

# Severity and Treatment Outcome Based on Phenotypes and Endotypes Classifications of Chronic Rhinosinusitis

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**Published Date:** February 15, 2016

## ABSTRACT

Chronic rhinosinusitis is one of the most common chronic diseases with multi-factorial origin and different underlying pathophysiologies that has a great impact on quality of life with. It is generally agreed that there are many subgroups or “phenotypes” of chronic rhinosinusitis defined by clinical observable characteristics, such as the presence or absence of nasal polyps. These phenotypes are useful for therapeutic decision. However, it doesn’t provide complete understanding about all underlying cellular and molecular pathophysiologic mechanisms of this pathology. The concept of multiple groups of biological subtypes, or “endotypes” which are identified by corresponding biomarkers has been recently studied. Classification of chronic rhinosinusitis according to phenotypes and endotypes may allow the identification of subgroups in relation to treatment response. Better identification of phenotypes and especially endotypes may improve individualization of therapy that can be targeted against specific biomarkers as recently developed, such as anti-IL-5 and anti-IgE. Literature review is essential for better developing general classification of chronic rhinosinusitis and better prediction of treatment outcome.

**KEYWORDS:** Chronic rhinosinusitis, Phenotype, Endotype, Outcome, Biomarkers, Nasal polyposis

# INTRODUCTION

Chronic rhinosinusitis (CRS) is one of the most common chronic diseases with multi-factorial origin that has a great impact on quality of life (QOL) [1]. In the United States; it affects approximately 14 to 16% of the population with 1.5% of all office visits and high national health care costs, estimated \$8.6 billion per year [2-4]. Consensus guidelines have defined CRS as a presence of clinical characteristic symptoms combined with objective evidence of mucosal inflammation for at least 12 consecutive weeks duration [5]. This complex inflammatory disorder involves the mucosa of the nose and paranasal sinuses, but little is understood about its pathogenesis.

It is generally agreed that there are many CRS phenotypes defined by clinical observable characteristics, such as the presence or absence of nasal polyps [5,6]. CRS phenotype is useful for therapeutic decision. However, it doesn't provide complete understanding about all underlying cellular and molecular pathophysiologic mechanisms of CRS. The concept of multiple groups of biological subtypes, or "endotypes" which are identified by corresponding biomarkers has been recently studied [7-9]. Classification of CRS according to phenotypes and endotypes may allow the identification of subgroups in relation to treatment response [10]. The objective of this literature review is to collect and understand all the existing CRS phenotypes and endotypes and their relation with medical and surgical treatment outcome.

## PHENOTYPES OF CRS

### Nasal polyps

Most clinicians and investigators used nasal polyps (NP) to classified CRS into two groups: CRS without nasal polyps (CRSsNP) and CRS with nasal polyps (CRSwNP). This phenotypical classification suggests an individual therapeutic approach for each group [10]. Nasal polyps (NP) are mucosal nasal and paranasal growths as "polypus" due to their resemblance to the sea-polyp, as defined by Hippocrates [11]. They commonly arise from the lateral nasal wall and middle meatus. They are found in up to 4% of the population and approximately in 20% of patients with CRS [12]. The mechanisms of mucosal degeneration into polyps are still unknown. Much research has suggested that the development of nasal polyposis requires host individual susceptibility, in addition to environmental factors such as immunologic and microorganisms stimuli [13-15].

The aim of CRS treatment is to reduce symptom and signs, improve patient's QOL and prevent disease progression and recurrence. There are two major type of management: medical and surgical treatments. In surgery, it is usually not ethical to do randomized controlled trials (RCT); because it can be ineffective and harmful for patients. The other problem is that many studies included patients with CRS with and without nasal polyps. In 2006, a systematic review by the Cochrane Group concluded that endoscopic sinus surgery (ESS) had not been demonstrated to confer additional benefit to that obtained by medical therapy, both in CRS with and without NP [16]. This conclusion was reached by study of 3 randomized trials that did not compare ESS to

medical therapy in patients who had previously failed initial standard medical management [17-19]. The thinking that sinus surgery must be always practiced after various medical treatments and it is often suggested for patients with refractory medical therapy render comparison of medical treatment with surgery very difficult. Many case series, case-control and cohort studies have been published and collected from thousands of patients with CRS concerning especially sinus surgery after medical therapy failure, and it seems unreasonable to ignore this high quality evidence.

The general management for CRS patients consists of medical treatment and surgery in cases of failure after maximal medical therapy (Table 1) [5,29]. Because of their anti-inflammatory properties, corticosteroids are the most effective anti-inflammatory treatment for both CRSwNP and CRSsNP. However, topical intranasal corticosteroids are more effective for CRS phenotype with NP than for other phenotype without NP (Table 1) [30-32]. The European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2012 update proposed treatment for both CRSwNP and CRSsNP based on severity of symptoms using subjective and objective parameters of sinonasal inflammation (VAS and endoscopic score) [5,33].

**Table 1:** Treatment evidence and recommendations for adults with chronic rhinosinusitis with and without nasal polyps.

Therapy	Grade of recommendation	
	CRSsNP	CRSwNP
Topical steroid [20]	A	A
Oral steroid [21]	C	A
Nasal saline irrigation [5]	A	D (for only symptomatic relief)
Oral antibiotic therapy short term (< 4 weeks) [22]	B (during exacerbation)	C
Oral antibiotic therapy long term (≥ 12 weeks) [23]	C (especially if IgE is not elevated)	C
Bacterial Lysates [24]	A (unclear)	-
Capsaicin [25]	-	C
Proton pump inhibitors [5]	D	C
Aspirin desensitization [26]	-	D
Topical and systemic antimycotics [27]	A(-)	A(-)
Other medical treatment [5]	D	D
Functional endoscopic sinus surgery (FESS) [5,28]	C	C

**CRSsNP:** Chronic Rhinosinusitis without Nasal Polyps

**CRSwNP:** Chronic Rhinosinusitis with Nasal Polyps

**A(-):** Grade A recommendation not to use

In earlier studies, the presence of nasal polyps in CRS has been thought to have a negative effect on QOL outcomes after ESS [34-38]. Many other and recent data found no significant difference outcomes after surgery between CRSwNP and CRSsNP groups [39-43]. In a prospective cohort

study from the National Comparative Audit, CRSwNP patients demonstrated more improvement following sinus surgery than CRSsNP [44]. However, surgery for nasal polyps has been associated with a high rate of revision [44-46]. In regards to specific symptoms, patients with NP tended to have greater improvement in nasal obstructive symptoms after surgery than did patients without NP. In contrast, symptoms of headache and facial pressure tended to persist in patients with NP after surgery [45,47]. In addition to these disease-specific measures, other possible benefits of surgery include improvement in asthma and a decrease in oral steroid use [45,47]. This discordance in the literature may be explained by the presence of different endotype subgroups in both CRS groups with and without NP. There is need, however, for different CRS endotypes in further studies to evaluate outcome of medical and surgical treatment.

## Comorbidities

### Allergy and atopy

The concept of mucosal continuation of the nasal airway with that of the paranasal sinuses, suggest the association between atopy and rhinosinusitis. Based on the presence of a positive skin prick test and/or serum specific IgE determinations, the reported incidence of atopy in CRS patients ranges from 50% to 80%, which is superior to the incidence in general population [48,49]. The frequency of atopy is equally associated with CRSwNP and CRSsNP [50]. Overall, the role of allergy in CRS remains unclear; it appears that allergy represents a predisposing factor for CRS and its severity [48,51-56].

Reports on potential negative impact of allergy on surgery outcomes are various. There are a number of studies indicating a poor surgery outcome of atopy [16,46,57]. However, other studies demonstrate that allergy status, eosinophilia, and IgE levels were not related to improvement after surgery [58-62].

### Asthma

Asthma is frequently associated with CRS with and without polyps. Epidemiological studies showed approximately fourfold higher prevalence of asthma in patients with CRS than in normal population [63-65]. However, for patients with CRSwNP, the same does not seem to hold for Chinese population [60,61]. The inverse association also holds true, up to 80% of asthmatic patients had radiological evidence of rhinosinusitis compared to only 10% to 20% of the general population [63,68]. Many studies suggest that CRS and asthma represent upper and lower airway manifestations of the same underlying pathophysiological process [69,70]. Concomitant asthma was associated with worse postoperative endoscopy findings, but had no influence on other outcome parameters [43,46,62,71]. Asthma with and without aspirin intolerance was shown to be a determinant factor of recurrence and revision surgery after functional endoscopic sinus surgery (FESS) especially in patients with CRSwNP [72-74], but not in all studies [60,75]. There is also evidence that aggressive treatment of rhinosinusitis can subsequently lead to an improvement of asthma severity [76-79].

## Cystic fibrosis

Cystic fibrosis (CF) is a lethal autosomal recessive disease. Involvement of the sinonasal mucosa is observed in up to 100% of CF patients either by clinical or radiological examination. Up to two-thirds of patients with CF demonstrate CRSwNP [80]. Recent systematic reviews found overall improvement in sinonasal symptoms but no improvement in pulmonary function after FESS [81,82]. The baseline measures of disease severity are worse in the CF population, but objective and QOL improvements for adult patients with CF are comparable to patients without CF [83]. It was observed that paranasal sinuses in CF may serve as a source for pseudomonas aeruginosa induced lung infections; and massive local lavages help to prevent recurrent CRS and lung infection [84].

## Ciliary Dysfunction

Abnormalities in ciliary function can result in stasis of mucus and impaired mucociliary clearance which may lead to recurrent and chronic infections of the entire respiratory tract including CRS. This dysfunction can be either primary or secondary. Early descriptions of Primary ciliary dyskinesia (PCD) were known as Kartagener triad (sinusitis, bronchiectasis, and situs inversus) [85]. Much research identified a 100 % frequency of chronic rhinitis and/or sinusitis in patients with PCD [85]. The CRS in these patients is very difficult to manage, and diagnosis is established by mucosal biopsy [86].

## Gastroesophageal reflux disease

One study showed that only gastroesophageal reflux disease (GERD) was statistically significant as a predictor of poor outcome [87]. However, other studies have failed to find this result [88].

## Environmental Factors

### Smoking status

The effect of smoking on sinus surgery outcome is unclear. Most studies show no effect of smoking on FESS outcomes [62,89,90]. Although other studies found that smoking status has been associated with the need for revision surgery and poor surgical outcomes [91,92].

### Occupational exposure

It was recently observed that occupational exposure appears to be a risk factor for the occurrence of CRS and for its recurrence and need for more revision surgery [93].

## Other Factors

### Demographic factors

**Gender:** In most studies, there was no statistically significant difference in outcomes after FESS between men and women [94,95].

**Age:** Reported symptomatology and QOL outcomes before and after sinus surgery does not differ between younger and elder CRS patients, but postoperative objective findings seem to improve more in the elderly patients [94,96]. However, complications occurred significantly more frequently in geriatric patients especially orbital complications [97,98].

### **History of prior sinus surgery**

Of all the evaluated factors proposed to be a predictor of surgical outcome in CRS, most studies report that history of prior sinus surgery was a poor prognosis after revision surgery [46,62,99-103]. However, little research found no evidence of a negative surgical outcome in the revision sinus surgery group in comparison with the primary sinus surgery group [37,104-106]. This finding suggests that the first surgical intervention is extremely important.

### **Objective factors and extent of disease at baseline**

The sino-nasal extension of CRS with and without NP is measured by two objective examinations: endoscopy and CT scan. These examinations are based on two validated scores: the Lund-Kennedy endoscopic score and the Lund-Mackay scanographic score [107,108].

Extent of pathological changes in the preoperative objective scores is one of the factors of disputable significance on treatment outcomes [34,36,62,72,100,109-112]. However, recent studies found no correlation between endoscopic and CT scan scores and patient reported symptoms [109-112]. Other research, suggested that patients with extensive disease measured by objective scores are at higher risk for the development of recurrences after FESS, but not a positive neither a negative predictor of surgical outcome [76,100,109,110].

The frontal recess is the most common site of recurrence, because it is easily stenosed after surgery. Although, some surgeons avoid surgical management of frontal sinus at primary surgery, others advocate early intervention [113,114]. Frontal sinus involvement is believed to reflect a more severe disease phenotype, and revision surgery occurs at a high rate in patients with frontal sinus involvement [114,115].

### **Subjective factors and severity of disease at baseline**

There is now growing acceptance that CRS has a significant impact on quality of life (QOL) and patient's point of view is essential in the delivery of high quality care [116]. Patient reported outcome measures (PROMs) are measures of health-related quality of life (HRQOL) that are self reported by patient. In addition to regarding overall severity of CRS using the visual analogue scale (VAS), individual symptom severity, or general health instruments, disease-specific instruments are now frequently used in the evaluation of CRS. By using these specific validated questionnaires that are able to capture symptoms in greater detail, the evaluation of therapeutic interventions concerning CRS becomes more reliable and sensitive.

The way CRS affects daily QOL, is far more important than the results of endoscopy or CT scan [117]. The most used validated questionnaires are listed in Table 2.

**Table 2:** Treatment evidence and recommendations for adults with CRS.

	Instrument	Items / Domains	Score range
FNSS [118]	Fairley Nasal Symptom Score (1993)	12 / 1	0-36
RSOM-31 [119]	Rhinosinusitis Outcome Measurement (1995)	31 / 7	0-155
CSS [120]	Chronic Sinusitis Survey (1995)	6 / 2	0-100
RSDI [121]	Rhinosinusitis Disability Index (1997)	30 / 3	0-120
SNOT-16 [122]	Sinonasal Outcome Test (1999)	16 / 1	0-80
SNOT-20 [1]	Sinonasal Outcome Test (2002)	20 / 1	0-100
SNAQ-11 [123]	Sinonasal Assessment Questionnaire (2002)	11 / 1	0-55
SNOT-22 [44,116]	Sinonasal Outcome Test (2003)	22 / 5	0-110
RSI [124]	Rhinosinusitis Symptom Inventory (2003)	20/1	0-100
RhinoQOL [125]	Rhinosinusitis Quality of Life Survey (2005)	17 / 3	14-100

Many studies have reported greater improvement among patients with high CRS severity baseline based essentially on poor QOL [62,99,100,126]. However, some authors proposed that poor QOL at baseline was a negative predictor outcome after FESS [109].

In a recent study by DeConde et al., psychological and sleep dysfunction in the five SNOT-22 domains were significantly more likely to have a greater relative influence on patients electing surgical therapy [127]. Other study, found that “runny nose” predicted greater improvement, whereas “sadness” and “cough” were significantly predictive of lesser improvement after FESS [62].

## ENDOTYPES OF CRS

### Sinonasal tissue eosinophilia

The number of eosinophils in sinonasal tissue seems to be an important endotype factor in the study of CRS treatment and outcome. The eosinophils in sinonasal tissue are increased in patients with CRSwNP, allergic fungal rhinosinusitis, non allergic fungal rhinosinusitis, and aspirin-exacerbated respiratory disease (AERD) [128-131]. There is currently no consensus for quantitatively definition of sinonasal tissue eosinophilia. The proposed in the literature to define eosinophilic CRS (E CRS) was tissue eosinophil amount >5% of all leukocytes in 5 visual fields or >5 cells / HPF [132-134]. Recently, Soler et al. [135] proposed an optimal cut-point of >10 eosinophils/HPF defining E CRS and non-E CRS, because this reflects the largest absolute difference in QOL score changes after FESS.

There is a contradiction in the association between tissue eosinophilia and asthma [133-136]. E CRS patients have more severe endoscopic and CT scores than non-E CRS patients, but not SNOT-22 and osteitis scores [133-136]. Tissue eosinophilia predicts significantly less improvement of symptoms, QOL, and relapse after FESS [73,100,135,137-141]. Other studies have not demonstrated the same thing [142].

CRSsNP is commonly associated with neutrophil dominant inflammation, especially in cases of bacteria, primary ciliary dyskinesia (PCD), cystic fibrosis (CF), or a foreign body [143]. In a recent study, eosinophilic CRSsNP group was associated with the worst FESS outcome [135]. These findings favor further classification based on tissue eosinophilia.

## Aspirin intolerance

Aspirin hypersensitivity is believed to be related to an elevation of leukotriene synthesis. The leukotrienes then induce increased nasal mucosal edema, mucus secretion, and eosinophilic migration [144]. Symptomatically, patients with aspirin hypersensitivity have more severe clinical presentation of CRS and asthma [145].

First described by Samter and Beers, aspirin-exacerbated respiratory disease (AERD), or also known as ASA triad or Samter's triad, is a clinical triad of nasal polyposis, asthma, and aspirin intolerance [81]. Nasal polyps in AERD are different from other types of polyps. They are more aggressive and contain higher concentration of eosinophils [146,147]. AERD patients are at high risk for treatment failure and recurrence of polyps following FESS and often require multiple revisions [145,148,149]. This known genetic defects disease requires more aggressive management [146]. Aspirin desensitization has been shown to improve asthma control, decrease the need for corticosteroid and repeat sinus surgery, but did not lead to complete remission [26,150,151].

## Bacterial biofilm

Bacterial biofilm is an organized aggregation of bacteria that adheres to mucosal surfaces and expresses a unique molecular profile. This molecule facilitates genetic alterations, resistance to antibiotics, and increases capabilities resistance to host immunity [152,153]. It has been discussed that biofilm play a role in both CRSwNP and CRSsNP. However, no significant association was found between biofilm and other prognostic factors like nasal polyps, allergy, Samter's triad, smoking status, age, or gender [154]. Different biofilm species are associated with different disease phenotypes; *Haemophilus influenzae* biofilm is typically found in patients with mild disease, whereas *Staphylococcus aureus* is associated with a more severe, surgically recalcitrant disease [155]. Patients with biofilms have more severe disease outcome after surgery, supporting the concept that biofilms may be an important contributor to treatment-resistance [75,156-160].

## Allergic Fungal Sinusitis

In 1994, Bent and Kuhn defined the diagnostic criteria for Allergic Fungal Sinusitis (AFS) as fungal type 1 hypersensitivity, with positive sinonasal fungal stains/cultures, characteristic radiographic findings on CT, eosinophilic mucin without fungal tissue invasion, and nasal polyposis [161]. A recent study suggested that CRS with histological confirmation of eosinophilic mucin and the presence of type 1 hypersensitivity meets the criteria for the diagnosis of AFS [162]. Others suggest that the macroscopic presence of eosinophilic mucin is sufficient [163-165].



Initial treatment consists of surgical removal of polyps and eosinophilic mucin with maintenance of nasal topically administered steroids in suspension [166]. The benefit of fungal immunotherapy is still unknown and there is no role for topical or systemic antifungal therapy [27,167,168].

## Cell-mediated immunity

Several studies have suggested that tissue eosinophilia may impact in CRS treatment outcomes [73,100,135, 137-141]. The presence of tissue eosinophilia is related to interleukin 5 (IL-5), and essentially T helper 2 (Th-2) cytokine (type-2 inflammatory cytokines and chemokines) [66]. There was a clearly differences on inflammation type between CRSwNP and CRSsNP; the first has an increased type-2 inflammatory signature compared to sinonasal tissue from healthy or CRSsNP patients [130,169-173]. The second type of CRS without NP has a predominant type-1 inflammation characterized by elevated interferon gamma (IFN $\gamma$ ) [130,171,174,175]. Type-1 inflammation are also predominant in neutrophilic, cystic fibrosis related CRSwNP [130]. However, recent study observed low levels of IFN $\gamma$  expression in CRSsNP group [173]. Consequently, the differentiation of CRS with IL-5 expressing TH2-biased versus non-TH2-biased CRS is of clinical relevance [176]. Recently, other possible existence of TH type cells expression in CRS was suggested [171,177].

Type 2 innate lymphoid cells (ILC2s) have recently been identified in human nasal polyps as a potentially important effectors cell in type 2 inflammatory diseases [178]. ILC2s are significantly elevated in patients with CRSwNP compared to patients with CRSsNP and controls [179,180]. Also, ILC2s are significantly elevated in patients with eosinophilic nasal polyps compared to non-eosinophilic polyps [181]. Further, there was a significant lower level of ILC2s after treatment with systemic corticosteroid in the same group of patients with eosinophilic polyps [181]. The ILC2 frequencies were significantly correlated with nasal symptom score, indicating that these cells may be responsible for symptom severity in patients with CRS [182,183].

Future research on better classification of TH subsets in patients with CRS might lead to a better understanding of disease mechanisms and response to medical and surgical treatments.

## Cytokines and chemokines

### Th1-related cytokines

Th1 cytokines have been associated with CRSsNP with neutrophilic inflammation and secondary CRSwNP (CF and PCD) [130,184]. Th1-related cytokines such as IFN- $\gamma$ , IL-2, and transforming growth factor beta (TGF- $\beta$ ) were elevated in CRSsNP phenotype and Chinese CRSwNP [130,169,185].

### Th2-related cytokines

Many Th2 cytokines have been associated with CRSwNP, especially eosinophilic endotype. Eosinophilic CRSwNP are associated with elevated IL-5 levels and eosinophilic cationic protein (ECP) to myeloperoxidase (MPO) ratio of more than 1 [66,130]. Recent studies have implicated IL-25, IL-33 and eotaxin-3 as a link between epithelial cells response and Th2-mediated

inflammation and also these cytokines were correlated with poorer endoscopic and CT scan scores [186]. Based on this result, anti-IL-5 antibodies were used as a treatment for CRSwNP and two randomized, double blind, placebo controlled trials have objective that anti-IL-5 antibodies reduce the number of blood and tissue eosinophils and the size of nasal polyps with a greater benefit for patients with high levels of IL-5 in nasal secretions [187,188]. The 2012 update of EPOS consensus recommended (grade A) the use of antibodies against IL-5 for the treatment of patients with CRSwNP [5]. In other studies, transforming growth factor beta (TGF- $\beta$ ) was over expressed in CRSsNP patients, resulting in an upregulation of collagen deposition and fibrosis by stimulating extracellular matrix protein production. Conversely, TGF- $\beta$  is downregulated in CRSwNP [189,190]. TGF-b may exert its anti-inflammatory effects through antagonism of IL-5-mediated eosinophil inflammation [191].

## Staphylococcus aureus enterotoxin (superantigen)-specific IgE (SE-specific IgE)

Much recent research has shown that Staphylococcus aureus endotoxins may be important in the development of CRS. These endotoxins act as superantigens in the immune response of the upper airway. They activate various populations of T lymphocytes and induce IgE production with Th-2 cytokine cascade, without the activation of the regulatory cytokines interleukin-10 and TFG- $\beta$ 1 [193,194]. In fact, these Staphylococcus aureus superantigens increase eosinophilic and lymphocytic tissue infiltration which is characteristic of CRS with nasal polyps [195]. Many studies have associated S. aureus has with poor outcomes following FESS [155,158,160, 196,197].

In fact, it is clear that there is local IgE formation in nasal polyp tissue, which might be triggered by staphylococcal superantigens [198]. Many studies with one recent randomized, double-blind, placebo-controlled, showed a significant reduction of polyp size, an improvement of bronchial and nasal symptoms, including smell, quality of life, and sinus CT scan score after anti-IgE therapy [199,200]. The study suggests that anti-IgE therapy does work in patients with CRSwNP and comorbid asthma, preferentially after ESS, with clinical benefit in both the lower and upper airways.

## CONCLUSION

One of the major obstacles to improving CRS treatment is the failure to understand the different underlying pathophysiologies. Traditional clinical phenotyping of CRS has failed to evaluate clinical presentation and treatment response. It will be necessary to add more classification based on endotypes according to the underlying disease mechanism to improve our understanding of CRS. This classification will facilitate the development of future novel therapeutic targets. In addition, the use of combined phenotype-endotype classification is expected to identify patient groups that will benefit most from new and existing treatments which improve CRS patient selection and management. Current data are insufficient to propose a general classification especially for endotypes in patients with CRS.

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