of individuals in the general population suffered from chronic nasal discharge. However, a recent population-based survey found that 16% of the adult population suffered from signs of CRS (GA³LEN [Global Allergy and Asthma European Network] survey, unpublished data).

The prevalence of CRSwNP in the general population is commonly considered low [17]. Valid epidemiologic studies are lacking, and that an endoscopic examination is necessary for diagnosis further complicates such approaches. In a postal questionnaire survey of a population-based random sample of 4300 adult women and men 18 to 65 years old in southern Finland, the prevalence of CRSwNP was 4.3%, and nasal polyposis and aspirin sensitivity were associated with an increased risk of asthma [18]. The prevalence of doctor-diagnosed aspirin sensitivity was 5.7%. The incidence was higher in men than in women and increased significantly after the age of 40 years [19].

Pathophysiology

A distinct pathophysiology was proposed for the different CRS subgroups. CRSsNP displays a predominantly neutrophilic inflammation, whereas CRSwNP is dominated by eosinophilic inflammatory mechanisms in about 80% of cases and may be accompanied by aspirin sensitivity and asthma. Recently, the role of bacterial infection in CRSsNP [20] was challenged, whereas a modifying role of colonizing *Staphylococcus aureus* in CRSwNP was introduced.

Fungal disease

Fungi are increasingly recognized as important pathogens in sinusitis. Fungal infection, mainly by molds, can impose severe, acute, and chronic sinusitis in the immunocompromised host. In contrast, fungi are regarded as frequent innocent bystanders when cultured from the respiratory tract of immunocompetent hosts [21]. The concept of fungi involvement in CRS should be that the ubiquitous airborne fungi become entrapped in sinonasal mucus, are attacked by eosinophils, and cause—via the release of toxic granules from eosinophils—secondary mucosal inflammation in susceptible individuals. If this is true, fungal eradication via intranasal antifungals should improve the course of the disease. However, in a double-blind, placebo-controlled, multicenter trial, no benefit of adding amphotericin B nasal lavages to intranasal steroids and irrigations in patients with CRSwNP or CRSsNP with a previous history of endoscopic sinus surgery was shown [22]. These results confirm the concept of extramucosal fungi being innocent bystanders in the upper respiratory tract and playing no demonstrable role in the pathophysiology of CRS in immunocompetent patients.

Cystic fibrosis

In children suffering from nasal polyp formation, systemic diseases such as CF must be considered. CF is the most common fatal inherited disease among Caucasians, affecting approximately 1 in 2000 live births. The basic metabolic derangement is related to a mutation in the gene regulating the chloride transport in epithelial cells. Although bacterial infection is widely accepted as a major factor in the pathogenesis of acute exacerbations and chronic progression of lung disease in CF, it remains unclear if the CF-specific sinonasal pathogens, of which *S. aureus*, *Pseudomonas aeruginosa*, *Haemophilus influenza*, and anaerobes are the most common, play a particular role in the pathogenesis of CF with nasal polyposis (CF-NP). Because of the disease’s ubiquitous and persistent nature and the often transient effect of surgery, sinus surgery should only be performed in cases of sufficient symptoms or before lung transplantation. The development of functional endoscopic sinus surgery has decreased the morbidity of sinus surgery and reduced the recurrence of nasal polyposis in CF [23–25]. A careful postoperative follow-up is mandatory but often difficult in young patients. Nasal irrigations with saline solution may help to clean the cavities after surgery.

Signs and symptoms

The pattern of symptoms and signs caused by CRS is somewhat overlapping in all patients with chronic sinus inflammation, with most symptoms occurring in CRSsNP and CRSwNP. However, looking at the symptom profiles in more detail, patients suffering from CRSwNP have a more pronounced nasal obstruction and loss of smell, while CRSsNP patients complain more of headache and postnasal drip [26••]. In particular, the partial or complete loss of smell with a subsequent effect on taste and the loss of the ability to discriminate subtleties of flavor is a typical feature of CRSwNP. Even with obstructed sinuses, CRSwNP patients with no prior surgery rarely complain of facial pain or headache, although they have more extensive opacifications on CT scan as evaluated with the Lund-Mackay score compared with CRSsNP patients.

Cytokines, Mediators, and Cellular Profiles

To differentiate more clearly between the different disease entities that comprise chronic sinus disease, identifying inflammatory cells and the array of cytokines and mediators they release may prove very useful. It was demonstrated that CRSsNP, CRSwNP, and CF-NP are dissociated disease entities with distinct cytokine, mediator, and cellular profiles (Fig. 1A and Fig. 1B) [26••]. These groups share a T-cell-mediated immune response, although different T-lymphocyte subsets contribute to it. When analyzing diseased tissue from CRSsNP and CRSwNP patients, a clear T-helper type 1 (Th1)/Th2 polarization becomes clear, with interferon- γ (Th1 related) characterizing CRSsNP, whereas interleukin (IL)-5 (Th2 related) is emblematic for CRSwNP. Moreover, inflammation in CRSwNP is accompanied by abundant eosinophils and IgE formation, again stressing the Th2 bias in this disease. Eosinophilic inflammation is a key feature of CRSwNP, with highly increased concentrations of eosinophil cationic protein (ECP) as a marker of eosinophil activation and of eotaxin, a CC chemokine that cooperates with IL-5 to recruit and activate eosinophils [27]. Interestingly, these markers of eosinophilic inflammation, which are increased in CRSwNP compared with control patients and with CRSsNP patients, are further increased in polyps with IgE antibodies to *S. aureus* enterotoxins, pointing toward a modifying role for these bacterial superantigens in the pathophysiology of CRSwNP. Staphylococcal superantigens induce a polyclonal T-cell and B-cell activation with multiclonal IgE formation and T-cell activation, severely amplifying the eosinophilic inflammation [28,29]. In contrast, specific IgE to enterotoxins and multiclonal IgE formation in tissue is a rare finding in CRSsNP and CF-NP [30], although *S. aureus* belongs to the usual germ flora, particularly in upper airway manifestations of CF [31].

Nasal polyps in CF patients also show edema formation and matrix disruption but display a prominent neutrophilic rather than eosinophilic inflammation and

a significantly lower tissue ECP concentration compared with CRSwNP, suggesting that the typical edema formation in CRSwNP may not be exclusively dependent on tissue eosinophilia and eosinophilic activation. The apparent neutrophilic inflammation in CF-NP is characterized by high IL-8 (a CXC chemokine), myeloperoxidase (MPO, released by neutrophil granulocytes), and proinflammatory mediator IL-1 β concentrations.

CRSwNP and CF-NP not only differ in terms of inflammatory cell and cytokine patterns but also in terms of expression of innate markers [30]: CF-NP is associated with the upregulation of human β -defensin 2 and Toll-like receptor 2, whereas the expression of the macrophage mannose receptor dominates the innate defense in non-CF-NP. These apparent differences point toward a variable inflammatory background in CRSwNP and nasal polyps in CF.

T-cell biology

T-cell polarization of CRSsNP (Th1) and CRSwNP (Th2) is controlled by intracellular mechanisms that initiate differentiation of naïve T cells toward the distinct T-cell subtypes based on the expression of certain transcription factors. T-box transcription factor (T-bet) involves commitment toward Th1 cells; GATA-3 is critical for commitment toward Th2 cells and controls the expression of IL-4 and IL-5. T-regulatory cells (Tregs)—another T-cell subset characterized by the transcription factor forkhead box P3 (FoxP3)—control the balance between Th1 and Th2 cells and limit chronic inflammation. Interestingly, we recently showed a decreased expression of FoxP3 mRNA and protein immunohistochemistry in CRSwNP tissue, which reflects a deficiency of Tregs in this often persistent, severely inflamed sinus mucosa [32••]. Consequently, lower transforming growth factor (TGF)- β 1 protein levels were found in this group, which led to a defective suppression of Th1 and Th2 transcription signals in CRSwNP. In contrast, adequate expression of FoxP3 with increased TGF- β 1 protein levels was found in CRSsNP, which resulted in maintained control over Tbet and GATA-3 expression and suggested adequate Treg function in this sinus disease subgroup. These differences in T-cell biology again clearly distinguish CRSwNP from CRSsNP entities.

In addition to Th1/Th2/Tregs, other T-cell subsets such as the recently described Th17 cells can be used to further divide and characterize disease entities within the CRSwNP group. Although clinical appearance, mucosal edema formation, T-effector cell activation, and Treg impairment (decreased FoxP3 expression) are shared by nasal polyps in European and Asian populations, the pattern of inflammation is remarkably different between the disease groups, with a Th1/Th17 dominance in South Chinese and a Th2 dominance in Belgian polyps [33••]. This Th1/Th17 effector cell polarization in South Chinese CRSwNP was characterized by Tbet expression, interferon- γ protein formation, and IL-17 and related IL-1 β

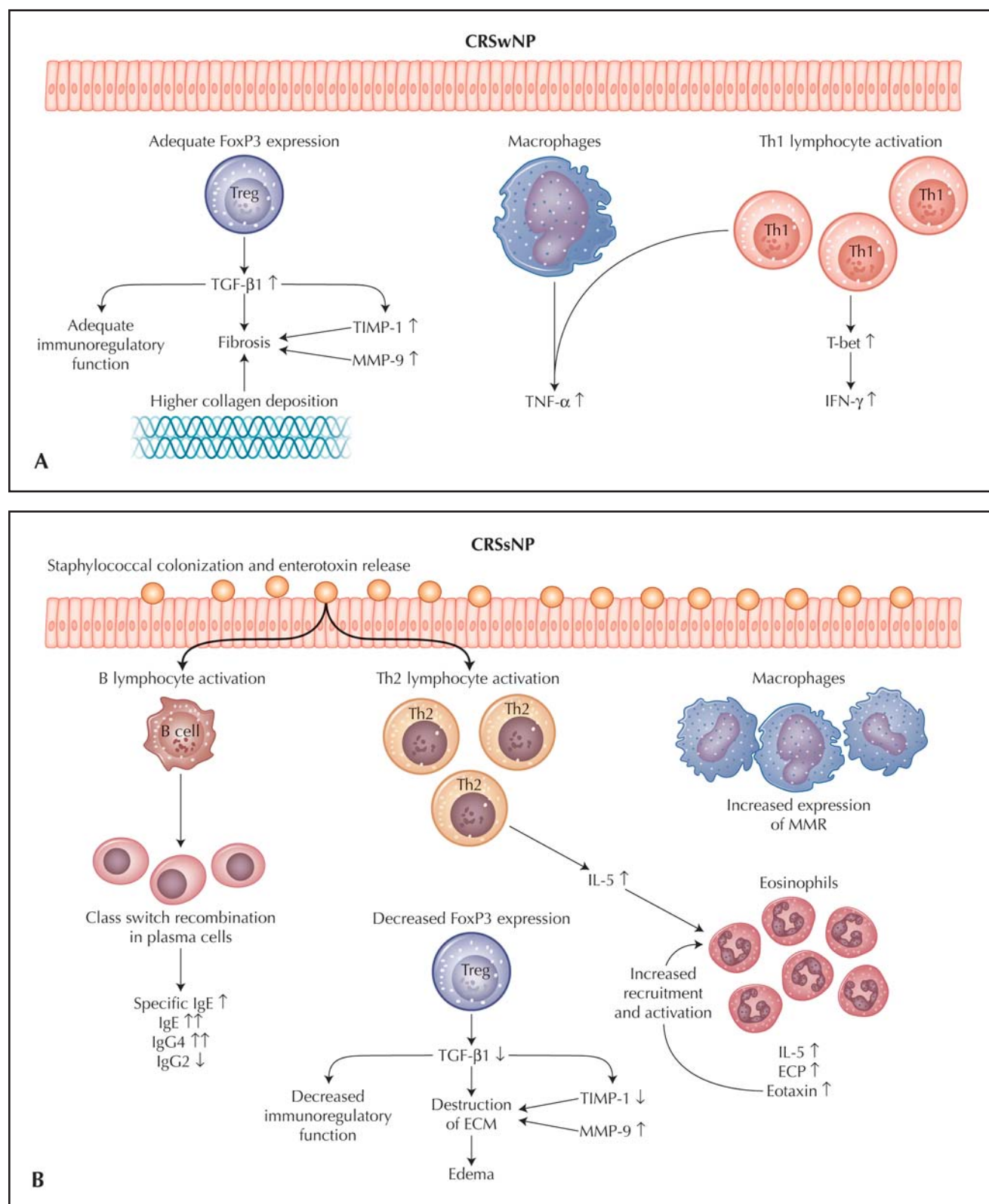


Figure 1. Chronic rhinosinusitis without (A) and with (B) nasal polyps. CRSsNP—chronic rhinosinusitis with nasal polyps; CRSwNP—chronic rhinosinusitis without nasal polyps; ECM—extracellular matrix; ECP—eosinophil cationic protein; FoxP3—forkhead box P3; IFN—interferon; IL—interleukin; MMP—matrix metalloproteinase; MMR—macrophage mannose receptor; T-bet—T-box transcription factor; TGF—transforming growth factor; Th—T-helper cell; TIMP—tissue inhibitor of matrix metalloproteinase; TNF—tumor necrosis factor; Treg—T-regulatory cell.

and IL-6 protein synthesis in tissue homogenates, whereas Belgian CRSwNP demonstrated increased GATA-3 expression with consequently raised IL-5 protein levels compared with control tissue. Moreover, these differences in T-cell biology are reflected by a distinguished neutrophil and eosinophil granulocyte activation bias in South Chinese and Belgian CRSwNP, respectively, which is reflected in a significantly lower ECP/MPO ratio in South Chinese compared with Belgian CRSwNP. These findings largely affect treatment approaches for CRSwNP, as treatment in daily practice in Europe and the United States focuses on eosinophils, with topical and systemic corticosteroids and humanized anti-IL-5 monoclonal antibodies becoming a treatment option in the future. It is very unlikely that the anti-IL-5 concept will be appropriate in neutrophilic IL-17-biased CRSwNP in Asia or CF-NP in Europe [33••].

Remodeling

Chronic inflammation in the nose and paranasal sinuses eventually results in tissue destruction and remodeling processes within the mucosa that are characterized by changes in the extracellular matrix (ECM) protein deposition and tissue structure. A major role in airway remodeling is played by TGF- β , a pleiotropic and multifunctional growth factor with important immunomodulatory and fibrogenic characteristics. Interestingly, the distinct disease entities within chronic sinus disease display significantly different levels of TGF- β 1, with high levels of TGF- β 1 in CRSsNP and conversely low TGF- β 1 levels in CRSwNP [26••,29,32••]. These low TGF- β 1 levels may reflect the decreased Treg function in CRSwNP, which was confirmed by low FoxP3 levels. However, the high TGF- β 1 levels and adequate expression of FoxP3 in CRSsNP mirror the adequate control of inflammation. Moreover, recent immunohistochemistry findings confirm these data and show increased TGF- β 1 receptor expression and increased active intracellular signal in CRSsNP [34].

In addition to its immunomodulatory effect, TGF- β plays a crucial role in ECM metabolism, as it acts as a master switch in the induction of fibrosis. TGF- β counteracts tissue destruction that can result from inflammation by inducing fibrogenesis. Moreover, it induces the expression of ECM proteins in mesenchymal cells and stimulates the production of tissue inhibitor of matrix metalloproteinase (TIMP)-1, which prevents enzymatic breakdown of the ECM [35]. In CRSsNP, matrix metalloproteinase (MMP)-9 and TIMP-1 are upregulated, while in CRSwNP, MMP-9, but not TIMP-1, is upregulated, which is in line with the observed edema formation in CRSwNP. The observed lack of upregulation of TIMP-1 can be related to the low TGF- β 1 levels in CRSwNP [36–38]. Furthermore, the ECM remodeling pattern in CRSwNP is characterized by a low amount of collagen compared with control tissue, without thick collagen fibers. The lack of TGF- β 1 in CRSwNP can be interpreted as a lack of tissue repair, reflected by loose connective tissue and edema formation in a severely

inflamed tissue. In contrast, remodeling in CRSsNP results in a higher collagen content compared with controls. This is indicative of excessive tissue repair and fibrosis formation in CRSsNP. These differences in TGF- β signaling clearly support the distinction of CRSsNP and CRSwNP as separate disease entities.

Role of SAE

The finding of IgE antibodies to *S. aureus* enterotoxins in CRSwNP tissue homogenates indicates that superantigens could be involved in this disease's pathogenesis [39•]. We previously reported an increased colonization rate of *S. aureus* in CRSwNP patients but not in CRSsNP patients [28]. Colonization with *S. aureus* was present in more than 60% of patients with CRSwNP, with rates as high as 87% in the subgroup with asthma and aspirin sensitivity, which were significantly higher than those seen in controls and patients with CRSsNP (33% and 27%, respectively).

IgE antibodies to *S. aureus* enterotoxins were present in 28% of polyp samples, with rates as high as 80% in the subgroup with asthma and aspirin sensitivity, compared with 15% seen in controls and 6% in patients with CRSsNP. The presence of specific IgE against *S. aureus* enterotoxins also coincided with higher levels of IL-5, eotaxin, and ECP. Moreover, an increased number of T cells expressing the T-cell receptor β -chain variable region known to be induced by microbial superantigens was detected in CRSwNP and correlated with the presence of specific IgE against *S. aureus* enterotoxin [40]. These findings confirm the role played by *S. aureus* enterotoxins as disease modifiers specifically in CRSwNP. Interestingly, stimulation of CRSwNP tissue with staphylococcal enterotoxin B results in significantly higher release of pro-inflammatory cytokines compared with controls. Besides induction of T-cell activation, staphylococcal enterotoxin B introduced a bias toward Th2 cytokines, as IL-4 and IL-5 production was favored [41].

The strikingly high correlation between IL-5 and IgE antibody concentrations in CRSwNP homogenates supports the hypothesis that *S. aureus* enterotoxins, apart from T cells, also modify B and plasma cells [27]. In fact, accumulating evidence indicates that *S. aureus* enterotoxins can directly affect the frequency and activation of the B-cell repertoire. We recently described a markedly increased number of plasma cells in sinonasal mucosal tissue samples from CRSwNP patients as compared with those from CRSsNP patients and controls. We have recently extended these findings with *S. aureus*-specific data. In a follow-up study, high concentrations of IgE, IgA, and IgG were measured in CRSwNP homogenates, and these concentrations were significantly greater in CRSwNP than in CRSsNP patients and controls. These changes were not reflected in the serum of patients; the presence of *S. aureus* enterotoxin-IgE antibodies in tissue or serum did not influence immunoglobulin concentrations in serum, confirming the notion of a local impact of superantigens—via direct action

on B cells or indirectly via T-cell–derived cytokines—on immunoglobulin synthesis [42].

Our group is currently investigating the functional role played by local IgE antibodies in CRSwNP, and others have called it into question by observations in ragweed-sensitive polyp patients who do not exhibit specific seasonal changes in symptoms or mediators [43]. In laboratory experiments in which basophils armed with specific IgE to enterotoxin B were exposed to the superantigen, however, the basophils degranulated rapidly [44]. Thus, enterotoxin-specific IgE antibodies could contribute to the disease via degranulation of mast cells in polyp tissue, as well as other IgE antibodies with specificities against inhalant allergens. Indeed, because of the multiclonality, hundreds of allergens could induce a constant degranulation of those mast cells, a condition that has been observed in polyp tissue [41]. Based on these observations, anti-IgE treatment could suppress the IgE-mediated inflammatory cascade in a nonallergic disease such as CRSwNP, similar to its activity in allergic respiratory disorders. A proof-of-concept study is currently being conducted at the Ear, Nose and Throat Department of the Ghent University Hospital.

These findings provide increasing evidence that *S. aureus*–derived enterotoxins modify inflammation in CRSwNP but not in CRSsNP.

Treatment

Medical treatment consisting of nasal corticosteroids (sprays/drops) and antibiotics with anti-inflammatory activities is the first step in treatment, but surgery is indicated for CRSsNP and CRSwNP in the case of failure. Clear diagnosis and management schemes for both CRSsNP and CRSwNP for general practitioners; non-ear, nose, and throat specialists; and ear, nose, and throat specialists are published in the EP3OS position paper, which summarizes the current knowledge [45•]. Functional endoscopic sinus surgery has become the standard procedure to restore sinus ventilation and drainage by opening the key areas while preserving sinus mucosa. An overall success rate of 85% is reported in primary functional endoscopic sinus surgery, with a 2% to 24% failure rate because of recurrence of disease or poor healing because of persistent inflammation and/or bacterial colonization [46,47]. In approximately 18% of patients, poor healing is linked to abnormal scarring, superinfection, and fibrosis formation, with these complications potentially leading to revision surgery [48]. The healing prognosis in CRSwNP patients is worse compared with patients with CRSsNP, especially if CRSwNP is associated with asthma and/or aspirin sensitivity. Previous data from our group demonstrated that preoperative and postoperative levels of MMP-9 are significantly and independently predictive of the healing outcome [49]. This was clinically linked to the diagnosis of CRSwNP rather than CRSsNP, as well as to previous surgery. Indeed, patients with high concentrations of MMP-9 (and probably other MMPs, not

balanced by TIMPs) in the preoperative and late postoperative period suffered from poor healing. Moreover, recent data support the hypothesis that MMP-9 can serve as a target for therapeutic intervention to achieve better healing quality [50].

Consistent with current knowledge on the pathophysiology of CRSwNP, new therapeutic approaches could focus on eosinophilic inflammation, eosinophil recruitment, the T cell as the orchestrating cell, and IgE antibodies, as well as on tissue destruction and remodeling processes. The introduction of monoclonal humanized antibodies recently yielded new perspectives that are being evaluated in clinical studies. An IL-5 antagonist, reslizumab, induced a reduction of blood eosinophil numbers and concentrations of ECP up to 8 weeks after treatment in serum and nasal secretions [51•]. Individual nasal polyp scores improved in only half of the verum-treated patients for up to 4 weeks. Upon careful analysis of responders and nonresponders in a post hoc analysis, only CRSwNP patients with increased baseline levels of IL-5 (> 40 pg/mL) in nasal secretions seemed to benefit from the anti-IL-5 treatment. Furthermore, nasal IL-5 levels decreased only in responders, while they increased in nonresponders. These data show that in at least 50% of the CRSwNP patients, IL-5 and eosinophils play a key role (IL-5 dependent) in sustaining polyp size, whereas in others, eosinophils may be dependent on other factors (IL-5 independent) or lacking [51•].

As mentioned previously, our group is evaluating the principle of IgE antagonism in CRSwNP to suppress the IgE-mediated inflammatory cascade. Other therapies focus on neutralization of CCR3 or eotaxin and their role in the regulation of eosinophil, basophil, and potentially Th2 and mast cell recruitment. Moreover, future therapies in CRSwNP may consist of anti-IL-4, anti-IL-13, MMP inhibitors, or immunosuppression with ciclosporin, for example. However, until now, none of these therapies have been evaluated in randomized, placebo-controlled clinical trials in CRSwNP.

We have demonstrated in several studies the microbial involvement in CRSwNP [28,52]. In that respect, doxycycline was evaluated as systemic treatment, based on its antimicrobial and anti-inflammatory effects. In a double-blind, placebo-controlled trial, doxycycline showed an effect on bilateral CRSwNP, as it reduced polyp size and postnasal drip and increased peak nasal inspiratory flow. Furthermore, doxycycline significantly reduced local inflammation in terms of ECP, IgE, MPO, and MMP-9. The reduction of ECP reflects a downregulation of eosinophil activation. Together with the decrease in IgE, it may reflect the antistaphylococcal activity, while the drop in MPO reflects diminished neutrophilic activity. The MMP-9 suppressive effect, which represents a specific activity of tetracyclines, favors a beneficial remodeling of the polyp tissue, leading to a reduction in matrix degradation and edema formation. The observed decrease in polyp size therefore may require the antimicrobial and anti-inflammatory effect of doxycycline.

Another anti-inflammatory approach is long-term treatment with macrolide antibiotics. Several clinical reports demonstrated that long-term, low-dose macrolide antibiotics are effective in treating CRS that is not curable via surgery or glucocorticosteroid treatment, with an improvement in symptoms varying between 60% and 80% [45•]. The exact mechanism of action is unknown but may involve downregulation of the local host immune response as well as downgrading of the virulence of the colonizing bacteria. However, placebo-controlled studies are necessary to clarify whether macrolide therapy is acceptable as evidence-based medicine in chronic sinus disease.

Conclusions

CRS is a heterogeneous group of inflammatory conditions in the nose and paranasal cavities. Differentiation between disease entities is mandatory to achieve progress in the diagnosis and treatment of CRSwNP and CRSsNP. The orchestrating T-effector cells, remodeling patterns, and type of inflammation clearly differ between groups. The use of disease markers, which may be manifold, will allow clear differentiation and accurate diagnosis, resulting in more precise and focused treatment. This principle may increase the success rate of medicinal and surgical treatment, as therapies could be modified according to the specific disease entity. It will be our task to phenotype patients based on clinical and biologic markers so as to recommend an optimal individualized treatment for CRS patients in the near future.

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Disclosure

No potential conflicts of interest relevant to this article were reported.

References and Recommended Reading

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

- Of importance
- Of major importance

1. Goetzel RZ, Hawkins K, Ozminkowski RJ, Wang S: The health and productivity cost burden of the "top 10" physical and mental health conditions affecting six large U.S. employers in 1999. *J Occup Environ Med* 2003, 45:5–14.
2. Ray NF, Baraniuk JN, Thamer M, et al.: Healthcare expenditures for sinusitis in 1996: contributions of asthma, rhinitis, and other airway disorders. *J Allergy Clin Immunol* 1999, 103:408–414.
3. Durr DG, Desrosiers MY, Dassa C: Impact of rhinosinusitis in health care delivery: the Quebec experience. *J Otolaryngol* 2001, 30:93–97.
4. Gwaltney J: Microbiology of sinusitis. In *Sinusitis: Pathophysiology and Treatment*. Edited by Druce HM. New York: Marcel Dekker; 1994:41–56.
5. Baraniuk J: Physiology of sinusitis. In *Sinusitis: Pathophysiology and Treatment*. Edited by Druce HM. New York: Marcel Dekker; 1994:19–40.
6. Stammberger H: Endoscopic endonasal surgery—concepts in treatment of recurring rhinosinusitis. Part I. Anatomic and pathophysiologic considerations. *Otolaryngol Head Neck Surg* 1986, 94:143–147.
7. Collins JG: Prevalence of selected chronic conditions: United States, 1990–1992. *Vital Health Stat* 10 1997, Jan:1–89.
8. Benninger MS: Rhinitis, sinusitis, and their relationships to allergies. *Am J Rhinol* 1992, 6:37–43.
9. Ratjen F, Doring G: Cystic fibrosis. *Lancet* 2003, 361:681–689.
10. Schubert MS: Allergic fungal sinusitis. *Otolaryngol Clin North Am* 2004, 37:301–326.
11. Bousquet J, Van Cauwenberge P, Khaltaev N: Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001, 108:S147–S334.
12. Hens G, Vanaudenaerde BM, Bullens DM, et al.: Sinonasal pathology in nonallergic asthma and COPD: 'united airway disease' beyond the scope of allergy. *Allergy* 2008, 63:261–267.
13. Miles-Lawrence R, Kaplan M, Chang K: Methacholine sensitivity in nasal polyposis and the effects of polypectomy [abstract]. *J Allergy Clin Immunol* 1982, 69:102.
14. Blackwell DL, Collins JG, Coles R: Summary health statistics for U.S. adults: National Health Interview Survey, 1997. *Vital Health Stat* 10 2002, May:1–109.
15. Chen Y, Dales R, Lin M: The epidemiology of chronic rhinosinusitis in Canadians. *Laryngoscope* 2003, 113:1199–1205.
16. Gordts F, Clement PA, Buisseret T: Prevalence of sinusitis signs in a non-ENT population. *ORL J Otorhinolaryngol Relat Spec* 1996, 58:315–319.
17. Hosemann W, Gode U, Wagner W: Epidemiology, pathophysiology of nasal polyposis, and spectrum of endonasal sinus surgery. *Am J Otolaryngol* 1994, 15:85–98.
18. Hedman J, Kaprio J, Poussa T, Nieminen MM: Prevalence of asthma, aspirin intolerance, nasal polyposis and chronic obstructive pulmonary disease in a population-based study. *Int J Epidemiol* 1999, 28:717–722.
19. Moloney JR: Nasal polyps, nasal polypectomy, asthma, and aspirin sensitivity. Their association in 445 cases of nasal polyps. *J Laryngol Otol* 1977, 91:837–846.
20. Meltzer EO, Hamilos DL, Hadley JA, et al.: Rhinosinusitis: establishing definitions for clinical research and patient care. *Otolaryngol Head Neck Surg* 2004, 131:S1–S62.
21. Uffredi ML, Mangiapan G, Cadranet J, Kac G: Significance of *Aspergillus fumigatus* isolation from respiratory specimens of nongranulocytopenic patients. *Eur J Clin Microbiol Infect Dis* 2003, 22:457–462.
22. Ebbens FA, Scadding GK, Badia L, et al.: Amphotericin B nasal lavages: not a solution for patients with chronic rhinosinusitis. *J Allergy Clin Immunol* 2006, 118:1149–1156.
23. Gysin C, Althman GA, Papsin BC: Sinonasal disease in cystic fibrosis: clinical characteristics, diagnosis, and management. *Pediatr Pulmonol* 2000, 30:481–489.
24. Coste A, Idrissi F, Beutru R, et al.: [Endoscopic endonasal ethmoidectomy in severe sinusitis of cystic fibrosis. Mid-term results in 12 patients]. *Ann Otolaryngol Chir Cervicofac* 1997, 114:99–104.
25. Jones JW, Parsons DS, Cuyler JP: The results of functional endoscopic sinus (FES) surgery on the symptoms of patients with cystic fibrosis. *Int J Pediatr Otorhinolaryngol* 1993, 28:25–32.

- 26.●● Van Zele T, Claeys S, Gevaert P, et al.: **Differentiation of chronic sinus diseases by measurement of inflammatory mediators.** *Allergy* 2006, 61:1280–1289.

This paper focuses on the possibility of identifying chronic sinus disease subgroups via inflammatory mediators. It clearly shows the T-cell polarization in CRSsNP (Th1) versus CRSwNP (Th2), suggesting different pathomechanisms in the distinct disease groups.

27. Bachert C, Gevaert P, Holtappels G, et al.: **Nasal polyposis: from cytokines to growth.** *Am J Rhinol* 2000, 14:279–290.
28. 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, 114:981–983.
29. 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, 107:607–614.
30. Claeys S, Van Hoecke H, Holtappels G, et al.: **Nasal polyps in patients with and without cystic fibrosis: a differentiation by innate markers and inflammatory mediators.** *Clin Exp Allergy* 2005, 35:467–472.
31. Muhlebach MS, Stewart PW, Leigh MW, Noah TL: **Quantitation of inflammatory responses to bacteria in young cystic fibrosis and control patients.** *Am J Respir Crit Care Med* 1999, 160:186–191.
- 32.●● Van Bruaene N, Perez-Novo CA, Basinski TM, et al.: **T-cell regulation in chronic paranasal sinus disease.** *J Allergy Clin Immunol* 2008, 121:1435–1441.

This paper demonstrated for the first time a deficit in FoxP3 expression in CRSwNP compared with control tissue, reflecting a deficiency in Tregs leading to inadequate control of inflammation. Conversely, adequate FoxP3 expression was found in CRSsNP, mirroring ample disease control.

- 33.●● 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 paper shows the differentiation within the CRSwNP group, with a Th1/Th17 polarization in South Chinese CRSwNP versus Belgian CRSwNP depicting the neutrophilic IL-17-biased CRSwNP in Asia.

34. Van Bruaene N, Derycke L, Perez-Novo CA, et al.: **TGF-beta signaling and collagen deposition in chronic rhinosinusitis.** *J Allergy Clin Immunol* 2009 (in press).
35. 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 vs nasal polyposis.** *Allergy* 2004, 59:54–60.
36. Kostamo K, Tervahartala T, Sorsa T, et al.: **Metalloproteinase function in chronic rhinosinusitis with nasal polyposis.** *Laryngoscope* 2007, 117:638–643.
37. Lechapt-Zalcman E, Coste A, d'Ortho MP, et al.: **Increased expression of matrix metalloproteinase-9 in nasal polyps.** *J Pathol* 2001, 193:233–241.
38. Chen YS, Langhammer T, Westhofen M, Lorenzen J: **Relationship between matrix metalloproteinases MMP-2, MMP-9, tissue inhibitor of matrix metalloproteinases-1 and IL-5, IL-8 in nasal polyps.** *Allergy* 2007, 62:66–72.
- 39.● Bachert C, Zhang N, Patou J, et al.: **Role of staphylococcal superantigens in upper airway disease.** *Curr Opin Allergy Clin Immunol* 2008, 8:34–38.

This review summarizes the evidence of the implication of *S. aureus* in CRSwNP as a disease-modifying factor.

40. Tripathi A, Kern R, Conley DB, et al.: **Staphylococcal exotoxins and nasal polyposis: analysis of systemic and local responses.** *Am J Rhinol* 2005, 19:327–333.
41. Patou J, Gevaert P, Van Zele T, et al.: **Staphylococcus aureus enterotoxin B, protein A, and lipoteichoic acid stimulations in nasal polyps.** *J Allergy Clin Immunol* 2008, 121:110–115.
42. 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.
43. Keith PK, Conway M, Evans S, et al.: **Nasal polyps: effects of seasonal allergen exposure.** *J Allergy Clin Immunol* 1994, 93:567–574.
44. Leung DY, Harbeck R, Bina P, et al.: **Presence of IgE antibodies to staphylococcal exotoxins on the skin of patients with atopic dermatitis. Evidence for a new group of allergens.** *J Clin Invest* 1993, 92:1374–1380.
- 45.● Fokkens W, Lund V, Mullol J; European Position Paper on Rhinosinusitis and Nasal Polyps Group: **EP3OS 2007: European position paper on rhinosinusitis and nasal polyps 2007. A summary for otorhinolaryngologists.** *Rhinology* 2007, 45:97–101.
46. Corey JJP, Bumsted RRM: **Revision endoscopic ethmoidectomy for chronic rhinosinusitis.** *Otolaryngol Clin North Am* 1989, 22:801–808.
47. Moses RL, Cornetta A, Atkins JP Jr, et al.: **Revision endoscopic sinus surgery: the Thomas Jefferson University experience.** *Ear Nose Throat J* 1998, 77:190.
48. Senior BA, Kennedy DW, Tanabodee J, et al.: **Long-term results of functional endoscopic sinus surgery.** *Laryngoscope* 1998, 108:151–157.
49. Watelet JB, Claeys C, Van Cauwenberge P, Bachert C: **Predictive and monitoring value of matrix metalloproteinase-9 for healing quality after sinus surgery.** *Wound Repair Regen* 2004, 12:412–418.
50. Huvenne W, Zhang N, Tijsma E, et al.: **Pilot study using doxycycline-releasing stents to ameliorate postoperative healing quality after sinus surgery.** *Wound Repair Regen* 2008, 16:757–767.
- 51.● Gevaert P, Lang-Loidolt D, Lackner A, et al.: **Nasal IL-5 levels determine the response to anti-IL-5 treatment in patients with nasal polyps.** *J Allergy Clin Immunol* 2006, 118:1133–1141.

This was the first study to use humanized anti-IL-5 monoclonal antibody to treat CRSwNP, showing a promising effect in a predictable subpopulation of patients. Currently, an ongoing trial with repeated injections of anti-IL-5 is showing superior clinical efficacy.

52. Gevaert P, Holtappels G, Johansson SG, et al.: **Organization of secondary lymphoid tissue and local IgE formation to Staphylococcus aureus enterotoxins in nasal polyp tissue.** *Allergy* 2005, 60:71–79.