Nasal polyposis: an inflammatory condition requiring effective anti-inflammatory treatment

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Purpose of review
Recent literature in chronic rhinosinusitis with nasal polyps (CRSwNP) has focussed on inflammatory mechanisms underlying the disease. Endotyping the histopathological features of the disease, rather than simple clinical phenotypes, reflects a change in our understanding of the disease and approach to management. This is paralleled by renewed evidence for the need for wide postsurgical access and topical anti-inflammatory therapy.

Recent findings
Recent research into patterns of dysfunction in innate immunity suggests a crucial role of respiratory epithelium in mediating the inflammatory response. Elevated interleukins, IL-25 and IL-33, from sinus mucosa in CRSwNP and their interaction via innate lymphoid cells may represent the link between the host-environment interface and T-helper 2 dominated inflammation that characterizes CRSwNP. While thorough immunological profiling of CRSwNP is not routinely available, classification of CRS as eosinophilic (ECRS) or noneosinophilic is practical and correlates with disease severity and prognosis. The practice and utility of endoscopic sinus surgery to create a single neosinus for topical corticosteroid delivery is a logical conclusion founded on the inflammatory basis of CRSwNP/ECRS.

Summary
There is mounting evidence for CRSwNP as a predominantly inflammatory disease. Even simple histopathological classification on the basis of degrees of tissue eosinophilia reflects the underlying pathogenic mechanisms with diagnostic and prognostic implications. Optimal treatment involves topical anti-inflammatory therapy delivered locally via a wide, postsurgical corridor.

Keywords
chronic rhinosinusitis, corticosteroid, endoscopic sinus surgery, eosinophilic, irrigations

INTRODUCTION

The diagnosis chronic rhinosinusitis (CRS) with nasal polyps (CRSwNP) represents a clinical phenotype rather than a condition with histological or immunological homogeneity. Although the role of bacteria, fungi, allergens and superantigens is extensively reported in the literature [1], these associated factors may represent exacerbative rather than causative factors. Contemporary concepts focus on inflammatory processes secondary to dysregulated local immune function, with a fundamental defect involving the inability to maintain integrity of the epithelial barrier and regulate an appropriate, coordinated inflammatory response to foreign antigens [2,3]. Key to understanding this philosophy is the acknowledgement that both CRSwNP and normal patients are exposed to the same allergens, fungi and bacteria (including *Staphylococcus aureus*), yet only the first group has a heightened proinflammatory immune response. Recent evidence suggests a crucial role for the epithelial-derived cytokines that mediate the cells of the immune system.

The goal of this article is to review important and recent findings relating to the pathogenesis of CRSwNP. The rationale for a disease classification based on histopathological characteristics is discussed. Current concepts in therapeutic approach towards managing the condition are summarized.

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KEY POINTS

- CRSwNP is a predominantly inflammatory disease associated with dysregulated interaction between sinus epithelium and the innate lymphoid system.
- Endotyping CRS patients, using histopathological classification into simple eosinophilic versus noneosinophilic chronic rhinosinusitis (ECRS versus non-ECRS), reflects an underlying inflammatory process associated with increased disease severity and poorer prognosis.
- During surgery, although the removal of established polyps occurs, the goal in CRSwNP/ECRS is to create a wide, postsurgical corridor rather than simple polypectomy for effective delivery of topical anti-inflammatory therapy.

CHRONIC RHINOSINUSITIS WITH NASAL POLYPS AS AN INFLAMMATORY DISEASE

The evidence for a predominant inflammatory aetiology for CRSwNP is abundant. CRSwNP is characterized by excessive T-helper 2 (Th2) inflammation, prominent eosinophilic infiltration [4] and decreased regulatory T-cell (Treg) function. The cytokine profile is characterized by increased interleukin (IL)-5 and elevated ratio of eosinophilic cationic protein (ECP) to myeloperoxidase (MPO), ECP/MPO more than 1 [5].

With the advance in our understanding of the inflammatory processes, it is clear that although CRSwNP is a clinical diagnosis, it encompasses a variety of conditions with heterogeneity in the pattern of inflammation. Although research in mainland Chinese populations has identified a subgroup of CRSwNP patients in whom there is a predominant Th1/Th17, intermediate-eosinophilic pattern of inflammation [6], this is neither represented in other south-east Asian countries nor in Asian populations in western countries. A Th2 and IL-5 dominated eosinophilic process remains more common than noneosinophilic inflammation [7,8▪], with the most recent study reporting an eosinophilic phenotype in 76%, including 36% who had a mixed eosinophilic–neutrophilic pattern [8▪].

A mixed inflammatory pattern in CRS has been previously reported. Initially, investigation into the inflammatory cytokine profile, with respect to histological characteristics, seemed to suggest that it was the balance of proeosinophilic versus proneutrophilic cytokines that determined the resultant histologic phenotype. However, recent research suggests that CRS is neither an eosinophilic nor neutrophilic disorder. The cytokine profile characterized by high levels of IL-5 without either IL-17 or interferon was associated with increased tendency for eosinophilic inflammation [5]. In Asian patients with intermediate-eosinophilic CRSwNP, the regulation of IL-17 activity may be a critical factor in determining the relative degree of neutrophilic or eosinophilic inflammation [6]. In Chinese CRSwNP, enhanced IL-17 was found in both eosinophilic and noneosinophilic inflammation, but high expression of IL-17 receptor D (IL-17 RD) was associated with the noneosinophilic phenotype [7]. Most importantly, these findings suggest that a disordered inflammatory response, predominantly involving eosinophils, is occurring in these patients and represents an acknowledgement that this is not the classic inflammatory pattern that occurs in primary infective conditions.

The upstream mechanisms that incite the Th2 response may hold the key to understanding how extrinsic factors influence the pathogenesis of CRSwNP (Fig. 1). There is growing evidence that the respiratory epithelium mediates the Th2 response [9–12]. Whether this is a result of a dysfunctional epithelium (i.e. permanently or temporarily damaged) or as the result of local sinus factors is still a topic of debate. IL-25 and IL-33 are both produced in sinonasal epithelial cells and are thought to play an important role in promoting Th2 inflammation in CRSwNP. Baseline and stimulated expression of IL-33 have been demonstrated in epithelial cells from CRSwNP that was not responsive to treatment [13]. Both are overexpressed in eosinophilic compared with noneosinophilic CRS and expression was significantly associated with degree of tissue eosinophilia and overall inflammatory severity [14▪▪]. IL-25 has been shown to enhance thymic stromal lymphoprotein (TSLP)-induced Th2 cell expansion and function [15]. Specifically, both act on a non-B-non-T (NBNT) population of innate lymphoid cells, independent of the adaptive immune response, to produce Th2 cytokines, for example IL-5 and IL-13 [16,17]. An increased concentration of NBNT cells was found in nasal polyp tissue compared with nasal mucosa from healthy individuals and their activation by IL-25 and IL-33 resulted in increased production of IL-13 [18▪]. Thus, IL-25 and IL-33 may be the crucial link between epithelial cells and the Th2 inflammatory response that characterizes eosinophilic CRSwNP.

TSLP has been implicated as a key mediator in driving inflammation at the epithelial cell–dendritic cell interface [19]. TSLP is produced by dendritic cells, mast cells and basophils and is thought to equip dendritic cells with the ability to produce a variety of inflammatory cells, including

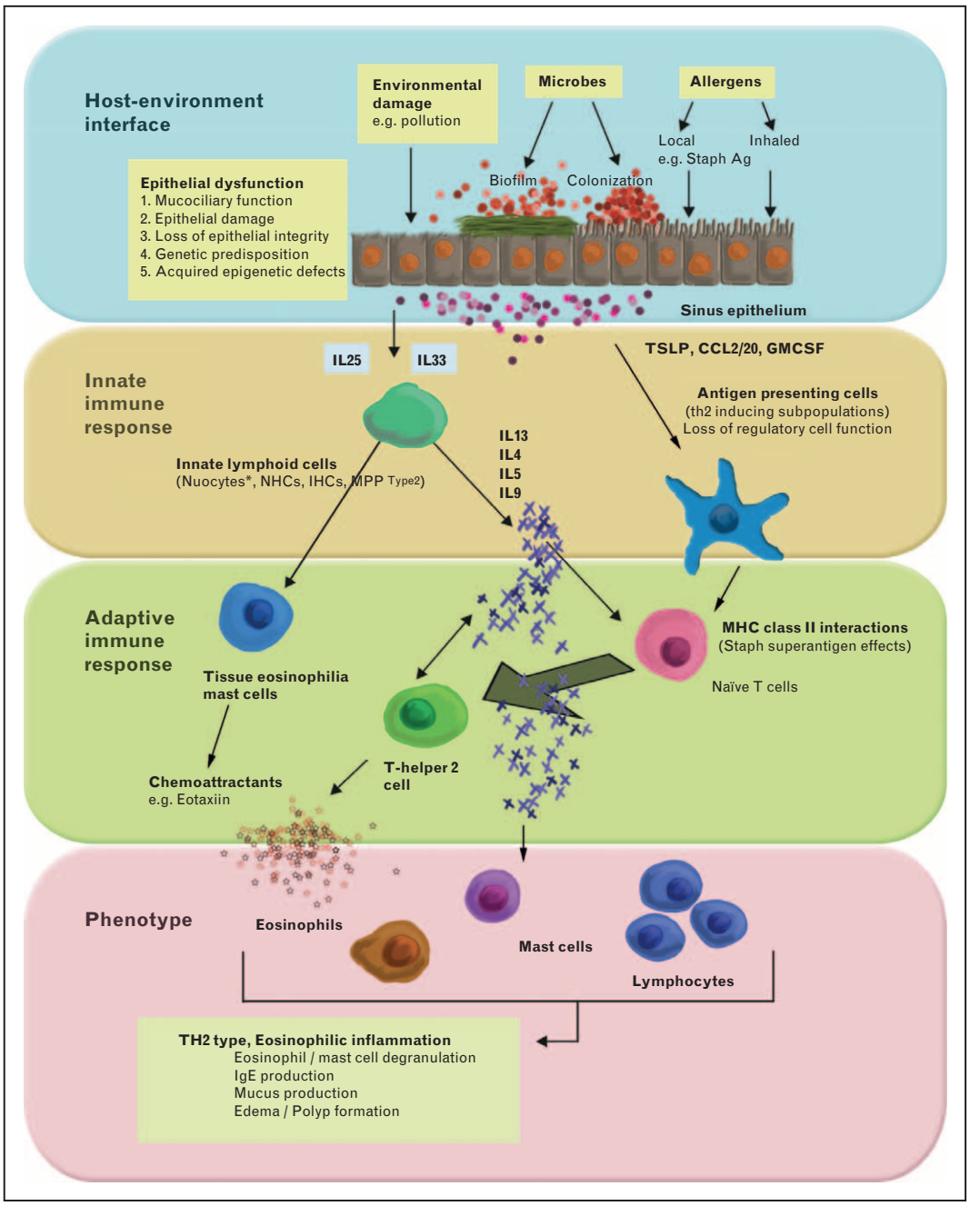


FIGURE 1. The current understanding of epithelial mediation of the Th2 immune response and a local tissue eosinophilia. Even though there may be sinus lumen antigens (fungus, staph, biofilms etc) that might be implicated in the process, these microbial flora are often present in normal patients and this highlights the disordered inflammatory response in patients with chronic rhinosinusitis with nasal polyps.

Th2 lymphocytes and eosinophils. There is increased expression of TSLP in nasal polyps versus allergic rhinitis [8▪]. However, this difference was only detected when the polyp tissue from CRSwNP patients was compared with the mucosal tissue of allergic rhinitis patients. In fact, when nonpolyp sinus mucosal tissue from these CRSwNP patients was used for comparison with the allergic rhinitis patients instead of the actual polyp tissue, no significant difference was observed. This suggests TSLP may be overexpressed in nasal polyp tissue only. In another study, the TSLP receptor was increased in CRS (with and without nasal polyps) versus controls [20]. In a more recent study, there was no difference in TSLP mRNA expression between eosinophilic versus noneosinophilic inflammation in CRS

[14▪▪]. Although the precise role of TSLP in CRS requires further clarification, it appears to facilitate, rather than drive, Th2 inflammation [21]. There are examples of TSLP-dominated asthma subtypes [22,23] and it is likely that such a subgroup with recalcitrant features does exist in the upper airway.

Evidence for decreased Treg activity in CRSwNP is consistent with the concept of immune dysregulation as a main pathogenic process. Diminished forkhead box P3 gene (FoxP3) expression, a marker of Treg activity [24], has been demonstrated in CRSwNP versus allergic rhinitis [25] and is associated with increased Th2 cell activity [6,26]. Another critical effect of decreased Treg activity is altered tissue remodelling via a decrease in transcription growth factor β (TGF-β). TGF-β attracts, induces and promotes fibroblasts activity and enhances production of extracellular matrix. In contrast to CRS without nasal polyps (CRSsNP), TGF-β is significantly reduced in CRSwNP [27]. The accumulation of tissue albumin and edema stemming from reduced production of extracellular matrix and fibroblast activity permits development of nasal polyps, a defining feature of CRSwNP. These processes represent the downstream endpoint in the nasal polyp formation and, not surprisingly, entail less heterogeneity in terms of cellular markers [28▪].

INTERACTION OF THE UPPER AND LOWER AIRWAY

With increasing severity, the inflammatory disease and immune dysregulation which characterize CRSwNP are also manifested in the lower airways. Histological characteristics of the lower respiratory tract do not permit the development of polyposis [29]; however, the results of inflammation present clinically loosely as asthma, with bronchial reactivity and mucus hypersecretion.

The evidence for an association between upper and lower airways inflammation, aptly named the unified, united or common airway, is abundant. Historically, the most obvious phenotype was the Samter's triad of nasal polyposis, asthma and aspirin intolerance. This was more recently named aspirin-exacerbated respiratory disease (AERD) [30]. However, the association between CRSwNP and nonatopic, late-onset (or adult onset) asthma is not limited to patients with AERD. Epidemiologically, up to 60% of patients with CRSwNP also had clinically overt asthma [31]. As in CRSwNP, increased local IL-5, Th2-dominated immune response and tissue eosinophilia are associated with asthma [5,32]. Such links in the common immunologic process underlying airway inflammation in these patients explain the close clinical associations that are seen. The degree of sputum eosinophilia can predict the upper airway severity [33] and conversely, the degree of nasal eosinophilia can predict the lower airway reactivity and asthma severity by bronchodilator response [34,35]. The lower proportion of ECRS patients in the Chinese patients with CRSwNP might also explain the lower risk of asthma in this ethnic population [6].

It has been more than 10 years since Braunsthal and colleagues published on segmental lower airway provocation generating upper airway eosinophilia [36] and the same process in reverse [37]. A process of shared inflammation that is systemically mediated is generally accepted, although the mediators are still debated [38,39]. However, this describes the clinical associations rather than causative factors of an airway working as an integrated unit. It is highly likely that the same environmental and epigenetic events that have resulted in epithelial-driven Th2 inflammatory events are likely to be patchy and distributed across the entire airway.

Finally, improvement in asthma symptoms [40–43] and/or reduction in asthma medication requirement after endoscopic sinus surgery (ESS) [44] lend further evidence to the hypothesis of the unified airway and suggest that these patients do benefit from management of sinonasal disease in addition to that for the lower airways.

HISTOLOGICAL SUBCLASSIFICATION OF CHRONIC RHINOSINUSITIS WITH NASAL POLYPS

A histological approach to classifying CRSwNP represents the first logical step for improved prognostication and evidence-based management of the condition. In the white population, tissue eosinophilia is strongly associated with the nasal polyp phenotype [45▪▪]. However, with structured histopathology of sinus tissue using defined criteria for eosinophilic CRS or greater than 10 eosinophils per high power field, an additional 20% of CRSsNP would be classified as ECRS [46▪] (Fig. 2 a and b).

The diagnosis of ECRS has prognostic implications. ECRS is associated with greater clinical and radiological severity [35,46▪], higher risk of asthma [35] and higher risk of polyp recurrence when compared to non-ECRS [47]. Serum eosinophilia, although associated with ECRS and predictive of asthma [35], is less representative of the localized inflammatory processes [48], and was less sensitive for ECRS [46▪]. Nasal cytology as an estimate of tissue eosinophilia has been proposed [49]; however, the diagnostic accuracy and clinical correlations require further definition.

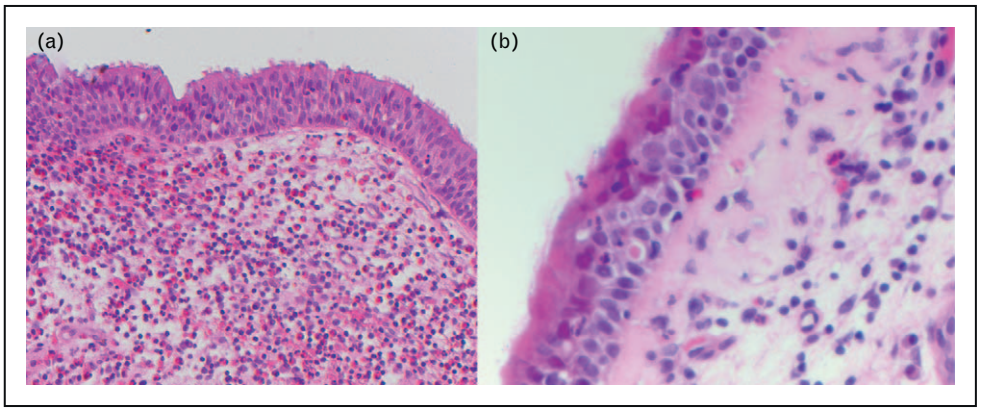


FIGURE 2. (a and b) Histological appearance of eosinophilic and noneosinophilic tissue from patients with chronic rhinosinusitis (CRS). (a) Eosinophilic CRS with more than 10 eosinophils per high power field. (b) Noneosinophilic CRS.

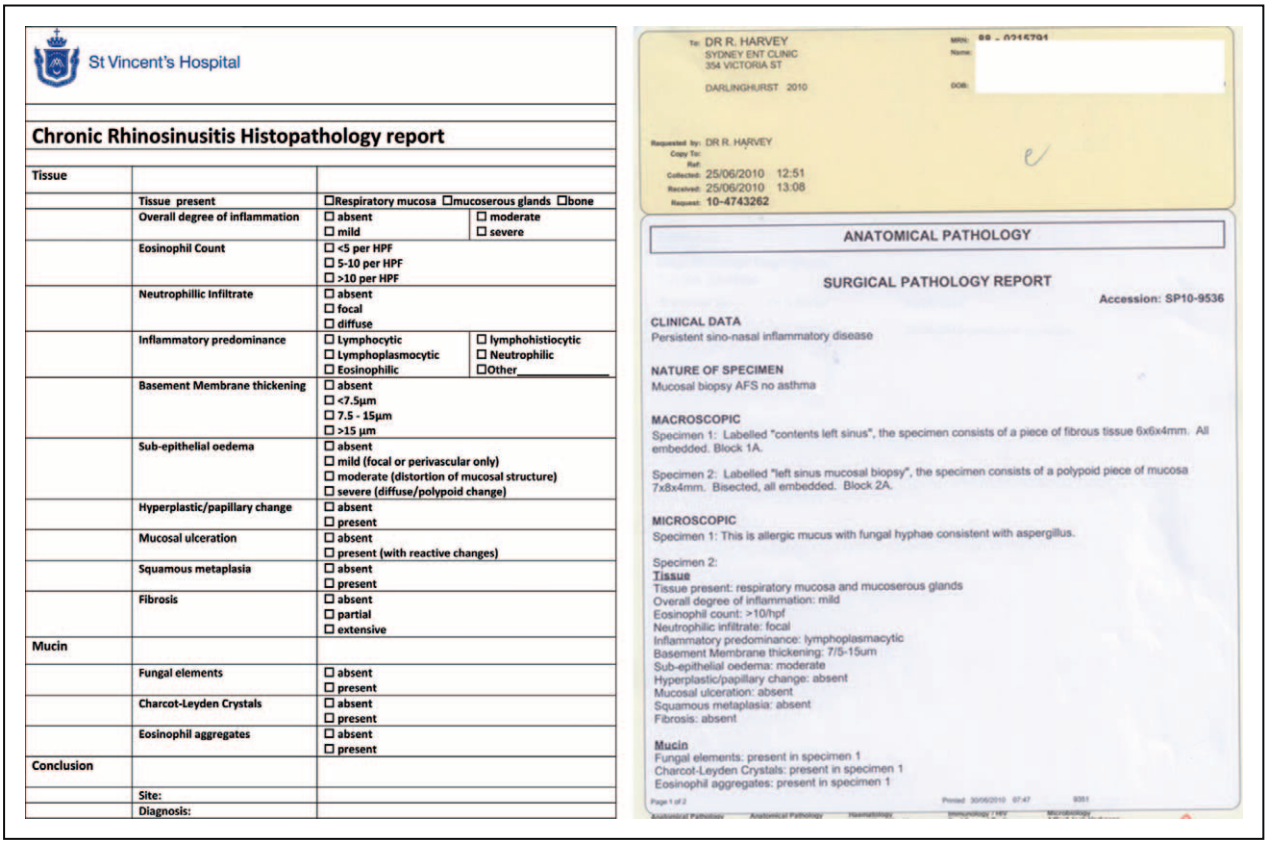
Validation of the concept of ECRS versus non-ECRS requires further research, especially in nonwhite populations, in which a significant proportion of CRSwNP may have lower eosinophilia. Although a thorough inflammatory profile including Th2 cytokines (IL-4, IL-5, IL-13) along with Treg processes (TGF-B, IL-10, IL-17) and even evidence of Staphylococcal colonization (Immunoglobulin E, Staphylococcal exotoxins) may represent the ultimate in describing our current understanding of the driving forces behind CRSwNP, this is simply not available to routine clinical practice. This does not imply apathy to the histological process and relevant data can be rendered available if tissue histology is described in a structured synoptic format rather than qualitative descriptions. For standardization, structured histopathology reporting is encouraged (an example of which is shown in Fig. 3) and developed in conjunction with pathologists for integration into routine practice.

THE ENDPOINT FOR INTERVENTIONS IN NASAL POLYPS

The appropriate management for nasal polyps must focus on controlling the common inflammatory process rather than on treatment of polyps *per se*. This is further emphasized with a shift towards the concept of treating ECRS as an inflammatory disorder, similar to asthma or dermatitis. At present, corticosteroids are the foundation of anti-inflammatory therapy. However, the risk–benefit ratio of prolonged systemic steroids for nasal polyps is unacceptably high. Local (or topical) delivery provides an effective method of disease control with minimal risk of complications. With regards to CRSwNP, it may not be an overstatement to say that if oral corticosteroids had no side-effects then there would be little role for surgery.

Effective local delivery of pharmaceuticals to the paranasal sinus is a demanding equation. It is a product of both the surgical state of the sinuses and the method of topical delivery. Simple nasal sprays and polypectomy do not achieve an advancement of the patient's situation to control the condition. The goal of sinus surgery in CRSwNP or ECRS is to create permanent wide access for long-term topical therapy rather than for relieving sinus obstruction or promoting sinus drainage and aeration (Fig. 4 a and b). Neither CRSwNP nor ECRS are diseases that are due to ostiomeatal occlusion [50,51▪]. The variation in the size of surgically created access greatly affects topical delivery and distribution [52,53]. Complete distribution of sinus irrigation is optimized by a wide post-ESS surgical corridor [54]. In a meta-analysis comparing topical steroids versus placebo, one of the key findings was that the subgroup with sinus surgery had greater reduction in nasal polyposis than those without sinus surgery [55▪▪]. Conversely, minimally invasive procedures have a limited impact on topical access as ostial size greater than 4–5 mm is required [56] and can even reduce distribution of nasal irrigation to the maxillary sinus, presumably due to uncinate deflection or secondary ostium formation which is common in these procedures [57].

The options in topical delivery can be classified into either high volume high-pressure systems (e.g. nasal irrigation with netipot, squeeze bottles) or low volume low-pressure systems (e.g. nasal drops and sprays). In the presence of a wide surgical corridor, nasal irrigation facilitates mechanical lavage of the hypersecretory mucus that occurs in CRSwNP in addition to drug delivery [53]. High volume,



St Vincent's Hospital

Chronic Rhinosinusitis Histopathology report

Tissue			
	Tissue present	☐Respiratory mucosa ☐mucoserous glands ☐bone	
	Overall degree of inflammation	☐ absent ☐ mild	☐ moderate ☐ severe
	Eosinophil Count	☐ <5 per HPF ☐ 5-10 per HPF ☐ >10 per HPF	
	Neutrophillic Infiltrate	☐ absent ☐ focal ☐ diffuse	
	Inflammatory predominance	☐ Lymphocytic ☐ Lymphoplasmocytic ☐ Eosinophilic	☐ lymphohistiocytic ☐ Neutrophilic ☐Other_____
	Basement Membrane thickening	☐ absent ☐ <7.5µm ☐ 7.5 - 15µm ☐ >15 µm	
	Sub-epithelial oedema	☐ absent ☐ mild (focal or perivascular only) ☐ moderate (distortion of mucosal structure) ☐ severe (diffuse/polypoid change)	
	Hyperplastic/papillary change	☐ absent ☐ present	
	Mucosal ulceration	☐ absent ☐ present (with reactive changes)	
	Squamous metaplasia	☐ absent ☐ present	
	Fibrosis	☐ absent ☐ partial ☐ extensive	
Mucin			
	Fungal elements	☐ absent ☐ present	
	Charcot-Leyden Crystals	☐ absent ☐ present	
	Eosinophil aggregates	☐ absent ☐ present	
Conclusion			
	Site:		
	Diagnosis:		

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ANATOMICAL PATHOLOGY

SURGICAL PATHOLOGY REPORT

Accession: SP10-9536

CLINICAL DATA
Persistent sino-nasal inflammatory disease

NATURE OF SPECIMEN
Mucosal biopsy AFS no asthma

MACROSCOPIC
Specimen 1: Labelled "contents left sinus", the specimen consists of a piece of fibrous tissue 6x6x4mm. All embedded. Block 1A.

Specimen 2: Labelled "left sinus mucosal biopsy", the specimen consists of a polypoid piece of mucosa 7x8x4mm. Bisected, all embedded. Block 2A.

MICROSCOPIC
Specimen 1: This is allergic mucus with fungal hyphae consistent with aspergillus.

Specimen 2:
Tissue
Tissue present: respiratory mucosa and mucoserous glands
Overall degree of inflammation: mild
Eosinophil count: >10/hpf
Neutrophilic infiltrate: focal
Inflammatory predominance: lymphoplasmacytic
Basement Membrane thickening: 7/5-15um
Sub-epithelial oedema: moderate
Hyperplastic/papillary change: absent
Mucosal ulceration: absent
Squamous metaplasia: absent
Fibrosis: absent

Mucin
Fungal elements: present in specimen 1
Charcot-Leyden Crystals: present in specimen 1
Eosinophil aggregates: present in specimen 1

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FIGURE 3. Structured histopathology reporting for chronic rhinosinusitis with or without nasal polyps.

positive pressure delivery systems can enhance removal of mucus, inflammatory products and disruption of bacterial biofilms [58]. When mixed into nasal irrigation, topical steroids may even be safer than nasal drops as only 5% of the total dose remains in fluid residuals [53] compared with up to 100% for nasal drops which may be swallowed and absorbed via the gastrointestinal tract [59]. High volume steroid irrigations are not a 'high dose' treatment and such a description is a misnomer. Common regimes of 1 mg budesonide in 240 ml squeeze bottle represents a 4.2 µg/ml dose and only approximately 10–20 ml (80 µg) is delivered, whereas a four-spray dose (apart from being

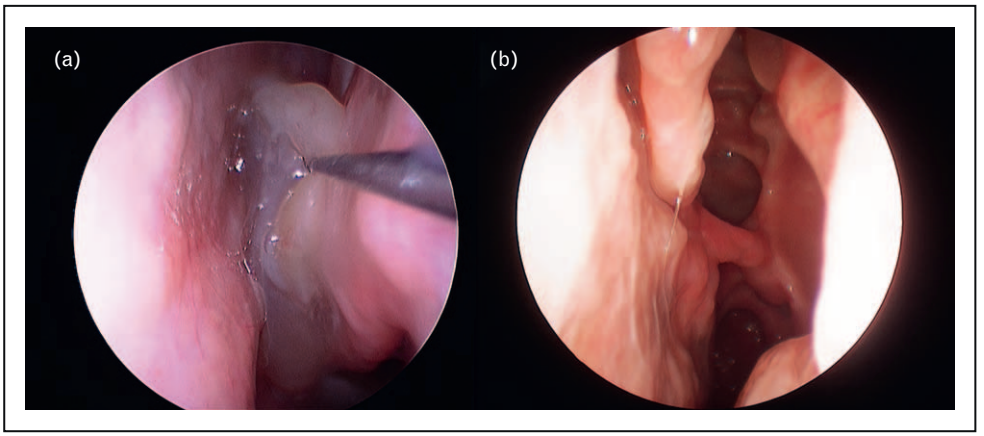

FIGURE 4. (a and b) Creation of a wide surgical corridor after sinus surgery for eosinophilic chronic rhinosinusitis. (a) Preoperative endoscopic picture showing the dysfunctional sinuses of a patient with nasal polyposis. (b) Three years postoperative endoscopy of the same patient showing a single neosinus cavity with good access for topical therapy.

ineffectively delivered to the target organ) represents a 256 μg dose. Wide sinus surgery and then post-ESS steroid irrigation has been shown to be effective for disease control with failure of local therapy in 6% of CRSwNP [60▪]. Poor response to oral prednisone preoperatively may predict steroid resistance and these patients may not be good candidates for topical steroid therapy. A greater response to oral prednisone was demonstrated in eosinophilic versus noneosinophilic nasal polyposis [8▪]. This finding further supports the usefulness of histopathologic (ECRS) as a valid refinement of simple phenotype-based diagnoses (CRSwNP). The question of the relative effectiveness of nasal irrigation (high volume, high pressure) versus nasal spray (low volume, low pressure) needs to be addressed with a double-blinded randomized controlled trial and such a study is currently in progress.

CONCLUSION

Although multiple aetiologies for nasal polyps have been studied, it is evident that dysregulated inflammation at the epithelium has a central role in the development of CRSwNP. It is not a systemic condition but is characterized by sporadic involvement of the airway for most affected patients. A histological classification of ECRS and its severity is recommended as it is associated with increased disease severity and the need for long-term local anti-inflammatory control. Topical steroids, when effectively delivered, are associated not only with symptom control but objective endoscopic resolution and mucosal control. Like asthma, ECRS should be considered a condition to be controlled rather than cured with the use of long-term anti-inflammatory treatment and a maintenance regime achieved. At present, optimal treatment involves regular topical steroid, via nasal irrigation, in the setting of a wide, postsurgical corridor.

Acknowledgements

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Conflicts of interest

D.C. has no financial disclosures or conflicts of interest. R.J.H. has previously received grant support from NeilMed, served on an advisory board for Schering-Plough and Glaxo-Smith-Kline, is a consultant with Medtronic and Olympus and is on the speaker's bureau for Merck Sharp & Dohme and Arthrocare.

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- ▪ of special interest
- ▪▪ of outstanding interest

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