



Systemic biomarkers of eosinophilic chronic rhinosinusitis

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Purpose of review

The current understanding of eosinophilic chronic rhinosinusitis (CRS) has developed rapidly over the past decades. Classification of CRS based on the inflammatory endotype more accurately reflects the underlying pathophysiology and better directs treatment. Corticosteroids and more recently biologic agents, target the eosinophil inflammatory that drives this subtype of CRS. Tissue sampling is not always accessible or available and surrogate markers are sought to define this endotype of CRS. The purpose of this review is to assess current systemic predictors of eosinophilic CRS (eCRS) diagnosis.

Recent findings

Blood eosinophils are a moderate surrogate predictor of eCRS. A blood eosinophil count of more than $0.24 \times 10^9/l$ predicts eCRS with tissue eosinophilia of more than 10 eosinophils per high-power field. It has been further shown that a blood eosinophil count more than $0.45 \times 10^9/l$ is associated with need for long-term systemic therapy following endoscopic sinus surgery. Other biomarkers reviewed include IgE, eosinophil cationic protein, eosinophil-derived neurotoxin, eosinophil peroxidase, IL-5, periostin, eotaxin-3 and IL-16.

Summary

There remains limited data surrounding the prognostic use of biomarkers in eCRS. However, peripheral eosinophilia best predicts the eosinophilic density that best predicts the eCRS phenotype. In addition, it is also prognostic of need for more intensive therapy. Simple haematoxylin and eosin stained sinus mucosa still remains the most reliable tissue for assessment and is more accessible than bronchial biopsies

Keywords

biomarker, chronic rhinosinusitis, eosinophils, nasal polyps, polyposis

INTRODUCTION

The understanding of chronic rhinosinusitis (CRS) has progressed far from the simplistic historical concepts of simple osteomeatal complex obstruction resulting in hypo-oxygenation, reduced ventilation of the sinuses, with subsequent mucociliary dysfunction resulting in the production of thick mucus secretions and allowing for secondary bacterial infection of the sinuses [1]. Currently, CRS is recognized as a chronic inflammatory condition of the sinuses, with classification of CRS into different phenotypes and endotypes, reflective of the heterogeneous nature of the disease and the differing underlying pathophysiology [2].

There has been significant progress in our understanding of the pathogenesis of CRS in recent years. There are major limitations into the classification of CRS into traditional phenotypes based on the presence (CRSwNP) or absence of nasal polyps (CRSsNP). For many patients, high tissue eosinophilia exists with non-polypoid changes and has been shown in

up to 27.5% [3]. Even in those patients with polypoid changes, non-eosinophilic inflammation can predominate [4[¶]].

Emerging phenotypes of CRS are more reflective of the underlying inflammatory process, with classifications of central compartment atopic disease, eosinophilic CRS (eCRS) and non-eosinophilic CRS (non-eCRS) [5[¶]]. Neutrophilic infiltrate is very variable and likely depends on many factors, including concurrent bacterial colonization [6]. Phenotypes

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KEY POINTS

- In the diagnosis of eCRS, simple tissue eosinophil count by haematoxylin and eosin stained sinus mucosa is easy to obtain during sinus surgery and best characterizes the phenotype at more than 10 eosinophils/high-powered field.
- Peripheral eosinophilia is a surrogate marker of eCRS diagnosis at more than 0.24×10^9 cells/l, but has poor negative predictive value of 64.5%.
- At a cut-off of more than 0.45×10^9 cells/l, peripheral eosinophilia predicts the need for systemic medication use.
- Biomarkers including those assessing eosinophil activation require further research in eCRS.

such as eCRS are part of a broader inflammatory disease process, with associated widespread airway inflammation, reflective of the united airways hypothesis.

Recognition of these different CRS phenotypes is essential in the management of patients with primary CRS as this allows otolaryngologists to implement precision medicine and appropriately direct treatment, especially when applying long-term macrolide therapy or biologic agents.

THE EOSINOPHILIC ENDOTYPE OF CHRONIC RHINOSINUSITIS

eCRS is driven by eosinophilic inflammation through the TH2 inflammatory response. Recognition of this endotype is especially important as compared with non-eCRS, eCRS patients often clinically present with loss of smell in early stages, bilateral polyps and diffuse inflammation in all sinuses on computed tomography (CT) imaging [7].

It is often more difficult to treat, as it can be resistant to current medical and surgical interventions. It is also associated with high disease

recurrence, resulting in repeated corticosteroid courses and multiple revision surgeries to achieve disease control [7–9]. The meta-analysis by McHugh *et al.* [10[■]] reported high rates of disease recurrence in eCRS following functional endoscopic sinus surgery (16.7% in Western populations, 28.9% in Asian populations).

For patients with eCRS, the goal is to treat the inflammatory disorder by ensuring topical therapy through large volume corticosteroid irrigation in an adequately wide-open surgical cavity [11[■],12]. Patients may require short courses of oral corticosteroids as rescue medication.

Targeted biotherapeutics have recently been developed and are emerging as a potential treatment modality in eCRS, targeting TH2 inflammation-associated mediators including IL-5, IL-4 and IgE [13[■],14]. Biologics are particularly promising given the successful treatment of patients with severe eosinophilic asthma, a disease also driven by TH2 eosinophilic inflammation, resulting in decreased frequency of asthma exacerbations and need for systemic steroids [15].

The use of targeted biologics in eCRS is has only just been approved for use with dupilumab and other agents, such as mepolizumab, will likely follow shortly after [13[■]]. There are no clear guidelines on when biologics should be used given the current limited evidence, however in clinical practice are generally reserved for use in patients with recalcitrant disease [16[■]].

GOLD STANDARD OF DEFINING EOSINOPHILIC CHRONIC RHINOSINUSITIS

Sinus mucosa eosinophil density identified on haematoxylin and eosin (H&E) staining has been used widely in the literature for the definition of eCRS [17,18] (Fig. 1). The current definition of eCRS is based on greater than 10 eosinophils per high-powered field (HPF) ($\times 400$ magnification in at least two fields), which has been generally associated with poorer outcomes and overall prognosis [17,19].

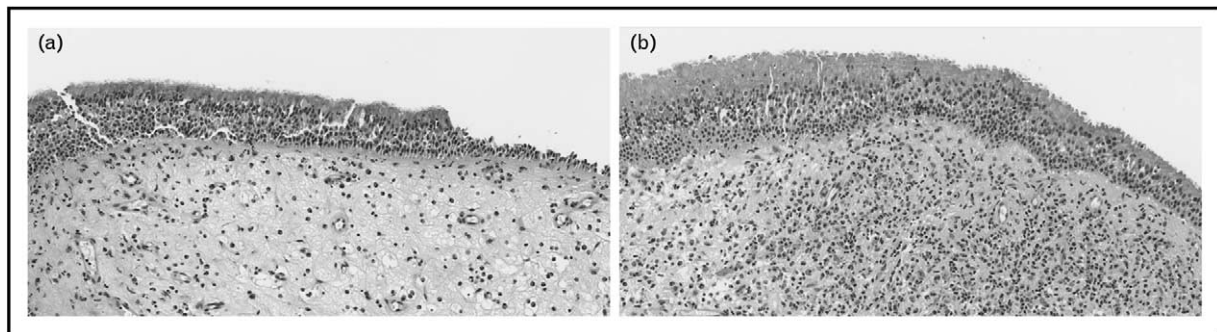


FIGURE 1. Haematoxylin and eosin staining for diagnosis of eosinophilic chronic rhinosinusitis. (a) 10–100 eosinophils/high-powered field (b) 100 eosinophils/high-powered field.

However, there exists significant variation within the literature, ranging from more than 5 to more than 120 eosinophils per HPF [20[¶]]. These differences in definitions may also be influenced by ethnic and environmental backgrounds [21], but mainly by the definition of what the threshold implies. High levels more than 50 eosinophils/HPF are likely to select out a subpopulation that is particularly refractory to surgery and simple therapies. However, those with eosinophils more than 10 eosinophils/HPF are likely to better define the eCRS/polypoid phenotype that is associated with asthma.

Eosinophil accumulation occurs in a self-amplifying process, driven among several other pathological processes by IL-5, which regulates growth, differentiation, activation, and survival of eosinophils. Eosinophil count greater than 55 per HPF has been associated with recurrence and treatment failure in eCRS following endoscopic sinus surgery [10[¶]]. Increased eosinophil density and eosinophil inflammation is associated with disease severity and treatment outcomes [8,22].

eCRS has also been defined based on concentrations of tissue inflammatory cytokine markers, with patients categorized into IL-5 positive and IL-5 negative clusters [2]. In the IL-5 positive cluster, further division has been proposed into a subgroup of moderate IL-5 concentration with mixed CRSwNP and CRSsNP and an IL-5 high subgroup which presents exclusively as CRSwNP and had high asthma comorbidity. It is this high IL-5 tissue concentration subgroup that is consistent with the true eCRS cohort of patients.

Eosinophil cationic protein (ECP) has also been described as a potential biomarker for the diagnosis of eCRS, as this is thought to more accurately reflect the active eosinophilic inflammation [23]. However, there was wide variation in establishing a 'normal' level of ECP and further studies are required to establish the role of ECP in eCRS.

Radiologic criteria based on the Lund–Mackay scoring system have shown that an optimal cut-off score of more than 2.59 for the ethmoid sinus/maxillary sinus CT score was both sensitive (94%) and specific (90%) for eCRS with nasal polyps [24].

Clinical diagnostic criteria for defining eCRS have also been proposed through the Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis (JESREC) scoring system. The JESREC score assess bilateral disease, presence of nasal polyps, CT findings (shadow of ethmoid cells $\geq$ shadow of maxillary sinus) and peripheral blood eosinophilia to diagnose eCRS with a sensitivity of 83% and specificity of 66% [7]. Similarly, blood eosinophilia and CT findings have had moderate sensitivity and high specificity for diagnosis of eCRS [25].

It is important to have a clinically available reference to standardize diagnosis of eCRS internationally. Histopathological profiling of the sinus mucosa should not only assess the degree of tissue eosinophilia but also the status of tissue inflammation and mucin. A structured histopathology report has been developed by the Rhinology and Skull Base group at St Vincent's Hospital, Sydney to standardize reporting of sinonasal mucosa by pathologists (Fig. 2). Features assessed include inflammatory predominance, remodelling changes such as basement membrane thickening and fibrosis as well as assessing features of eosinophilic activation within the mucin including the presence of Charcot–Leyden crystals and eosinophil aggregates. Charcot–Leyden crystals form following the degranulation of eosinophils and are associated with active eosinophilic inflammation, resulting in damage to the sinonasal and respiratory epithelium.

Certainly, the abundance of tissue from sinus surgery compared with bronchoscopic examination allows for better assessment of eosinophilic CRS compared with the diagnosis of eosinophilic asthma.

SYSTEMIC BIOMARKERS OF EOSINOPHILIC CHRONIC RHINOSINUSITIS

A literature search was performed to systematically identify all published literature evaluating systemic biomarkers in eosinophilic CRS using Ovid MEDLINE (1946 to August 2019). The following search terms were used to identify published literature for eosinophilic CRS [terms: ('eosinophil*' AND '*sinusitis') OR 'ECRS' OR 'Eosinophilic chronic rhinosinusitis' and reviewed for articles assessing systemic biomarkers]. Human and English language articles were evaluated.

There are currently only a limited number of clinical biomarkers that are available routinely to the otorhinolaryngologist. These include peripheral blood eosinophil count, total IgE and specific IgE. A further number of markers have been the focus of current research however presently are only available within the research setting – these include ECP, eosinophil-derived neurotoxin (EDN), eosinophil peroxidase (EPO), IL-5, periostin, eotaxin-3 and IL-16.

CLINICALLY AVAILABLE BIOMARKERS

Blood eosinophils

Assessment of eosinophils in blood is a readily available investigation in the assessment of patients with eCRS. Peripheral eosinophilia has been identified as a surrogate marker for tissue eosinophilia in both

 St Vincent's Hospital		
Chronic Rhinosinusitis Histopathology report		
Tissue		
	Tissue present	☐ Respiratory mucosa ☐ mucoserous glands ☐ bone
	Overall degree of inflammation	☐ Absent ☐ Moderate ☐ Mild ☐ Severe
	Eosinophil Count	☐ <10 per HPF ☐ 10-100 per HPF ☐ >100 per HPF
	Neutrophil Infiltrate	☐ Absent ☐ Focal ☐ <20 per HPF ☐ ≥20 per HPF
	Inflammatory predominance	☐ Lymphocytic ☐ lymphohistiocytic ☐ Lymphoplasmocytic ☐ Neutrophilic ☐ Eosinophilic ☐ Other _____
	Basement Membrane thickening	☐ <7.5µm (normal) ☐ 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

FIGURE 2. Histopathologic profiling of sinus mucosa as a structured inflammation report. (<https://sydneyentclinic.com/richard-harvey/chronic-rhinosinusitis-histopathology-report-2012-version/>).

diagnostic and prognostic studies [26–28]. A blood eosinophil count of more than $0.24 \times 10^9/l$ predicted eCRS (diagnosed based on tissue eosinophilia more than 10/HPF) with moderate sensitivity and specificity [29]. It has been further shown that a blood eosinophil count more than $0.45 \times 10^9/l$ is associated with need for long-term systemic therapy following endoscopic sinus surgery in eCRS, with a high negative predictive value (98.7%) [16]. Eosinophils as a percentage of white cell count have also been proposed as a biomarker for predicting eCRS however again there is large variation within the literature, ranging from 3 to 6% [25,26,29].

It is evident from these studies that blood eosinophilia is only a limited surrogate for tissue eosinophilia. This may be related to the eosinophil itself, as circulating eosinophil counts can be falsely elevated by comorbid parasite infection, allergy, autoimmune disorders or adverse drug events [30]. In addition, local eosinophil actions at the tissue level such as activation and migration often occur without elevation of blood eosinophils [31]. Blood eosinophils also represent a useful potential prognostic marker in eCRS, predicting likelihood of recurrence and the need for further surgery, as well as response to treatment [28].

IgE

IgE has a key role in driving allergic inflammation. Local, rather than systemic, IgE is thought to be responsible for the inflammatory process in eCRS, independent of atopic status. Total serum IgE, positive skin prick testing or ImmunoCAP testing for serum specific IgE have shown no significant association with eCRS [16[■],27,29[■],32,33]. However, total serum IgE has been shown to be elevated in an eosinophilic inflammatory endotype in recurrent CRS compared with other inflammatory clusters [34[■]].

RESEARCH ONLY BIOMARKERS

Markers of eosinophilic activation

Eosinophils contain enzymatic and nonenzymatic cationic proteins within their granules which upon activation of eosinophils, are actively secreted by degranulation. Eosinophilic granule proteins include major basic protein, ECP, EPO and EDN and are responsible for airway inflammation, tissue damage and remodelling [35].

Eosinophilic cationic protein

ECP is produced secondary to eosinophilic activation and inflammation. Serum ECP has been shown to be significantly elevated in patients with eCRS compared with patients with other sinus diseases [36[■]]. ECP has also been previously shown to be increased in the serum of CRSwNP patients [37]. In a CRS population, elevated serum ECP correlated with both raised blood eosinophils and increased eosinophil concentration on nasal smears [38]. In addition, ECP measured within nasal secretions shows significant correlation with blood eosinophils [39].

Eosinophil-derived neurotoxin

EDN is closely linked with the activation and maturation of dendritic cells, further driving the TH2 immune response. Serum EDN levels are significantly elevated in eCRS compared with non-eCRS and controls and correlate with polyp score and peripheral eosinophilia [36[■]]. In response to IL-5 and IL-13, EDN is hypothesized to induce local production of matrix metalloproteinase 9 (MMP-9) resulting in tissue remodelling and nasal polyposis in eCRS.

Eosinophil peroxidase

EPO is involved in generating potentially toxic reactive oxygen species in eosinophil activation. Serum

EPO has been previously implicated in asthma. However, no association has been identified with regard to serum EPO and eCRS [36[■]].

IL-5

IL-5 plays a key role in eosinophil development, function and survival, mediating key stages including chemotaxis, differentiation and activation. Increased expression of IL-5 at both mRNA and protein levels have been identified in nasal polyps compared with sinus mucosa, and is associated with comorbid asthma, revision surgery and nasal polyposis [40–42]. An upregulation of IL-5 mRNA expression within tissue has been associated with eCRS [33,43,44]. Furthermore, IL-5 as well as IL-6 mRNA expression has been shown to be significantly elevated in the frontal sinus mucosa compared with ethmoid sinus mucosa within the same eCRS patient, which may be a factor contributing to recurrence [44].

Periostin

Periostin is an extracellular matrix protein involved in the pathologic remodelling changes that are seen in eosinophilic inflammation. It is secreted from epithelial cells in response to IL-4 and IL-13. In eCRS, there was a significant positive correlation between serum periostin levels and IL-5 expression [45]. Serum periostin has been shown to be elevated in patients with severe eCRS in comparison with mild eCRS and non-eCRS [46]. Furthermore, in CRSwNP, serum periostin is elevated in patients with eosinophilic polyps compared with non-eosinophilic polyposis [47].

Eotaxin-3/CC chemokine ligand 26

Eotaxin-3 is a cytokine produced at the epithelial level which induces chemotaxis of eosinophils, basophils, and TH2 lymphocytes. Plasma eotaxin-3 has been shown to be significantly elevated in patients with tissue eosinophils more than 55 per HPF and may be useful as a marker for disease recurrence [48[■]].

IL-16

IL-16 is highly chemotactic for eosinophils and promotes persistent eosinophil activation. Serum IL-16 is significantly elevated in patients with eCRS compared with healthy controls [49]. However, research has been limited in the role of IL-16, not only in eCRS but also CRS.

DISCUSSION

Implications for current practice

Tissue eosinophil assessment is gold standard for the diagnosis of eCRS, however, despite the number of sinus surgeries performed, is unfortunately not widely assessed from sinus surgery and still remains limited to tertiary practice. While research assessing non-histopathological predictors of eCRS remains limited, peripheral eosinophilia is a readily available test which represents a satisfactory predictor of eCRS diagnosis and treatment outcomes.

A blood eosinophil count of more than $0.24 \times 10^9/l$ predicts eCRS with tissue eosinophilia of more than 10 eosinophils per high-power field [29]. It has been further shown that a blood eosinophil count more than $0.45 \times 10^9/l$ is associated with need for long-term systemic therapy following endoscopic sinus surgery [16]. High preoperative peripheral eosinophilia should alert the clinician to patients likely to have tissue eosinophilia and require close follow-up for management of their eCRS to prevent treatment failure.

Implications for future research

Several biomarkers have been identified which predict both the diagnosis and prognosis of eCRS. Analogous to severe eosinophilic asthma, high blood eosinophilia and other biomarkers may represent a useful cut-off for the provision of biologic therapy in the management of recalcitrant eCRS.

Further analysis, particularly looking at markers of eosinophilic activation, such as IL-5, CD44, carbonic anhydrase IV and EPO, would be valuable to identify the subpopulation of patients with eCRS likely to fail contemporary management and to both require and respond to systemic therapy with biologic therapies.

CONCLUSION

There remains limited data surrounding the prognostic use of biomarkers in eCRS. However, serum eosinophilia best predicts the eosinophilic density that best predicts the eCRS phenotype. In addition, it is also prognostic of need for more intensive therapy. Simple H&E stained sinus mucosa still remains the most reliable tissue for assessment and is more accessible than bronchial biopsies.

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Conflicts of interest

R.J.H. is a consultant with Medtronic, Olympus and NeilMed pharmaceuticals. He has also been on the speakers' bureau for Seqirus and MEDA pharmaceuticals. J.H. and P.E. have no financial disclosures or conflicts of interest.

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