Published in final edited form as:

J Allergy Clin Immunol Pract. 2016 ; 4(4): 575–582. doi:10.1016/j.jaip.2016.04.015.

Chronic Rhinosinusitis without Nasal Polyps

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Abstract

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 non-allergic upper and lower airway diseases, epithelial cell disorders, immunodeficiencies, autoimmune diseases, and some infectious diseases. Additionally, 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 CXCL-8, play a role in CRSsNP remodeling. However, there are conflicting data about CRSsNP endotypes, e.g., 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.

Keywords

Chronic rhinosinusitis without nasal polyps; phenotype; endotype

Introduction

Rhinosinusitis is one of the most common diseases of the upper respiratory tract and is characterized by chronic inflammation. Chronic rhinosinusitis without NP (CRSsNP) has been attributed to mechanical obstruction of the ostiomeatal complex, ¹ whereas CRSwNP

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Conflict of interest: The authors declare that they have no relevant conflicts of interest.

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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 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 28912 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 20–29 and 50–59 age groups, respectively. After age 60, the prevalence leveled off at 4.7%.¹² Physician-diagnosed electronic health records indicate that the incidence of CRSsNP decreases after age 65, while 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 two or more nasal/sinus symptoms, one of which is nasal obstruction or nasal discharge +/- facial pressure/pain and +/- reduced smell. In addition, endoscopic signs of mucopurulent discharge or edematous/mucosal obstruction of the middle meatus or CT 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 NP via endoscopic findings. Although clinical symptoms overlap between these two 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 which predispose to the development of CRSsNP include acute rhinosinusitis, usually triggered by a viral respiratory tract infection, allergic and non-allergic 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 are increased with a diagnosis of CRSsNP.^{13,17} A Taiwan population-based study also demonstrated that chronic obstructive pulmonary disease (COPD) 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 RS. However, this is not common because most acute RS is caused by a viral respiratory tract infection which 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 chronic variable immunodeficiency patients present with CRSsNP.²¹ Seventeen percent of individuals with both CRS phenotypes have a low serum IgA 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's granulomatosis and sarcoidosis.²³

Fewer eosinophils and plasma cells are found in mucosal tissue in CRSsNP versus CRSwNP. However, the number of neutrophils are 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 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}

The gene expression of multiple inflammatory markers is increased in CRSsNP versus control sinonasal tissues. These include T-bet, GATA-3, RORC, IFN- γ , 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 Th1-based with elevated IFN- γ .^{27,31,32} Th2 cytokines, such as IL-5, ECP, IgE and eotaxin are increased in CRSsNP compared to the 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. Since 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 Th1, Th2, and Th17 cell tissue infiltration even though the inflammatory disease is less eosinophilic with lower Th2 inflammatory changes compared to 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 1st degree relatives followed by a 1.4-fold increased risk for 2nd degree relatives. This suggests an inheritable component to develop CRSsNP. Spouses of CRSsNP subjects also exhibit a 2-fold increase risk, implying an environmental susceptibility. Several genes and single nucleotide polymorphisms (SNPs) are associated with CRSsNP. For example, there is a correlation between CRSsNP and two genes, Ring1A and YY1 binding protein (RYBP) and acyloxyacyl hydroxylase (AOAH). This association has been replicated in both Canadian Caucasian and Chinese Asian populations. There also are associations between CRSsNP and SNPs in these genes, e.g., rs4504543 in AOA (OR = 0.30) and rs4532099 in RYBP (OR = 2.45).

Several studies, in which the CRS phenotypes are not specified, show an association between CRS and interleukin-1 receptor-associated kinase 4 (IRAK4), interleukin 1 receptor-like 1 (IL1RL1), toll-like receptor-2 (TLR2), cystic fibrosis transmembrane conductance regulator (CFTR), transforming growth factor beta-1 (TGFB1) 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, e.g., IRAK4 and TLR2 are associated with toll-like receptor (TLR) signaling. The IL1RL1 gene not only is involved in regulating TLR signaling, but also is a receptor for IL-33. AOA is responsible for degrading lipopolysaccharide (LPS), which is confirmed by a study in AOA deficient mice demonstrating persistent inflammation following LPS stimulation.³⁹ Abnormal TLR1, TLR2 and TLR5 genes may be responsible for the decline in lung function in CF subjects.⁴⁰ CFTR mutation-induced inflammation also enhances upregulation of IL-8 and TLR2, 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.⁴⁵

Pathogenesis

CRSsNP is characterized by fibrosis, basement membrane thickening and goblet cell hyperplasia (Fig. 1).^{46,47} Levels of TGF- β , which promotes fibrosis and airway remodeling, are increased in subjects with CRSsNP versus CRSwNP and healthy controls.⁴⁸ TGF- β levels are expressed in higher concentrations in the early stages of CRSsNP, but pro-inflammatory neutrophils and Th1 markers and the T cell profile are not different versus controls.^{31,48} The remodeling process appears to occur in parallel with inflammation in the early stages of CRSsNP suggesting that the remodeling process plays an important role in the initiation of CRSsNP.⁴⁹ Additionally, 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 up-regulated in CRSsNP.⁵⁰

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 (HIF)- α expression, which triggers tissue remodeling markers such as VEGF, TGF- β , nitric oxide synthetase, and MMPs.^{3,4,51–54} Under hypoxic conditions, nasal tissue-derived fibroblasts also induce chemokines, such as IL-8 and CCL-11, and contribute to the recruitment of neutrophils and eosinophils.^{52,55} In vitro studies using cultured nasal epithelial cells under hypoxic conditions demonstrate the up-regulation 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. HIF-1 α is up-regulated in CRSsNP compared to the controls and positively correlates with the number of neutrophils, IL-8 and TGF- β 2 transcripts. TGF- β 2- and HIF-1 α -positive neutrophils are higher in CRSsNP.⁵⁶ 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 severe CRSsNP subjects, while those with nasal polyps show a significant decrease in mucous gland density.^{28,57–60} Glandular hypertrophy and mucous secretion in the airway mucosa are likely to be mediated by the cytokines, tumor necrosis factor (TNF)- α , IL-8 and IL-13.^{61–63} MUC5AC and MUC5B are the main secreted mucins in the human airway, with MUC5A produced primarily by goblet cells.⁶⁴ Viral and bacterial components up-regulate mucin mRNA 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 granulocyte-macrophage colony-stimulating factor (GM-CSF), are engaged in this process.^{65,66} Goblet cell metaplasia and mucous secretion are enhanced by neutrophils; their elastase activity occurs at the cell interface, leading to goblet cell secretion.^{67,68} Eosinophil-epithelial cell interaction also augments the secretion of MUC5AC, PDGF-AB, VEGF, TGF- β , and IL-8 in culture supernatants.⁶³

Neutrophils are regarded as acute response cells and have a relatively short tissue half-life; therefore, the reasons for their presence in CRSsNP is not clear.¹⁴ Similar mechanisms may be important in COPD and CF. Studies indicate that persistent neutrophilic inflammation occurs in these lung diseases.^{69,70} A mechanism which 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 COPD and CF.⁷¹ Leukotriene A4 hydrolase (LTA4H) degrades PGP and generates leukotriene B4 (LTB4), another neutrophil chemoattractant.⁷⁰ In acute neutrophil-driven inflammation, PGP is degraded by LTA4H, which facilitates the resolution of inflammation. In contrast, tobacco smoke selectively inhibits LTA4H aminopeptidase activity, leading to the accumulation of PGP and neutrophils.⁶⁹

Other than promoting neutrophilic inflammation, tobacco smoke also induces ST2 expression on macrophages and natural killer (NK) 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 NK cell function.⁷²

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 CRSsNP subjects.⁷³ Increased biofilms have been observed in CRSsNP subjects. Recovery rates of biofilms vary from 28.6–75%, most likely due to differences in detection methodology.^{74–77} Biofilms induce cellular and humoral immune responses and are resistant to antibiotics.⁷⁸ It remains uncertain as to the type of inflammation biofilms induce, i.e., eosinophilic, neutrophilic, or other. CRSsNP with biofilms is associated with more neutrophilia and Th1 inflammation.⁷⁹ However, one study did reveal higher levels of IL-5 in CRSsNP subjects with *Staphylococcus aureus* biofilm.⁸⁰

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.^{81,82} However, their role remains unclear.^{83,84} These environmental factors could not necessarily account for all of 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 which affect mucociliary flow, i.e., CF and ciliary dyskinesia.^{85,86}

In both of these CRS phenotypes, there is evidence for ciliary dysfunction in explanted epithelial cells and increased mucus viscosity correlates with disease severity.^{87,88} 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 nitric oxide (NO). It is proposed that NO may limit bacterial colonization of these structures⁸⁹ and also help regulate ciliary beat frequency.⁹⁰ Studies indicate low levels of nasal NO in CRSsNP.⁹¹

Prognostic factors

High tissue eosinophilia in CRSsNP and CRSwNP correlates with the need for revision surgery in the longitudinal studies.^{25,92} 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.⁹³ The presence of *Staphylococcus aureus* and *Pseudomonas aeruginosa* biofilms are associated with unfavorable surgical outcomes,⁷⁵ whereas *Hemophilus influenza* biofilms are associated with favorable outcomes.⁹⁴ The prevalence of both types of CRS is higher in smokers,⁹⁵ and they have a less favorable response to surgery.⁹⁶ 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's granulomatosis, and defects of the immune system.^{22,98,99}

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 are also helpful due to their easy access to the sinus cavities.¹⁴ There are limited data and no randomized control studies about the use of systemic corticosteroid in CRSsNP.¹⁰⁰ 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 (less than 4 weeks) antibiotics in CRSsNP.¹⁴ Several non-placebo controlled trials show clinical improvement and bacteriological resolution in CRSsNP subjects with acute exacerbation. Long-term low-dose macrolide therapy may be effective in CRSsNP, particularly in subjects with normal serum IgE levels.¹⁰¹ A placebo controlled randomized clinical trial in subjects with CRSsNP with daily roxithromycin for 12 weeks show 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 have a higher clinical response rate versus those with an high IgE. However, another placebo controlled randomized clinical trial with weekly azithromycin in subjects with CRSsNP and CRSwNP failed to show significant clinical response. These two trials may suggest that low dose long-term macrolides would be more effective in CRSsNP in subjects with a normal IgE. Macrolide antibiotics, due to their anti-inflammatory effects, may work via an immuno-modulatory rather than an anti-bacterial pathway. Potential immunomodulatory effects of macrolides include the ability to down-regulate 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.^{76,102} Long term use of systemic antibiotics are relatively safe but monitoring the potential risk of developing resistant bacterial strains is warranted. Some non-placebo 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 to normal saline. Therefore this treatment is not recommended.

Nasal irrigation is beneficial¹⁰³ even though it is not as effective as are INCS. There are conflicting data on the optimal tonicity of saline for nasal irrigation.^{104–108}

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. Re-oxygenation 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.⁵³ Although clinical trials providing high level evidence are lacking,¹⁰⁹ a number of large, well designed prospective studies show that FESS is safe and effective to manage patients with CRSsNP when medical treatment fails.^{14,110} FESS is more likely to be effective in improving nasal obstruction while headache, postnasal drip or hyposmia show limited improvement.^{111,112} Five-year follow-up outcomes from a large, prospective cohort study show 15.5% of patients of CRSsNP subjects require revision surgery even though postoperative concomitant medical therapy is utilized.¹¹⁰

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 further application of these biologic agents to refractory CRSsNP and possibly reduce the need for primary surgery or revision surgery for this disease.

Acknowledgments

This work was supported by grant support from NIH 1K23AI110731 and the American Heart Association 11SDG7590063.

Abbreviation used

CF	Cystic fibrosis
COPD	Chronic obstructive pulmonary disease
CRS	Chronic rhinosinusitis
CRSwNP	Chronic rhinosinusitis with nasal polyps
CRSsNP	Chronic rhinosinusitis without nasal polyps
IL	Interleukin
NP	Nasal polyp
RYBP	Ring1A and YY1 binding protein
AOAH	Acyloxyacyl hydroxylase
CFTR	Cystic fibrosis transmembrane conductance regulator
TLR	Toll-like receptor
LPS	lipopolysaccharide
PGP	N-acetyl Pro-Gly-Pro

LTA4H	Leukotriene A4 hydrolase
NO	nitric oxide
FESS	Functional endoscopic sinus surgery

References

1. Leung RM, Kern RC, Conley DB, Tan BK, Chandra RK. Osteomeatal complex obstruction is not associated with adjacent sinus disease in chronic rhinosinusitis with polyps. *Am J Rhinol Allergy*. 2011; 25:401–3. [PubMed: 22185744]
2. Kato A. Immunopathology of chronic rhinosinusitis. *Allergol Int*. 2015; 64:121–30. [PubMed: 25838086]
3. Payne SC, Early SB, Huyett P, Han JK, Borish L, Steinke JW. Evidence for distinct histologic profile of nasal polyps with and without eosinophilia. *Laryngoscope*. 2011; 121:2262–7. [PubMed: 21898422]
4. Payne SC, Borish L, Steinke JW. Genetics and phenotyping in chronic sinusitis. *J Allergy Clin Immunol*. 2011; 128:710–20. quiz 21–2. [PubMed: 21704364]
5. DeMarcantonio MA, Han JK. Nasal polyps: pathogenesis and treatment implications. *Otolaryngol Clin North Am*. 2011; 44:685–95. ix. [PubMed: 21621054]
6. Pleis JR, Lucas JW, Ward BW. Summary health statistics for U.S. adults: National Health Interview Survey, 2008. *Vital Health Stat*. 2009; 10:1–157.
7. Jarvis D, Newson R, Lotvall J, Hastan D, Tomassen P, Keil T, et al. Asthma in adults and its association with chronic rhinosinusitis: the GA2LEN survey in Europe. *Allergy*. 2012; 67:91–8. [PubMed: 22050239]
8. Shi JB, Fu QL, Zhang H, Cheng L, Wang YJ, Zhu DD, et al. Epidemiology of chronic rhinosinusitis: results from a cross-sectional survey in seven Chinese cities. *Allergy*. 2015; 70:533–9. [PubMed: 25631304]
9. Kim YS, Kim NH, Seong SY, Kim KR, Lee GB, Kim KS. Prevalence and risk factors of chronic rhinosinusitis in Korea. *Am J Rhinol Allergy*. 2011; 25:117–21. [PubMed: 21679523]
10. Pilan RR, Pinna FR, Bezerra TF, Mori RL, Padua FG, Bento RF, et al. Prevalence of chronic rhinosinusitis in Sao Paulo. *Rhinology*. 2012; 50:129–38. [PubMed: 22616073]
11. Ahn JC, Kim JW, Lee CH, Rhee CS. Prevalence and Risk Factors of Chronic Rhinosinusitis, Allergic Rhinitis, and Nasal Septal Deviation: Results of the Korean National Health and Nutrition Survey 2008–2012. *JAMA Otolaryngol Head Neck Surg*. 2016:1–7.
12. Chen Y, Dales R, Lin M. The epidemiology of chronic rhinosinusitis in Canadians. *Laryngoscope*. 2003; 113:1199–205. [PubMed: 12838019]
13. Tan BK, Chandra RK, Pollak J, Kato A, Conley DB, Peters AT, et al. Incidence and associated premorbid diagnoses of patients with chronic rhinosinusitis. *J Allergy Clin Immunol*. 2013; 131:1350–60. [PubMed: 23541327]
14. Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. *Rhinology*. 2012; 50:1–12. [PubMed: 22469599]
15. Richer SL, Truong-Tran AQ, Conley DB, Carter R, Vermeylen D, Grammer LC, et al. Epithelial genes in chronic rhinosinusitis with and without nasal polyps. *Am J Rhinol*. 2008; 22:228–34. [PubMed: 18588753]
16. Lam K, Hirsch AG, Tan BK. The association of premorbid diseases with chronic rhinosinusitis with and without polyps. *Curr Opin Otolaryngol Head Neck Surg*. 2014; 22:231–41. [PubMed: 24694654]
17. Hirsch AG, Yan XS, Sundaresan AS, Tan BK, Schleimer RP, Kern RC, et al. Five-year risk of incident disease following a diagnosis of chronic rhinosinusitis. *Allergy*. 2015
18. Chien CY, Tai SY, Wang LF, Lee CT. Chronic obstructive pulmonary disease predicts chronic rhinosinusitis without nasal polyps: A population-based study. *Am J Rhinol Allergy*. 2015; 29:e75–80. [PubMed: 25975242]

19. Garcia-Rodriguez JF, Corominas M, Fernandez-Viladrich P, Monfort JL, Dicenta M. Rhinosinusitis and atopy in patients infected with HIV. *Laryngoscope*. 1999; 109:939–44. [PubMed: 10369287]
20. Porter JP, Patel AA, Dewey CM, Stewart MG. Prevalence of sinonasal symptoms in patients with HIV infection. *Am J Rhinol*. 1999; 13:203–8. [PubMed: 10392239]
21. Oksenhendler E, Gerard L, Fieschi C, Malphettes M, Mouillot G, Jaussaud R, et al. Infections in 252 patients with common variable immunodeficiency. *Clin Infect Dis*. 2008; 46:1547–54. [PubMed: 18419489]
22. Chee L, Graham SM, Carothers DG, Ballas ZK. Immune dysfunction in refractory sinusitis in a tertiary care setting. *Laryngoscope*. 2001; 111:233–5. [PubMed: 11210866]
23. Min JY, Tan BK. Risk factors for chronic rhinosinusitis. *Curr Opin Allergy Clin Immunol*. 2015; 15:1–13. [PubMed: 25479315]
24. Tokunaga T, Sakashita M, Haruna T, Asaka D, Takeno S, Ikeda H, et al. Novel scoring system and algorithm for classifying chronic rhinosinusitis: the JESREC Study. *Allergy*. 2015; 70:995–1003. [PubMed: 25945591]
25. Soler ZM, Sauer D, Mace J, Smith TL. Impact of mucosal eosinophilia and nasal polyposis on quality-of-life outcomes after sinus surgery. *Otolaryngol Head Neck Surg*. 2010; 142:64–71. [PubMed: 20096225]
26. Polzehl D, Moeller P, Riechelmann H, Perner S. Distinct features of chronic rhinosinusitis with and without nasal polyps. *Allergy*. 2006; 61:1275–9. [PubMed: 17002702]
27. Van Zele T, Claeys S, Gevaert P, Van Maele G, Holtappels G, Van Cauwenberge P, et al. Differentiation of chronic sinus diseases by measurement of inflammatory mediators. *Allergy*. 2006; 61:1280–9. [PubMed: 17002703]
28. Cao PP, Li HB, Wang BF, Wang SB, You XJ, Cui YH, et al. Distinct immunopathologic characteristics of various types of chronic rhinosinusitis in adult Chinese. *J Allergy Clin Immunol*. 2009; 124:478–84. 84 e1–2. [PubMed: 19541359]
29. Kramer MF, Ostertag P, Pfrogner E, Rasp G. Nasal interleukin-5, immunoglobulin E, eosinophilic cationic protein, and soluble intercellular adhesion molecule-1 in chronic sinusitis, allergic rhinitis, and nasal polyposis. *Laryngoscope*. 2000; 110:1056–62. [PubMed: 10852530]
30. Lee HS, Majima Y, Sakakura Y, Shinogi J, Kawaguchi S, Kim BW. Quantitative cytology of nasal secretions under various conditions. *Laryngoscope*. 1993; 103:533–7. [PubMed: 8483371]
31. Derycke L, Eyerich S, Van Crombruggen K, Perez-Novo C, Holtappels G, Deruyck N, et al. Mixed T helper cell signatures in chronic rhinosinusitis with and without polyps. *PLoS One*. 2014; 9:e97581. [PubMed: 24911279]
32. Stevens WW, Ocampo CJ, Berdnikovs S, Sakashita M, Mahdavinia M, Suh L, et al. Cytokines in Chronic Rhinosinusitis. Role in Eosinophilia and Aspirin-exacerbated Respiratory Disease. *Am J Respir Crit Care Med*. 2015; 192:682–94. [PubMed: 26067893]
33. Oakley GM, Curtin K, Orb Q, Schaefer C, Orlandi RR, Alt JA. Familial risk of chronic rhinosinusitis with and without nasal polyposis: genetics or environment. *Int Forum Allergy Rhinol*. 2015; 5:276–82. [PubMed: 25677865]
34. Kim SH, Park HS, Holloway JW, Shin HD, Park CS. Association between a TGFbeta1 promoter polymorphism and rhinosinusitis in aspirin-intolerant asthmatic patients. *Respir Med*. 2007; 101:490–5. [PubMed: 16916603]
35. Castano R, Bosse Y, Endam LM, Desrosiers M. Evidence of association of interleukin-1 receptor-like 1 gene polymorphisms with chronic rhinosinusitis. *Am J Rhinol Allergy*. 2009; 23:377–84. [PubMed: 19671251]
36. Pinto JM, Hayes MG, Schneider D, Naclerio RM, Ober C. A genomewide screen for chronic rhinosinusitis genes identifies a locus on chromosome 7q. *Laryngoscope*. 2008; 118:2067–72. [PubMed: 18622306]
37. Park CS, Cho JH, Park YJ. Toll-like receptor 2 gene polymorphisms in a Korean population: association with chronic rhinosinusitis. *Otolaryngol Head Neck Surg*. 2011; 144:96–100. [PubMed: 21493395]
38. Bosse Y, Bacot F, Montpetit A, Rung J, Qu HQ, Engert JC, et al. Identification of susceptibility genes for complex diseases using pooling-based genome-wide association scans. *Hum Genet*. 2009; 125:305–18. [PubMed: 19184112]

39. Lu M, Varley AW, Ohta S, Hardwick J, Munford RS. Host inactivation of bacterial lipopolysaccharide prevents prolonged tolerance following gram-negative bacterial infection. *Cell Host Microbe*. 2008; 4:293–302. [PubMed: 18779055]
40. Haerynck F, Mahachie John JM, Van Steen K, Schelstraete P, Van daele S, Loeys B, et al. Genetic variations in toll-like receptor pathway and lung function decline in Cystic fibrosis patients. *Hum Immunol*. 2013; 74:1649–55. [PubMed: 23994582]
41. Martel G, Rousseau S. TPL2 signalling: from Toll-like receptors-mediated ERK1/ERK2 activation to Cystic Fibrosis lung disease. *Int J Biochem Cell Biol*. 2014; 52:146–51. [PubMed: 24530836]
42. Melvin TA, Lane AP, Nguyen MT, Lin SY. Sinonasal epithelial cell expression of Toll-like receptor 9 is elevated in cystic fibrosis-associated chronic rhinosinusitis. *Am J Rhinol Allergy*. 2013; 27:30–3. [PubMed: 23406596]
43. Li J, Johnson XD, Iazvovskaia S, Tan A, Lin A, Hershenson MB. Signaling intermediates required for NF-kappa B activation and IL-8 expression in CF bronchial epithelial cells. *Am J Physiol Lung Cell Mol Physiol*. 2003; 284:L307–15. [PubMed: 12388360]
44. Hisada K, Sanchez C, Endo TA, Endoh M, Roman-Trufero M, Sharif J, et al. RYBP represses endogenous retroviruses and preimplantation- and germ line-specific genes in mouse embryonic stem cells. *Mol Cell Biol*. 2012; 32:1139–49. [PubMed: 22269950]
45. Hsu J, Avila PC, Kern RC, Hayes MG, Schleimer RP, Pinto JM. Genetics of chronic rhinosinusitis: state of the field and directions forward. *J Allergy Clin Immunol*. 2013; 131:977–93. 93 e1–5. [PubMed: 23540616]
46. Li X, Meng J, Qiao X, Liu Y, Liu F, Zhang N, et al. Expression of TGF, matrix metalloproteinases, and tissue inhibitors in Chinese chronic rhinosinusitis. *J Allergy Clin Immunol*. 2010; 125:1061–8. [PubMed: 20392482]
47. Van Bruaene N, Derycke L, Perez-Novo CA, Gevaert P, Holtappels G, De Ruyck N, et al. TGF-beta signaling and collagen deposition in chronic rhinosinusitis. *J Allergy Clin Immunol*. 2009; 124:253–9. 9 e1–2. [PubMed: 19500825]
48. Van Bruaene N, CPN, Van Crombruggen K, De Ruyck N, Holtappels G, Van Cauwenberge P, et al. Inflammation and remodelling patterns in early stage chronic rhinosinusitis. *Clin Exp Allergy*. 2012; 42:883–90. [PubMed: 22093003]
49. Meng J, Zhou P, Liu Y, Liu F, Yi X, Liu S, et al. The development of nasal polyp disease involves early nasal mucosal inflammation and remodelling. *PLoS One*. 2013; 8:e82373. [PubMed: 24340021]
50. Sejima T, Holtappels G, Bachert C. The expression of fibrinolytic components in chronic paranasal sinus disease. *Am J Rhinol Allergy*. 2011; 25:1–6. [PubMed: 21711960]
51. Matsune S, Sun D, Ohori J, Nishimoto K, Fukuiwa T, Ushikai M, et al. Inhibition of vascular endothelial growth factor by macrolides in cultured fibroblasts from nasal polyps. *Laryngoscope*. 2005; 115:1953–6. [PubMed: 16319604]
52. Shun CT, Lin SK, Hong CY, Huang HM, Liu CM. Hypoxia induces cysteine-rich 61, vascular endothelial growth factor, and interleukin-8 expressions in human nasal polyp fibroblasts: An implication of neutrophils in the pathogenesis of nasal polyposis. *Am J Rhinol Allergy*. 2011; 25:15–8. [PubMed: 21711965]
53. Steinke JW, Woodard CR, Borish L. Role of hypoxia in inflammatory upper airway disease. *Curr Opin Allergy Clin Immunol*. 2008; 8:16–20. [PubMed: 18188012]
54. Sun D, Matsune S, Ohori J, Fukuiwa T, Ushikai M, Kurono Y. TNF-alpha and endotoxin increase hypoxia-induced VEGF production by cultured human nasal fibroblasts in synergistic fashion. *Auris Nasus Larynx*. 2005; 32:243–9. [PubMed: 16040218]
55. Early SB, Hise K, Han JK, Borish L, Steinke JW. Hypoxia stimulates inflammatory and fibrotic responses from nasal-polyp derived fibroblasts. *Laryngoscope*. 2007; 117:511–5. [PubMed: 17334314]
56. Shi LL, Xiong P, Zhang L, Cao PP, Liao B, Lu X, et al. Features of airway remodeling in different types of Chinese chronic rhinosinusitis are associated with inflammation patterns. *Allergy*. 2013; 68:101–9. [PubMed: 23157215]
57. Martinez-Anton A, Roca-Ferrer J, Mullol J. Mucin gene expression in rhinitis syndromes. *Curr Allergy Asthma Rep*. 2006; 6:189–97. [PubMed: 16579868]

58. Martinez-Anton A, Debolos C, Garrido M, Roca-Ferrer J, Barranco C, Alobid I, et al. Mucin genes have different expression patterns in healthy and diseased upper airway mucosa. *Clin Exp Allergy*. 2006; 36:448–57. [PubMed: 16630149]
59. Bolger WE, Butzin CA, Parsons DS. Paranasal sinus bony anatomic variations and mucosal abnormalities: CT analysis for endoscopic sinus surgery. *Laryngoscope*. 1991; 101:56–64. [PubMed: 1984551]
60. Malekzadeh S, McGuire JF. The new histologic classification of chronic rhinosinusitis. *Curr Allergy Asthma Rep*. 2003; 3:221–6. [PubMed: 12662471]
61. Kanoh S, Tanabe T, Rubin BK. IL-13-induced MUC5AC production and goblet cell differentiation is steroid resistant in human airway cells. *Clin Exp Allergy*. 2011; 41:1747–56. [PubMed: 22092504]
62. Bautista MV, Chen Y, Ivanova VS, Rahimi MK, Watson AM, Rose MC. IL-8 regulates mucin gene expression at the posttranscriptional level in lung epithelial cells. *J Immunol*. 2009; 183:2159–66. [PubMed: 19596978]
63. Shimizu S, Kouzaki H, Ogawa T, Takezawa K, Tojima I, Shimizu T. Eosinophil-epithelial cell interactions stimulate the production of MUC5AC mucin and profibrotic cytokines involved in airway tissue remodeling. *Am J Rhinol Allergy*. 2014; 28:103–9. [PubMed: 24717945]
64. Ding GQ, Zheng CQ. The expression of MUC5AC and MUC5B mucin genes in the mucosa of chronic rhinosinusitis and nasal polyposis. *Am J Rhinol*. 2007; 21:359–66. [PubMed: 17621824]
65. Yamaya M, Sekizawa K, Suzuki T, Yamada N, Furukawa M, Ishizuka S, et al. Infection of human respiratory submucosal glands with rhinovirus: effects on cytokine and ICAM-1 production. *Am J Physiol*. 1999; 277:L362–71. [PubMed: 10444531]
66. Smirnova MG, Guo L, Birchall JP, Pearson JP. LPS up-regulates mucin and cytokine mRNA expression and stimulates mucin and cytokine secretion in goblet cells. *Cell Immunol*. 2003; 221:42–9. [PubMed: 12742381]
67. Takeyama K, Agusti C, Ueki I, Lausier J, Cardell LO, Nadel JA. Neutrophil-dependent goblet cell degranulation: role of membrane-bound elastase and adhesion molecules. *Am J Physiol*. 1998; 275:L294–302. [PubMed: 9700090]
68. Voynow JA, Fischer BM, Malarkey DE, Burch LH, Wong T, Longphre M, et al. Neutrophil elastase induces mucus cell metaplasia in mouse lung. *Am J Physiol Lung Cell Mol Physiol*. 2004; 287:L1293–302. [PubMed: 15273079]
69. Snelgrove RJ, Jackson PL, Hardison MT, Noerager BD, Kinloch A, Gaggari A, et al. A critical role for LTA4H in limiting chronic pulmonary neutrophilic inflammation. *Science*. 2010; 330:90–4. [PubMed: 20813919]
70. Snelgrove RJ. Leukotriene A4 hydrolase: an anti-inflammatory role for a proinflammatory enzyme. *Thorax*. 2011; 66:550–1. [PubMed: 21502100]
71. Weathington NM, van Houwelingen AH, Noerager BD, Jackson PL, Kraneveld AD, Galin FS, et al. A novel peptide CXCR ligand derived from extracellular matrix degradation during airway inflammation. *Nat Med*. 2006; 12:317–23. [PubMed: 16474398]
72. Kearley J, Silver JS, Sanden C, Liu Z, Berlin AA, White N, et al. Cigarette smoke silences innate lymphoid cell function and facilitates an exacerbated type I interleukin-33-dependent response to infection. *Immunity*. 2015; 42:566–79. [PubMed: 25786179]
73. Goldstein-Daruech N, Cope EK, Zhao KQ, Vukovic K, Kofonow JM, Doghramji L, et al. Tobacco smoke mediated induction of sinonasal microbial biofilms. *PLoS One*. 2011; 6:e15700. [PubMed: 21253587]
74. Perloff JR, Palmer JN. Evidence of bacterial biofilms on frontal recess stents in patients with chronic rhinosinusitis. *Am J Rhinol*. 2004; 18:377–80. [PubMed: 15706985]
75. Psaltis AJ, Weitzel EK, Ha KR, Wormald PJ. The effect of bacterial biofilms on post-sinus surgical outcomes. *Am J Rhinol*. 2008; 22:1–6. [PubMed: 18284851]
76. Tatar EC, Tatar I, Ocal B, Korkmaz H, Saylam G, Ozdek A, et al. Prevalence of biofilms and their response to medical treatment in chronic rhinosinusitis without polyps. *Otolaryngol Head Neck Surg*. 2012; 146:669–75. [PubMed: 22241786]

77. Prince AA, Steiger JD, Khalid AN, Dogrhamji L, Reger C, Eau Claire S, et al. Prevalence of biofilm-forming bacteria in chronic rhinosinusitis. *Am J Rhinol*. 2008; 22:239–45. [PubMed: 18588755]
78. Sanderson AR, Leid JG, Hunsaker D. Bacterial biofilms on the sinus mucosa of human subjects with chronic rhinosinusitis. *Laryngoscope*. 2006; 116:1121–6. [PubMed: 16826045]
79. Wang X, Du J, Zhao C. Bacterial biofilms are associated with inflammatory cells infiltration and the innate immunity in chronic rhinosinusitis with or without nasal polyps. *Inflammation*. 2014; 37:871–9. [PubMed: 24497161]
80. Foreman A, Holtappels G, Psaltis AJ, Jarvis-Bardy J, Field J, Wormald PJ, et al. Adaptive immune responses in *Staphylococcus aureus* biofilm-associated chronic rhinosinusitis. *Allergy*. 2011; 66:1449–56. [PubMed: 21834937]
81. Ramakrishnan VR, Hauser LJ, Feazel LM, Ir D, Robertson CE, Frank DN. Sinus microbiota varies among chronic rhinosinusitis phenotypes and predicts surgical outcome. *J Allergy Clin Immunol*. 2015; 136:334–42. e1. [PubMed: 25819063]
82. Choi EB, Hong SW, Kim DK, Jeon SG, Kim KR, Cho SH, et al. Decreased diversity of nasal microbiota and their secreted extracellular vesicles in patients with chronic rhinosinusitis based on a metagenomic analysis. *Allergy*. 2014; 69:517–26. [PubMed: 24611950]
83. Corriveau MN, Zhang N, Holtappels G, Van Roy N, Bachert C. Detection of *Staphylococcus aureus* in nasal tissue with peptide nucleic acid-fluorescence in situ hybridization. *Am J Rhinol Allergy*. 2009; 23:461–5. [PubMed: 19807976]
84. Sachse F, Becker K, von Eiff C, Metze D, Rudack C. *Staphylococcus aureus* invades the epithelium in nasal polyposis and induces IL-6 in nasal epithelial cells in vitro. *Allergy*. 2010; 65:1430–7. [PubMed: 20456313]
85. Antunes MB, Gudis DA, Cohen NA. Epithelium, cilia, and mucus: their importance in chronic rhinosinusitis. *Immunol Allergy Clin North Am*. 2009; 29:631–43. [PubMed: 19879439]
86. Cutting GR. Modifier genetics: cystic fibrosis. *Annu Rev Genomics Hum Genet*. 2005; 6:237–60. [PubMed: 16124861]
87. Chen B, Antunes MB, Claire SE, Palmer JN, Chiu AG, Kennedy DW, et al. Reversal of chronic rhinosinusitis-associated sinonasal ciliary dysfunction. *Am J Rhinol*. 2007; 21:346–53. [PubMed: 17621822]
88. Saito DM, Innes AL, Pletcher SD. Rheologic properties of sinonasal mucus in patients with chronic sinusitis. *Am J Rhinol Allergy*. 2010; 24:1–5. [PubMed: 20109305]
89. Lundberg JO, Farkas-Szallasi T, Weitzberg E, Rinder J, Lidholm J, Anggaard A, et al. High nitric oxide production in human paranasal sinuses. *Nat Med*. 1995; 1:370–3. [PubMed: 7585069]
90. Lindberg S, Cervin A, Runer T. Low levels of nasal nitric oxide (NO) correlate to impaired mucociliary function in the upper airways. *Acta Otolaryngol*. 1997; 117:728–34. [PubMed: 9349871]
91. Lindberg S, Cervin A, Runer T. Nitric oxide (NO) production in the upper airways is decreased in chronic sinusitis. *Acta Otolaryngol*. 1997; 117:113–7. [PubMed: 9039491]
92. Matsuwaki Y, Ookushi T, Asaka D, Mori E, Nakajima T, Yoshida T, et al. Chronic rhinosinusitis: risk factors for the recurrence of chronic rhinosinusitis based on 5-year follow-up after endoscopic sinus surgery. *Int Arch Allergy Immunol*. 2008; 146(Suppl 1):77–81. [PubMed: 18504412]
93. Stewart PS, Costerton JW. Antibiotic resistance of bacteria in biofilms. *Lancet*. 2001; 358:135–8. [PubMed: 11463434]
94. Foreman A, Wormald PJ. Different biofilms, different disease? A clinical outcomes study. *Laryngoscope*. 2010; 120:1701–6. [PubMed: 20641074]
95. Houser SM, Keen KJ. The role of allergy and smoking in chronic rhinosinusitis and polyposis. *Laryngoscope*. 2008; 118:1521–7. [PubMed: 18758323]
96. Krzeski A, Galewicz A, Chmielewski R, Kisiel M. Influence of cigarette smoking on endoscopic sinus surgery long-term outcomes. *Rhinology*. 2011; 49:577–82. [PubMed: 22125789]
97. Cohen NA, Zhang S, Sharp DB, Tamashiro E, Chen B, Sorscher EJ, et al. Cigarette smoke condensate inhibits transepithelial chloride transport and ciliary beat frequency. *Laryngoscope*. 2009; 119:2269–74. [PubMed: 19418539]

98. Alqudah M, Graham SM, Ballas ZK. High prevalence of humoral immunodeficiency patients with refractory chronic rhinosinusitis. *Am J Rhinol Allergy*. 2010; 24:409–12. [PubMed: 21144219]
99. Ocampo CJ, Peters AT. Antibody deficiency in chronic rhinosinusitis: epidemiology and burden of illness. *Am J Rhinol Allergy*. 2013; 27:34–8. [PubMed: 23406598]
100. Lal D, Hwang PH. Oral corticosteroid therapy in chronic rhinosinusitis without polyposis: a systematic review. *Int Forum Allergy Rhinol*. 2011; 1:136–43. [PubMed: 22287332]
101. Wallwork B, Coman W, Mackay-Sim A, Greiff L, Cervin A. A double-blind, randomized, placebo-controlled trial of macrolide in the treatment of chronic rhinosinusitis. *Laryngoscope*. 2006; 116:189–93. [PubMed: 16467702]
102. Shinkai M, Henke MO, Rubin BK. Macrolide antibiotics as immunomodulatory medications: proposed mechanisms of action. *Pharmacol Ther*. 2008; 117:393–405. [PubMed: 18289694]
103. Harvey R, Hannan SA, Badia L, Scadding G. Nasal saline irrigations for the symptoms of chronic rhinosinusitis. *Cochrane Database Syst Rev*. 2007;CD006394. [PubMed: 17636843]
104. Kim CH, Hyun Song M, Eun Ahn Y, Lee JG, Yoon JH. Effect of hypo-, iso- and hypertonic saline irrigation on secretory mucins and morphology of cultured human nasal epithelial cells. *Acta Otolaryngol*. 2005; 125:1296–300. [PubMed: 16303677]
105. Low TH, Woods CM, Ullah S, Carney AS. A double-blind randomized controlled trial of normal saline, lactated Ringer's, and hypertonic saline nasal irrigation solution after endoscopic sinus surgery. *Am J Rhinol Allergy*. 2014; 28:225–31. [PubMed: 24598116]
106. Marchisio P, Varricchio A, Baggi E, Bianchini S, Capasso ME, Torretta S, et al. Hypertonic saline is more effective than normal saline in seasonal allergic rhinitis in children. *Int J Immunopathol Pharmacol*. 2012; 25:721–30. [PubMed: 23058022]
107. Rabago D, Pasic T, Zgierska A, Mundt M, Barrett B, Maberry R. The efficacy of hypertonic saline nasal irrigation for chronic sinonasal symptoms. *Otolaryngol Head Neck Surg*. 2005; 133:3–8. [PubMed: 16025044]
108. Ural A, Oktemer TK, Kizil Y, Ileri F, Uslu S. Impact of isotonic and hypertonic saline solutions on mucociliary activity in various nasal pathologies: clinical study. *J Laryngol Otol*. 2009; 123:517–21. [PubMed: 18957157]
109. Khalil HS, Nunez DA. Functional endoscopic sinus surgery for chronic rhinosinusitis. *Cochrane Database Syst Rev*. 2006;CD004458. [PubMed: 16856048]
110. Hopkins C, Slack R, Lund V, Brown P, Copley L, Browne J. Long-term outcomes from the English national comparative audit of surgery for nasal polyposis and chronic rhinosinusitis. *Laryngoscope*. 2009; 119:2459–65. [PubMed: 19780032]
111. Chester AC, Antisdell JL, Sindwani R. Symptom-specific outcomes of endoscopic sinus surgery: a systematic review. *Otolaryngol Head Neck Surg*. 2009; 140:633–9. [PubMed: 19393402]
112. Soler ZM, Mace J, Smith TL. Symptom-based presentation of chronic rhinosinusitis and symptom-specific outcomes after endoscopic sinus surgery. *Am J Rhinol*. 2008; 22:297–301. [PubMed: 18588763]

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.

Figure 1.
Schematic depiction of pathological mechanisms of chronic rhinosinusitis without nasal polyps. Solid lines: probable mechanisms, dotted lines: possible mechanisms