

Chronic Rhinosinusitis without Nasal Polyps



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Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

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List of Design Committee Members: Seong Ho Cho, MD, Dae Woo Kim, MD, PhD, and Philippe Gevaert, MD, PhD

Learning objectives:

1. To define the phenotype of chronic rhinosinusitis (CRS) without nasal polyps.
2. To identify histologic features of CRS without nasal polyps that differ from those of CRS with nasal polyps.
3. To identify inflammatory markers of CRS without nasal polyps that differ from those of CRS with nasal polyps.
4. To identify treatment of CRS without nasal polyps that differ from those of CRS with nasal polyps.

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Chronic rhinosinusitis without nasal polyps (CRSsNP) is more prevalent than chronic rhinosinusitis with nasal polyps (CRSwNP).

Certain diseases predispose to whereas others are associated with CRSsNP. Predisposing diseases include allergic and nonallergic upper and lower airway diseases, epithelial cell disorders, immunodeficiencies, autoimmune diseases, and some infectious diseases. In addition, environmental and host factors, examples of which include smoking, a higher incidence of abnormal biofilms, and innate immune defects, play a role in the pathogenesis of this disease. CRSsNP is characterized by histologic abnormalities, including basement membrane thickening (fibrosis) and goblet cell hyperplasia. Neutrophils and several chemokines, TGF- β and C-X-C motif chemokine ligand (CXCL)-8, play a role in CRSsNP remodeling. However, there are conflicting data about CRSsNP endotypes, for example, whether it is characterized by neutrophilia or eosinophilia or both. In spite of advancements and the understanding of the pathogenesis of this disease, additional study is necessary to better comprehend its underlying mechanisms, endotypes, and evidence-based treatment strategies. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology (*J Allergy Clin Immunol Pract* 2016;4:575-82)

Key words: Chronic rhinosinusitis without nasal polyps; Phenotype; Endotype

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Abbreviation used

AOAH- acyloxyacyl hydroxylase
 CF- cystic fibrosis
 CRS- chronic rhinosinusitis
 CRSsNP- chronic rhinosinusitis without nasal polyps
 CRSwNP- chronic rhinosinusitis with nasal polyps
 ECP- eosinophilic cationic protein
 FESS- functional endoscopic sinus surgery
 GATA-3- GATA binding protein 3
 ICAM-1- intercellular adhesion molecule 1
 IL- interleukin
 INCS- intranasal corticosteroid
 NO- nitric oxide
 NP- nasal polyp
 PGP- N-acetyl Pro-Gly-Pro
 TLR- Toll-like receptor
 VEGF- vascular endothelial growth factor

Rhinosinusitis is one of the most common diseases of the upper respiratory tract and is characterized by chronic inflammation. Chronic rhinosinusitis without nasal polyps (CRSsNP) has been attributed to mechanical obstruction of the ostiomeatal complex,¹ whereas chronic rhinosinusitis with nasal polyps (CRSwNP) has been regarded as a diffuse eosinophilic-based mucosal disease.² However, the obstruction theory explaining the pathogenesis of CRSsNP is not based on scientific evidence. It is now thought that this disease is a more complex mucosal disease with a variety of different underlying pathophysiologic mechanisms. Some investigators hypothesize that CRSsNP and CRSwNP are not distinct diseases but the latter is a result of more prolonged and severe inflammation.³⁻⁵ In summary, CRSsNP appears to be a heterogeneous disease, characterized by the absence of nasal polyps (NPs), needing additional definition to help guide its proper diagnosis and treatment. There is not enough information about endotyping CRSsNP because most CRS studies have focused on CRSwNP. This review outlines the clinical and immunologic characteristics of CRSsNP and proposes new direction for additional research.

EPIDEMIOLOGY

Most epidemiologic studies on CRS do not discriminate between CRSsNP and CRSwNP. Prevalent data vary according to geographic locations. For example, it is estimated that CRS of both phenotypes affects approximately 13% of the population in the United States,⁶ 11% in Europe,⁷ 8% in China,⁸ 7% in South Korea,⁹ and 6% in Sao Paulo, Brazil.¹⁰ The prevalence of endoscopic-assisted, physician-diagnosed CRSsNP versus a questionnaire-based diagnosis would be expected to be lower because the diagnostic criteria are better defined for the former. A cross-sectional study in South Korea indicates that endoscopic-assisted, physician-diagnosed prevalence in 28,912 normal adults was 5.8% for CRSsNP versus 2.6% for CRSwNP.¹¹ The prevalence of both CRS types in Canada was 2.7% and 6.6% in the 20- to 29-year-old and 50- to 59-year-old age groups, respectively. After age 60 years, the prevalence leveled off at 4.7%.¹² Physician-diagnosed electronic health records indicate that the incidence of CRSsNP decreases after age 65 years, whereas that of CRSwNP remains stable.¹³

In summary, CRSsNP versus CRSwNP is more prevalent in all ages but declines with age.

PHENOTYPES AND ENDOTYPES

CRS is defined as an inflammatory disease of the paranasal sinuses lasting at least 12 weeks in duration, characterized by 2 or more nasal/sinus symptoms, one of which is nasal obstruction or nasal discharge $\pm$ facial pressure/pain and $\pm$ reduced smell. In addition, endoscopic signs of mucopurulent discharge or edematous/mucosal obstruction of the middle meatus or computed tomography abnormalities, such as mucosal changes within the ostiomeatal complex or sinuses, support this diagnosis.¹⁴

The primary phenotypes of CRS are based on the presence or absence of NPs via endoscopic findings. Although clinical symptoms overlap between these 2 entities, nasal congestion and olfactory abnormalities are more typically associated with CRSwNP, whereas CRSsNP is more typically characterized by rhinorrhea and facial discomfort.¹⁵

Diseases that predispose to the development of CRSsNP include acute rhinosinusitis, usually triggered by a viral respiratory tract infection, allergic and nonallergic rhinitis, asthma, bronchitis, pneumonia, gastroesophageal reflux disease, adenotonsillitis, sleep apnea, and otitis media.¹⁶ In addition, the incidence of allergic conjunctivitis, atopic dermatitis, asthma, urinary tract infections, and skin/soft tissue infections is increased with a diagnosis of CRSsNP.^{13,17} A Taiwan population-based study also demonstrated that chronic obstructive pulmonary disease is independently associated with CRSsNP.¹⁸

Historically, CRSsNP, usually secondary to microbacterial colonization, has been assumed to occur as a consequence of unresolved or inadequately treated acute rhinosinusitis. However, this is not common because most acute rhinosinusitis is caused by a viral respiratory tract infection that usually resolves without treatment. Therefore, when CRSsNP is present, a variety of different underlying predisposing conditions should be considered. These include primary and secondary immunodeficiencies, such as common variable immunodeficiency and HIV, respectively; genetic defects, including cystic fibrosis (CF); and mucociliary diseases, such as ciliary dyskinesia. For example, there is a high prevalence of CRS in HIV-infected individuals most likely due to decreased cellular and humoral immunity.^{19,20} Thirty-six percent of patients with chronic variable immunodeficiency present with CRSsNP.²¹ Seventeen percent of individuals with both CRS phenotypes have a low serum IgA level and 6.2% have selective IgA deficiency, although the association between selective IgA deficiency and both forms of CRS remains uncertain.²² The prevalence of specific IgG antibody deficiency to *Streptococcus pneumoniae* is based on the existing antibody titers or response to the PNEUMOVAX vaccine (Merck & Co, Kenilworth, NJ). Such a deficiency is increased in both phenotypes of CRS. Both CRS phenotypes also can be associated with autoimmune diseases, such as Wegener granulomatosis and sarcoidosis.²³

Fewer eosinophils and plasma cells are found in mucosal tissue in CRSsNP versus CRSwNP. However, the number of neutrophils is similar or slightly lower in the former versus the latter.²⁴⁻²⁷ CD8⁺ T cells are found in a higher proportion in CRSsNP versus CRSwNP.²⁸ Likewise, neutrophilia and an elevated level of intercellular adhesion molecule 1 (ICAM-1), a neutrophilic chemoattractant, have been demonstrated in CRSsNP.^{29,30} However, the term "neutrophilic" rhinosinusitis is not considered appropriate for CRSsNP because neutrophils and other inflammatory cells coexist in the sinonasal tissues.^{26,28}

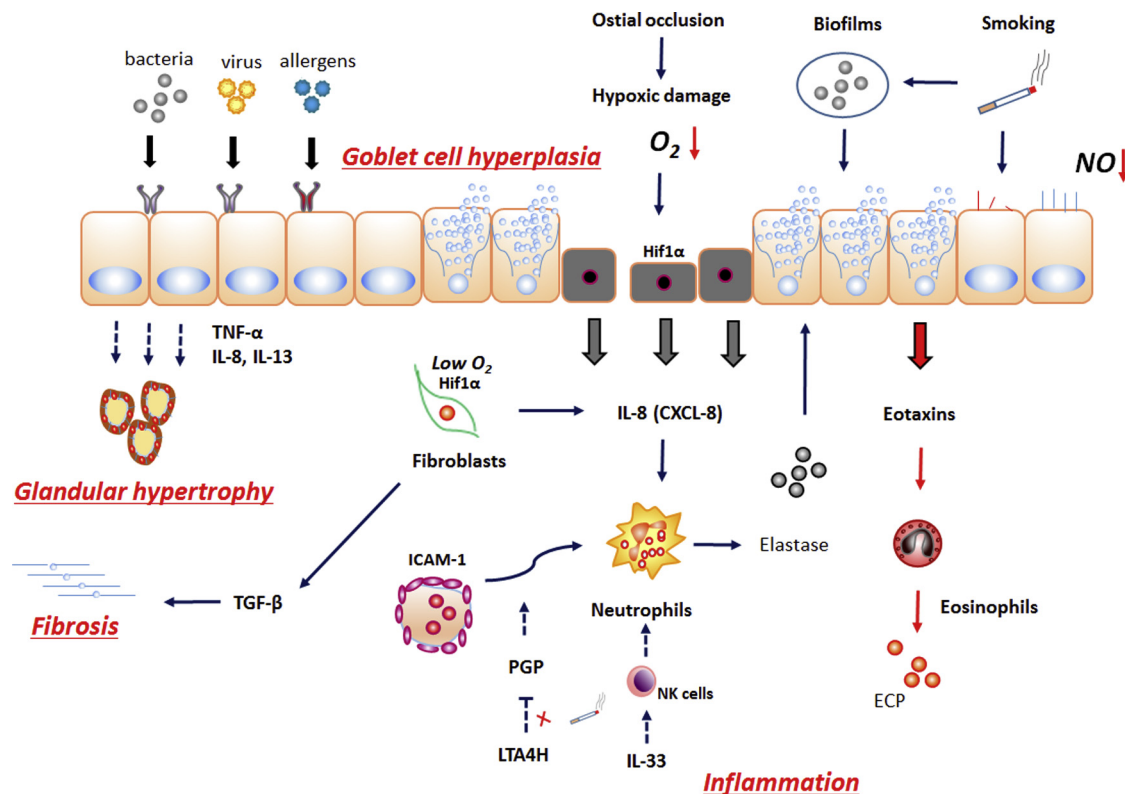


FIGURE 1. Schematic depiction of pathological mechanisms of CRSsNP. Solid lines, probable mechanisms; dotted lines, possible mechanisms. *CXCL-8*, C-X-C motif chemokine ligand-8; *ECP*, eosinophilic cationic protein; *HIF-1α*, hypoxia-inducible factor 1α; *ICAM-1*, intercellular adhesion molecule 1; *IL-8*, interleukin-8; *LTA4H*, leukotriene A4 hydrolase; *NK*, natural killer.

The gene expression of multiple inflammatory markers is increased in CRSsNP versus control sinonasal tissues. These include T-bet, GATA binding protein 3 (GATA-3), RAR-related orphan receptor C, IFN-γ, interleukin (IL)-5, IL-17A, IL-22, IL-23, and IL-10 gene expressions. Gene expression of IFN-γ is high but GATA-3, IL-5, and IL-10 expressions are low in CRSsNP versus CRSwNP.²⁸ However, there are conflicting results about cytokine protein levels in CRSsNP, even though this disease is reported to be T_H1-based with elevated IFN-γ.^{27,31,32} T_H2 cytokines, such as IL-5, eosinophilic cationic protein (ECP), IgE, and eotaxin, are increased in CRSsNP compared with controls although they are lower in CRSsNP versus CRSwNP.^{27,31} Most studies of cytokine expression are based on small sample sizes and need confirmation. Because the diagnosis of CRSsNP is based on the absence of NPs, and includes a wide range of endotypes, the cytokine profiles of this disease may depend, to some extent, on geographic and ethnic differences. Further studies are required to subclassify and endotype CRSsNP, especially for possible inflammatory pattern differences in various regions and ethnic populations of the world. In summary, it appears that CRSsNP is a mixed inflammatory disease with T_H1, T_H2, and T_H17 cell tissue infiltration even though the inflammatory disease is less eosinophilic with lower T_H2 inflammatory changes compared with CRSwNP.

GENETICS

There is a familial risk of CRSsNP and CRSwNP in a large population study.³³ It demonstrates that CRSsNP has a 2.4-fold

increased risk for first-degree relatives followed by a 1.4-fold increased risk for second-degree relatives. This suggests an inheritable component to develop CRSsNP. Spouses of subjects with CRSsNP also exhibit a 2-fold increased risk, implying an environmental susceptibility. Several genes and single nucleotide polymorphisms are associated with CRSsNP. For example, there is a correlation between CRSsNP and 2 genes, Ring1A and YY1 binding protein and acyl-coyl hydroxylase (AOAH). This association has been replicated in both Canadian Caucasian and Chinese Asian populations. There also are associations between CRSsNP and single nucleotide polymorphisms in these genes, for example, rs4504543 in AOA (odds ratio = 0.30) and rs4532099 in Ring1A and YY1 binding protein (odds ratio = 2.45).

Several studies, in which the CRS phenotypes are not specified, show an association between CRS and IL-1 receptor-associated kinase 4, IL-1 receptor-like 1, Toll-like receptor (TLR)-2, CF transmembrane conductance regulator, transforming growth factor beta-1, and AOA genes.³⁴⁻³⁸ These genes are of potential significance in the pathogenesis of CRSsNP because they play an important role in innate immunity; for example, IL-1 receptor-associated kinase 4 and TLR-2 are associated with TLR signaling. The IL-1 receptor-like 1 gene not only is involved in regulating TLR signaling but also is a receptor for IL-33. AOA is responsible for degrading LPS, which is confirmed by a study in AOA-deficient mice demonstrating persistent inflammation following LPS stimulation.³⁹ Abnormal *TLR-1*, *TLR-2*, and *TLR-5* genes may be responsible for the

decline in lung function in subjects with CF.⁴⁰ CF transmembrane conductance regulator mutation-induced inflammation also enhances upregulation of IL-8 and TLR-2, resulting in the initiation or perpetuation of airway inflammation.⁴⁰⁻⁴³ These genetic defects illustrate that the innate immune system is intimately involved in the pathogenesis of CRSsNP. Most of these observations about candidate genes have not resulted in any major breakthrough in understanding the pathogenesis of CRS. For new insights, a genome-wide association study is needed.⁴⁴

PATHOGENESIS

CRSsNP is characterized by fibrosis, basement membrane thickening, and goblet cell hyperplasia (Figure 1).^{45,46} Levels of TGF- β , which promotes fibrosis and airway remodeling, are increased in subjects with CRSsNP versus CRSwNP and healthy controls.⁴⁷ TGF- β levels are expressed in higher concentrations in the early stages of CRSsNP, but proinflammatory neutrophils and T_H1 markers and the T-cell profile are not different versus controls.^{31,47} However, the remodeling process appears to occur in parallel with inflammation in the early stages of CRSwNP.⁴⁸ These results suggest that the remodeling process is predominant in CRSsNP from the early stage of the disease. In addition, plasminogen activator inhibitor-1, which is associated with tissue remodeling, is elevated in CRSsNP and correlates with TGF- β levels, suggesting that the inhibition of fibrinolytic components may be upregulated in CRSsNP.⁴⁹

Occlusion of the nasal ostium may be a pathogenic mechanism in CRSsNP and contribute to the development of hypoxia of the sinus cavities. Hypoxia is important in tissue remodeling and accumulation of inflammatory cells. It also induces hypoxia-inducible factor- α expression, which triggers tissue remodeling markers such as vascular endothelial growth factor (VEGF), TGF- β , nitric oxide (NO) synthetase, and matrix metalloproteinases.^{3,4,50-53} Under hypoxic conditions, nasal tissue-derived fibroblasts also induce chemokines, such as IL-8 and C-C motif chemokine ligand (CCL)-11, and contribute to the recruitment of neutrophils and eosinophils.^{51,54} *In vitro* studies using cultured nasal epithelial cells under hypoxic conditions demonstrate the upregulation of IL-8, CCL-2, CCL-4, CXCL-12 (chemokines), and ICAM-1 and P-selectin (adhesion molecules). Consequently, this results in enhanced migration and adherence of neutrophils. Hypoxia-inducible factor-1 α is upregulated in CRSsNP compared with controls and positively correlates with the number of neutrophils, IL-8, and TGF- β 2 transcripts. TGF- β 2- and hypoxia-inducible factor-1 α -positive neutrophils are higher in CRSsNP.⁵⁵ Hypoxia, possibly secondary to sinus occlusion and subsequently poor ventilation of the sinuses, may lead to neutrophilic inflammation with overproduction of TGF- β 2 and subsequent fibrosis.

Mucus secretion and goblet cell and glandular hyperplasia is one of the signature features of CRSsNP upper airway remodeling. The increase in mucous gland density occurs in subjects with severe CRSsNP, whereas those with NPs show a significant decrease in mucous gland density.^{28,56-59} Glandular hypertrophy and mucous secretion in the airway mucosa are likely to be mediated by the cytokines, TNF- α , IL-8, and IL-13.⁶⁰⁻⁶² Mucin (MUC) 5AC and MUC5B are the main secreted mucins in the human airway, with MUC5AC produced primarily by goblet cells.⁶³ Viral and bacterial components upregulate mucin messenger RNA expression and stimulate mucin secretion in

goblet cells. Several inflammatory markers, including IL-1 α , IL-1 β , IL-6, IL-8, TNF- α , and GM-CSF, are engaged in this process.^{64,65} Goblet cell metaplasia and mucous secretion are enhanced by neutrophils; their elastase activity occurs at the cell interface, leading to goblet cell secretion.^{66,67} Eosinophil-epithelial cell interaction also augments the secretion of MUC5AC, PDGF-AB, VEGF, TGF- β , and IL-8 in culture supernatants.⁶²

Neutrophils are regarded as acute response cells and have a relatively short tissue half-life; therefore, the reasons for their presence in CRSsNP are not clear.¹⁴ Similar mechanisms may be important in chronic obstructive pulmonary disease and CF. Studies indicate that persistent neutrophilic inflammation occurs in these lung diseases.^{68,69} A mechanism that accounts for this neutrophilic inflammation is related to a tripeptide, *N*-acetyl Pro-Gly-Pro (PGP), a neutrophil chemoattractant, derived from the breakdown of the extracellular matrix of the lung tissue in chronic obstructive pulmonary disease and CF.⁷⁰ Leukotriene A4 hydrolase degrades PGP and generates leukotriene B4, another neutrophil chemoattractant.⁶⁹ In acute neutrophil-driven inflammation, PGP is degraded by leukotriene A4 hydrolase, which facilitates the resolution of inflammation. In contrast, tobacco smoke selectively inhibits leukotriene A4 hydrolase aminopeptidase activity, leading to the accumulation of PGP and neutrophils.⁶⁸

Other than promoting neutrophilic inflammation, tobacco smoke also induces ST2 expression on macrophages and natural killer cells and decreases ST2 expression on group 2 innate lymphoid cells, thus altering IL-33 responsiveness within the lung. Consequently, increased local IL-33 significantly amplifies type I proinflammatory responses via synergistic modulation of macrophage and natural killer cell function.⁷¹

Tobacco smoke is a causative factor in generating abnormal biofilms. Repetitive *in vitro* exposure to tobacco smoke enhances biofilm formation in bacteria isolated from the nasal cavities of subjects with CRSsNP.⁷² Increased biofilms have been observed in subjects with CRSsNP. Recovery rates of biofilms vary from 28.6% to 75%, most likely due to differences in detection methodology.⁷³⁻⁷⁶ Biofilms induce cellular and humoral immune responses and are resistant to antibiotics.⁷⁷ It remains uncertain as to the type of inflammation biofilms induce, that is, eosinophilic, neutrophilic, or other. CRSsNP with biofilms is associated with more neutrophilia and T_H1 inflammation.⁷⁸ However, one study did reveal higher levels of IL-5 in subjects with CRSsNP with *Staphylococcus aureus* biofilm.⁷⁹

Although tissue remodeling of CRSsNP is characterized by fibrosis and glandular hypertrophy associated with leukocytosis, understanding the interplay between the host and environment at the airway mucosal level will provide clues about the pathogenesis of CRSsNP. Many studies have addressed various hypotheses. These include the superantigen, fungal, dysfunctional eicosanoid, and immune barrier hypotheses.¹⁴ However, etiologies unique to CRSsNP are limited. Numerous studies challenge the role of bacteria; however, many are flawed and bacteria still may play a major role in the pathogenesis of this disease. A prospective study of samples obtained from the middle meatus, using the 16S ribosomal DNA technique, revealed polymicrobial flora that was distinct from controls.^{80,81} However, their role remains unclear.^{82,83} These environmental factors could not necessarily account for all the manifestations of CRSsNP; therefore, a dysfunctional host, in

part, may contribute to the pathogenesis. The relevance of physical defense to CRS is highlighted by the high prevalence of sinonasal inflammation observed in subjects with genetic defects that affect mucociliary flow, that is, CF and ciliary dyskinesia.^{84,85}

In both these CRS phenotypes, there is evidence for ciliary dysfunction in explanted epithelial cells and increased mucus viscosity correlates with disease severity.^{86,87} Barrier function—associated epithelial genes, such as S100A7, S100A8, and S100A9, are downregulated in both CRSsNP and CRSwNP. This suggests several genetic defects involving epithelial barrier maintenance and repair in the inflammatory state of these diseases.¹⁵ In addition, the sinuses physiologically produce very high concentrations of NO. It is proposed that NO may limit bacterial colonization of these structures⁸⁸ and also help regulate ciliary beat frequency.⁸⁹ Studies indicate low levels of nasal NO in CRSsNP.⁹⁰

PROGNOSTIC FACTORS

High tissue eosinophilia in CRSsNP and CRSwNP correlates with the need for revision surgery in the longitudinal studies.^{25,91} Bacterial biofilms can influence disease courses by inducing a local inflammatory reaction. They can be resistant to antibiotics at concentrations hundreds or even thousands of times of the minimum inhibitory concentration.⁹² The presence of *Staphylococcus aureus* and *Pseudomonas aeruginosa* biofilms is associated with unfavorable surgical outcomes,⁷⁴ whereas *Hemophilus influenza* biofilms are associated with favorable outcomes.⁹³ The prevalence of both types of CRS is higher in smokers,⁹⁴ and they have a less favorable response to surgery.⁹⁵ The other risk factors for refractory CRS include atopy, a disrupted mucociliary transport system, multiple medical conditions that affect the sinonasal mucosal tract, such as Wegner granulomatosis, and defects of the immune system.^{22,96,97}

MANAGEMENT OF CRSsNP

The goals of medical treatment for CRS are to reduce mucosal edema, enhance sinus drainage, and eradicate infections. This usually requires a combination of topical or oral glucocorticoids, oral antibiotics, and nasal saline irrigation. As mentioned above, the role of bacteria in the pathogenesis of chronic sinusitis remains elusive. However, an early diagnosis and intensive treatment, as indicated above, may result in symptom relief in most patients, many of whom can be cured. When medical therapy fails, functional endoscopic sinus surgery (FESS) may be indicated.

A meta-analysis of the use of intranasal corticosteroid (INCS) in CRSsNP shows that it improves symptoms and is not associated with major side effects. Direct delivery of INCS into the sinuses, via direct cannulation, also benefits CRSsNP. The postoperative use of INCS is also helpful due to their easy access to the sinus cavities.¹⁴ There are limited data and no randomized controlled studies about the use of systemic corticosteroids in CRSsNP.⁹⁸ For the most part, systemic corticosteroids are not recommended in CRSsNP considering the risk/benefit ratio, except for short-term use for acute exacerbation.

There are no randomized placebo-controlled trials of short-term (<4 weeks) antibiotics in CRSsNP.¹⁴ Several nonplacebo-controlled trials show clinical improvement and bacteriological resolution in subjects with CRSsNP with acute exacerbation.

Long-term low-dose macrolide therapy may be effective in CRSsNP, particularly in subjects with normal serum IgE levels.⁹⁹ A placebo-controlled randomized clinical trial in subjects with CRSsNP with daily roxithromycin for 12 weeks showed significant improvement in the sinonasal symptom score, nasal endoscopy score, and IL-8 levels. In this trial, a subgroup analysis demonstrates that subjects with normal IgE levels have a higher clinical response rate versus those with a high IgE level. However, another placebo-controlled randomized clinical trial with weekly azithromycin in subjects with CRSsNP and CRSwNP failed to show significant clinical response. These 2 trials may suggest that low-dose long-term macrolides would be more effective in CRSsNP in subjects with a normal IgE level. Macrolide antibiotics, due to their anti-inflammatory effects, may work via an immunomodulatory rather than an antibacterial pathway. Potential immunomodulatory effects of macrolides include the ability to downregulate protracted inflammation, decrease airway mucus secretion, inhibit bacterial biofilms, decrease the production of reactive oxygen species, inactivate neutrophils, enhance neutrophil apoptosis, and block the activation of nuclear transcription factors.^{75,100} Long-term use of systemic antibiotics is relatively safe but monitoring the potential risk of developing resistant bacterial strains is warranted. Some nonplacebo-controlled trials show a low level of evidence for topical antibiotic use in CRSsNP. However, several placebo-controlled trials fail to show any additive effect compared with normal saline. Therefore, this treatment is not recommended.

Nasal irrigation is beneficial¹⁰¹ even though it is not as effective as are INCS. There are conflicting data on the optimal tonicity of saline for nasal irrigation.¹⁰²⁻¹⁰⁶

The goal of FESS is to restore the normal flow of mucus from the sinuses by clearing the obstruction between the sinuses and the nasal passage while preserving the normal mucosa. Reversal of tissue hypoxia following the surgical opening of the obstructed sinuses could provide anti-inflammatory benefits. Reoxygenation of the sinus cavities may alleviate sinus inflammation by reducing the volume of inflammatory tissue in the sinuses and the cellular source for cytokines to recruit leukocytes and lymphocytes.⁵² Although clinical trials providing high-level evidence are lacking,¹⁰⁷ a number of large, well-designed prospective studies show that FESS is safe and effective to manage patients with CRSsNP when medical treatment fails.^{14,108} FESS is more likely to be effective in improving nasal obstruction while headache, post-nasal drip, or hyposmia show limited improvement.^{109,110} Five-year follow-up outcomes from a large, prospective cohort study show that 15.5% of subjects with CRSsNP require revision surgery even though postoperative concomitant medical therapy is used.¹⁰⁸

All clinical trials of biologic agents, such as monoclonal anti-IgE (omalizumab), anti-IL-5 (mepolizumab and reslizumab), and anti-IL-4 receptor alpha subunit (dupilumab) have been focused on CRSwNP. Success of these trials would lead to further application of these biologic agents to refractory CRSsNP and possibly reduce the need for primary surgery or revision surgery for this disease.

RESEARCH QUESTIONS AND FUTURE DIRECTIONS

1. Design CRSsNP-specific studies on epidemiology, genetics, comorbidity, pathophysiology, and treatment.

2. Endotype CRSsNP according to the nature of the inflammatory cells and cytokine.
3. Define phenotypes and endotypes of recalcitrant CRSsNP.
4. Determine biomarkers that project disease progression, prognosis, and treatment response.
5. Investigate the natural course of CRSsNP, whether it progresses toward CRSwNPs. If not, which endotype or phenotype causes the transition to NPs?
6. Design a large randomized clinical trial with long-term follow-up of FESS versus medical treatment for CRSsNP.

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