International Consensus Statement on Rhinology and Allergy: Rhinosinusitis

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I. Executive Summary

Abstract

Background: The 5 years since the publication of the first International Consensus Statement on Allergy and Rhinology: Rhinosinusitis (ICAR-RS) has witnessed foundational progress in our understanding and treatment of rhinologic disease. These advances are reflected within the more than 40 new topics covered within the ICAR-RS-2021 as well as updates to the original 140 topics. This executive summary consolidates the evidence-based findings of the document.

Methods: ICAR-RS presents over 180 topics in the forms of evidence-based reviews with recommendations (EBRRs), evidence-based reviews, and literature reviews. The highest grade structured recommendations of the EBRR sections are summarized in this executive summary.

Results: ICAR-RS-2021 covers 22 topics regarding the medical management of RS, which are grade A/B and are presented in the executive summary. Additionally, 4 topics regarding the surgical management of RS are grade A/B and are presented in the executive summary. Finally, a comprehensive evidence-based management algorithm is provided.

Conclusion: This ICAR-RS-2021 executive summary provides a compilation of the evidence-based recommendations for medical and surgical treatment of the most common forms of RS.

I.A. Introduction

The 5 years since the publication of the first International Consensus Statement on Allergy and Rhinology: Rhinosinusitis (ICAR-RS)[1] has witnessed foundational progress in our understanding and treatment of rhinologic disease. These advances are reflected within the more than 40 new topics covered within the ICAR-RS-2021 document including an emphasis on diagnostic algorithms, quality metrics, cost-effectiveness, and novel therapeutics. Furthermore, the structured methodology used to update each of the original 140 topics coupled with the contributions of a global network of experts has served to produce a truly comprehensive evidence-based compendium of our current body of knowledge regarding RS.

ICAR-RS-2021 provides a critical review of the diagnosis, pathophysiology, management, and complications of Acute RS (ARS), Recurrent ARS, Chronic RS (CRS) with and without nasal polyps (CRSwNP and CRSsNP), Acute Exacerbation of CRS (AECRS), and Pediatric RS. While the most up-to-date evidence has been incorporated into each of these areas, the novel application of biologic therapies for CRSwNP has emerged as perhaps the most informative. The precise immunopathologic underpinning of RS subtypes remains an evolving area of active investigation and has therefore been excluded from this summary. However, recent clinical data using biologic agents has not only validated that an elaboration of RS immunopathology can yield effective therapeutic targets but has also provided a standard for the execution of double-blind, randomized, clinical trials against which all future therapies are likely to be compared.

It is also of historical interest that the ICAR-RS-2021 document was actively assembled amidst the emergence of COVID-19 and includes a section on rhinologic considerations with regard to this unprecedented pandemic. While many of the upper airway manifestations of this viral syndrome became clear early on including high nasal/nasopharyngeal viral loads[2] and widespread acute chemosensory dysfunction,[3] other sequelae may yet become evident in the years to come. It should be noted that within the first 2 months of the pandemic the rhinologic community produced the

largest number of COVID-19 related manuscripts (n=41) among the Otolaryngology-Head and Neck Surgery sub-specialties (n=235), which themselves produced the most scholarly work of any surgical field (n=773).

While these numbers speak directly to the maturation of our field with regard to the pursuit of evidence-based care, ICAR-RS-2021 also acknowledges that there remain significant gaps in our understanding and treatment of RS. These topics have been detailed at the end of the document in an effort to help guide future research efforts toward the subjects most in need of continued investigation.

I.B. Methods

Each of 183 topics in RS was assigned to 1 of 85 rhinology experts worldwide. The amount of evidence in any given topic varied such that 34 were assigned as literature reviews. The remaining topics that had substantial evidence were assigned as evidence-based reviews with recommendations (EBRRs) or as evidence-based reviews (EBRs) only, if they did not lend themselves to providing a recommendation, such as those addressing diagnosis and pathogenesis. For EBRs and EBRRs, the methodology of Rudmik and Smith[4] was followed for each of these sections. Briefly, a systematic review was performed with grading of all evidence. An initial author drafted a summary of the evidence, with an aggregate evidence grade and, where applicable, a structured recommendation. A multistage online semi-blinded iterative review process then refined each section. Following this thorough EBR and EBRR development and review with 3 to 4 rhinologists for each topic, the section manuscripts were then combined into a cohesive single document. The entire manuscript was then reviewed by all authors for consensus.

I.C. Results

I.C.1. Definitions and Diagnostic Algorithms

RS is divided and defined based on the temporal course of its manifestation. Diagnosis of CRS requires confirmation of both subjective and objective criteria.

Table I-1: Diagnostic criteria for ARS

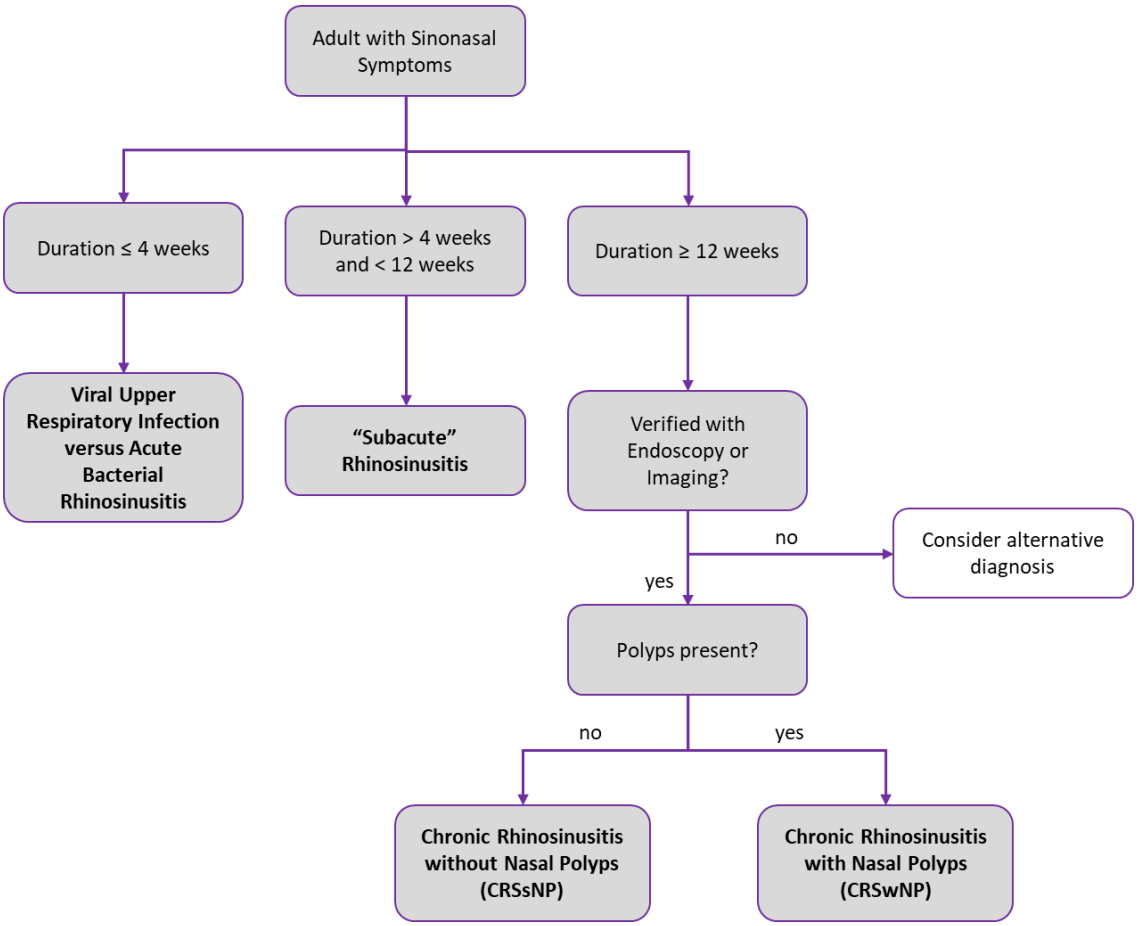
Acute Rhinosinusitis (ARS) Adult Sinonasal inflammation lasting less than 4 weeks associated with the sudden onset of symptoms. Symptoms must include both: Nasal blockage/obstruction/congestion OR nasal discharge (anterior/posterior) AND Facial pain/pressure OR reduction/loss of smell *Radiology and endoscopy are not required for diagnosis*
Acute Rhinosinusitis (ARS) Pediatric Sinonasal inflammation lasting less than 12 weeks associated with the sudden onset of symptoms. Symptoms must include two or more of the following: Nasal blockage/obstruction/congestion Discolored nasal discharge (anterior/posterior) Cough (daytime and night-time)

Radiology and Endoscopy are not required for diagnosis
Recurrent Acute Rhinosinusitis (RARS) Four or more episodes of ARS per year with distinct symptom-free intervals between each episode. Each episode must meet the above criteria for ARS.
Acute Exacerbation of Chronic Rhinosinusitis (AECRS) Sudden worsening of CRS symptoms with a return to baseline symptoms, often after treatment

Table I-2: Diagnostic criteria for diagnosis of CRS

Greater than or equal to 12 weeks of: Two or more of the following symptoms: Nasal discharge (rhinorrhea or post-nasal drip) Nasal obstruction or congestion Hyposmia Facial pressure or pain Cough (in Pediatric CRS) AND One or more of the following objective findings: Evidence of inflammation on nasal endoscopy or computed tomography Evidence of purulence coming from paranasal sinuses or ostiomeatal complex AND CRS is divided in to CRSsNP or CRSwNP based on the presence or absence of nasal polyps

Figure I-1. Diagnostic algorithm for RS



I.C.2. Incidence, Prevalence, and Endotype

ARS is one of the most commonly diagnosed diseases in the outpatient setting, accounting for 2-10% of primary care and otolaryngology visits.[5,6] The estimated incidence of ARS ranges from 1.39%-9% annually depending on the study methodology and population.[7-9] The incidence of acute bacterial RS (ABRS) is unknown, however it is thought to account for 0.5-2.0% of all viral infections.[10]

While CRS is thought to be common, the true prevalence is difficult to measure given the need for objective confirmation of the diagnosis. National surveys in the U.S. assessing for symptoms alone have estimated a prevalence ranging from 2.1%-13.8%.[9,11-13] In Europe, the prevalence for CRS symptoms have been reported to range from 6.9%-27.1%.[14] In China, a survey of 10,636 participants in 7 cities reported a prevalence ranging from 4.8%-9.7% depending on the city.[15] Billing codes have also been analyzed as a proxy for the incidence of CRS. In a Canadian population-based analysis of International Classification of Disease, 9th Revision (ICD-9) codes, the incidence of CRS was found to be 2.3-2.7 per 1000 people.[16] A similar analysis of ICD-9 codes in Pennsylvania found the average incidence of CRSsNP to be 1048±48 per 100,000 person-years.[17] Recently, two epidemiologic studies using radiologic confirmation of symptoms suggested a prevalence range of 1.7-8.8%.[18,19]

The epidemiology of CRSwNP has been investigated utilizing a variety of methods. In two survey studies 2.1-4.3% of European patients recalled being diagnosed with nasal polyps.[20,21] Using objective confirmation in a Swedish cohort, 2.7% were found to have nasal polyps.[22] This rate approximates the prevalence reported in the Korean National Health and Nutrition Examination

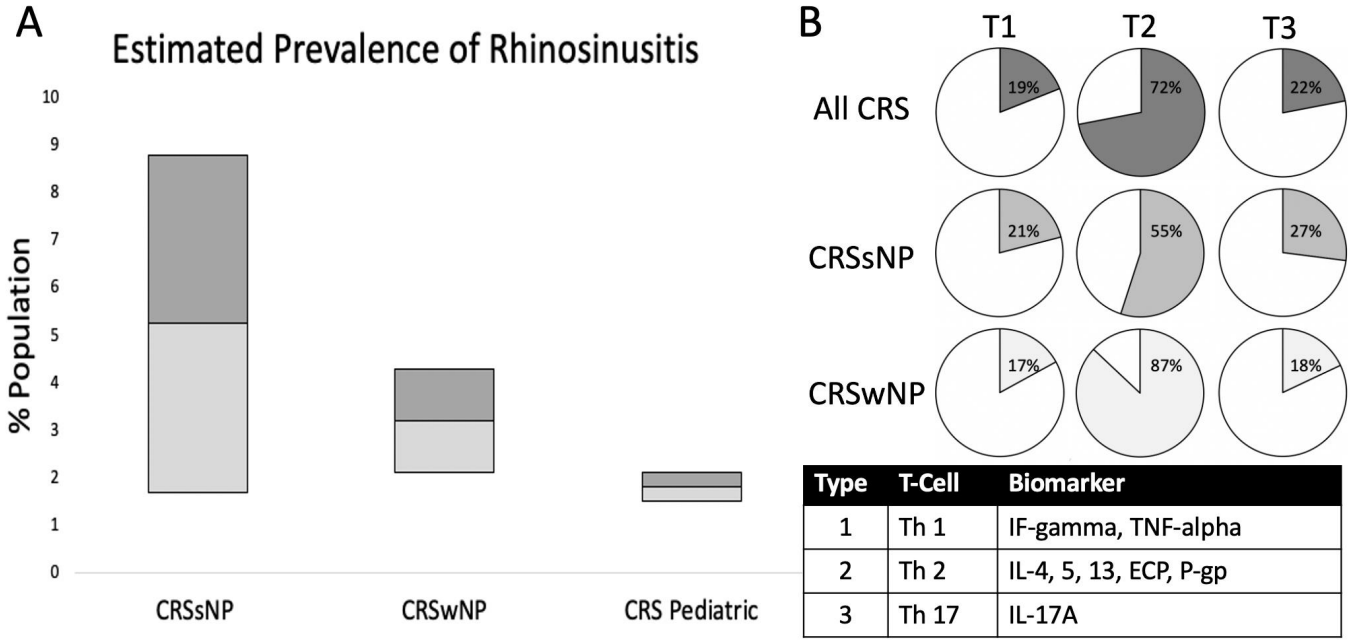
Survey from 2008-2012 in which the prevalence of CRSwNP was 2.6% among 28,912 subjects undergoing nasal endoscopy.[23] While these numbers appear to converge around similar rates, interestingly between 26 to 42% of autopsy specimens have been shown to contain NPs.[24,25]

Acute exacerbations of chronic rhinosinusitis (AECRS) are described as a worsening of CRS intensity with a return to baseline symptoms frequently after intervention with corticosteroids and/or antibiotics.[1,26-30] Patients reporting greater than 3 episodes of oral corticosteroids or antibiotics use in the prior 12 months constituted 17.8% of CRS patients in a study by Yamasaki *et al.*[28]

ARS is a common disorder within the pediatric population, usually occurring in the context of an upper respiratory infection (URI).[31-33] When defining pediatric ARS as URI symptoms exceeding two standard deviations (range 16-22 days) above the mean (7.3 days), the prevalence has been reported between 4-7.3%[34,35] Epidemiologic data on pediatric CRS are more limited. Studies from the from the US Center for Disease Control National Center for Health Statistics[36] and a Swedish population-based cohort study[37] suggest a prevalence between 1.5-2.1% in patients under 20 years old. Furthermore, the prevalence in patients with underlying comorbidities may be higher than in healthy children. Several studies estimate the presence of CRS in children with CF, primary ciliary dyskinesia (PCD), and common variable immunodeficiency to be 11-38%,[38] 40%,[39] and 36%;[40] respectively.

While the majority of epidemiologic, pathophysiologic, and therapeutic studies in CRS have utilized the presence of nasal polyps to distinguish CRS phenotypes, there has been greater recognition of substantial inflammatory heterogeneity and a continuum of pathophysiology between CRSwNP and CRSsNP patients.[41-45] Aided by advances in molecular and statistical techniques, several research groups have worked toward defining endotypes, or biological inflammatory subtypes of CRS, based on mucus and tissue biomarkers.[46-50] Overall, endotype research in CRS has drawn inspiration from a similar effort in the management of asthma,[51] which has led to improved understanding of the underlying pathophysiology and better outcomes in treatment refractory patients.[52,53] While there remains a lack of consensus on the identity of ideal biomarkers for endotyping, it is evident that Th1, Th2 and Th17 markers (also referred to as type 1, 2 and 3 immune reactions) should be included. Further complicating this effort is the recognition of substantial global variations in the distribution of CRS endotypes, likely driven by undefined environmental factors which merit further study.[54]

While specific biomarkers and biosignatures of each endotype will continue to be refined, there is already evidence that differentiating type 2 versus non-type 2 endotypes is clinically meaningful, as type 2 immune reactions are associated with asthma,[49] an increased risk of recurrence after surgery,[55] and are the basis for the use of innovative type 2 biologics.[56-60] As work in this field evolves, it is likely that future evidence-based recommendation statements will increasingly utilize endotypic classifications of disease.



Type	T-Cell	Biomarker
1	Th 1	IF-gamma, TNF-alpha
2	Th 2	IL-4, 5, 13, ECP, P-gp
3	Th 17	IL-17A

Figure I-2: A. Estimated prevalence of rhinosinusitis by phenotype (Boxes represent low, median, and high estimates based on best available evidence). B. Estimated prevalence of endotype (Types (T) 1, 2, and 3) within each phenotype and non-exhaustive list of associated endotypic biomarkers (T-helper (Th), Interferon (IF), Tumor Necrosis Factor (TNF), Interleukin (IL), Eosinophil Cationic Protein (ECP), P-glycoprotein (P-gp); adapted from Stevens *et al.*, J Allergy Clin Immunol, 2019[61])

I.C.3. Individual Burden of Disease

By definition, patients with CRS will suffer with some combination of cardinal sinonasal symptoms. However CRS can also have profound effects on functional well-being and general health-related quality of life (QoL). Using transformations of the Short Form 6D instrument (SF-6D), health states of 230 patients with CRS were found to average 0.65 (0=death, 1=perfect health), a valuation that was worse than congestive heart failure, chronic obstructive pulmonary disorder, and Parkinson's disease.[62] Similar studies have validated these findings using the Short-Form 36 (SF-36) and Euroqol 5 Dimension (EQD-5) questionnaires.[63-65] Interestingly, it is often the extra-sinus manifestations which drive overall health-state utility scores and patient decision-making.[66 65,67,68]

Severe fatigue is commonly reported by patients with CRS. The baseline median prevalence of fatigue was 54%, ranging from 11-73% across studies in a systematic review with meta-analysis.[69] Poor sleep quality is also a frequent complaint of patients with CRS and this impact has been the focus of recent investigations. The mean Pittsburgh Sleep Quality Index (PSQI) score in a multi-institutional cohort of 268 patients with CRS was 9.4, with 75% reporting "poor" sleep based on accepted cut-offs.[70] In this group, PSQI scores significantly correlated with sinus-specific QoL scores on both the Sino-Nasal Outcome Test 22 (SNOT-22) and Rhinosinusitis Disability Index (RSDI) instruments (r=0.55 and r=0.53 respectively).[71,72] Similarly, a large population-based study in Europe found that sleep problems were 50-90% more common among subjects with CRS as compared with the general population.[73]

The impact of CRS on cognitive function represents a more recent area of inquiry. A case-control study found that patients with CRS report significantly worse scores on the Cognitive Failures Questionnaire as compared with controls[74]. Several subsequent studies have found improvements

in patient-reported and objective cognitive function after both medical and surgical treatment of CRS.[75-77]

Another prominent factor that impacts overall QoL and wellbeing in patients with CRS is the presence of depression. A systematic review found prevalence rates for depression in CRS ranging from 11-40%.[78-84] This frequency of depression in CRS exceeds population norms of between 5-10% with a recent population study from Asia estimating an adjusted hazard ratio of 1.56 (95% CI: 1.43–1.70).[85,86]

I.C.4. Societal Burden of Disease

The combined prevalence of acute and chronic RS (12-15.2%) exceeds that of other common respiratory conditions such as hay fever (8.9%), acute asthma (3.8%) and chronic bronchitis (4.8%).[9,87] The direct costs of managing ARS and CRS are thought to exceed USD$11 billion per year.[88] In a study of 4.4 million patients, Bhattacharyya et. al. identified 4460 patients undergoing ESS.[89] The healthcare costs for CRS in the year leading up to ESS (therefore, medically refractory patients) were USD$2449, USD$1789 of which were attributable to facility and physicians' charges. In a recent population-based assessment Bhattacharyya determined that CRS patients are associated with significantly increased incremental healthcare utilization costs relative to adults without CRS. [90] Chung, *et al.* also found that non-US patients with CRS diagnoses incurred significantly higher outpatient costs (USD$953 versus USD$665; p<0.001) and total healthcare costs (USD$1318 versus USD$946; p<0.001) than those without CRS.[91] With respect to CRSwNP, Bhattacharyya *et al.* found an incremental increase in annual direct medical costs of USD$1067 for patients relative to controls without CRS.[92]

Among medically refractory patients, a systematic review specific to surgery found that the cost of outpatient ESS ranges from USD$8200 to USD$10,500 per procedure in 2014 USD. A large claims-based study found that although the mean surgical cost of ESS was USD$7,782, direct healthcare costs decreased steadily in the 3 years after surgery with greater than half of the patients resolving direct costs attributable to CRS.[93]

In contrast to these direct healthcare costs, the indirect healthcare costs of CRS include societal costs related to absence from work (absenteeism), decreased work productivity while at work (presenteeism) and other forms of lost productivity (*e.g.*, leisure time lost). Among the 15.2% of those reporting RS (ARS or CRS) annually in a national survey, an estimated 61.2 million potential workdays were missed per year among adults in the United States.[87,94] In a comprehensive review, DeConde and Soler found that the indirect costs related to total decreased productivity from CRS were estimated at USD$12.8 billion per year in the US.[14]

I.C.5. Management of RS

I.C.5.a. Evidence-Based Medical Management Recommendations for RS

The ICAR-RS document provides an evidence-based review with recommendations on 55 individual medical therapies for RS. The following tables represent all interventions with aggregate grade A or B evidence regarding their use and their associated policy levels.

Table I.3: Grade A/B evidence-based recommendations for medical management of ARS

Intervention	Grade	Benefit	Harm	Cost	Benefit-Harm Assessment	Policy Level
ARS: Antibiotic Treatment	B	Shorter symptom duration, reduced pathogen carriage	GI complaints, Resistance, Anaphylaxis; See Table II-1.	Low to Moderate	Benefit over placebo is small	Option: Consider watchful waiting in uncomplicated cases with institution after 7 days or with worsening/ mitigating circumstances
Pediatric ARS <10 days: Withholding Antibiotic Treatment	A	Avoidance of unnecessary medications	Potential progression of disease	None	Benefits likely outweigh harms and costs	Recommendation: Antibiotics should not be given for the first 10 days of uncomplicated pediatric ARS. If >10 days or complicated, amoxicillin-clavulanate is preferred antibiotic if not allergic
ARS: Intranasal Corticosteroids	A	Improved symptoms as monotherapy in mild to moderate cases and as adjuvant to antibiotics in severe cases. May shorten recovery	Minimal harm with rare adverse events; ; See Table II-1.	Low	Benefit over placebo small but tangible	Strong Recommendation: Consider use in ARS
ARS: Topical Saline Spray and Irrigation	B	No benefit to 10cc syringe but possible improvement in patency, rhinorrhea, and post-nasal drip with high volume irrigation	Unclear but possible ear fullness, or irritation; See Table II-1.	Low	Balance of benefit and harm	Option: Saline irrigation may be used in adjunct with antibiotics for acute bacterial rhinosinusitis.

Table I-4. Grade A/B evidence-based recommendations for medical management of CRS

Intervention	Grade	Benefit	Harm	Cost	Benefit-Harm Assessment	Policy Level
CRSsNP: Saline Irrigation, Drops, Sprays	B	Improvement in QoL, endoscopic appearance , and role in maintenance therapy. Benefit over control was shown with saline irrigations (≥60 ml) and at eight weeks duration	Minor and rare adverse effects. Nasal burning and irritation are more reported with hypertonic irrigation; See Table II-1.	Low	Preponderance of benefit over harm	Recommendation: Saline irrigation improves symptoms, QoL and nasal endoscopy. Duration of should be greater than eight weeks. Hypertonic saline is more effective but may be more irritating than isotonic saline. There is no advantage of heated over room temperature saline. Devices with volume greater than 60 ml bring greater benefits
CRSwNP: Oral Corticosteroids	A	Significant short-term improvements in subjective and objective measures. Duration may last 8-12 weeks in conjunction with topical INCS	GI symptoms, transient adrenal suppression, insomnia, and increased bone turnover. All established systemic corticosteroid risks exist, particularly with prolonged treatment; See Table II-1.	Low	Preponderance of benefit over harm with short-term treatment with follow-up	Strong recommendation: For short-term management of CRSwNP. Longer term use of is not supported by the literature and carries increased risk of harm
CRSsNP: Intranasal Corticosteroid Spray	A	Improved symptom scores, improved endoscopy scores.	Epistaxis, nasal irritation, headache; See Table II-1.	Low to Moderate	Possible mild benefit over harm	Option: Standard metered dose INCS could be used in treatment of CRSsNP, particularly if primary symptoms are

						that of rhinitis
CRSwNP: Intranasal Corticosteroid Spray	A	Improved symptoms, endoscopy score, polyp size, QoL, olfaction, airway analysis (NPIF), and polyp recurrence. Magnitude of the clinical effect is small	Epistaxis, nasal irritation, headache; See Table II-1.	Low to Moderate	Benefit outweighs harm	Strong Recommendation: INCS are recommended for CRSwNP before or after sinus surgery. Consideration for twice daily dosing if initial treatment effect is small
CRSsNP: Corticosteroid Irrigations	A	Improvement in HR-QoL, subjective symptom scores and endoscopic appearance in postoperative patients.	Epistaxis, nasal irritation; See Table II-1. No evidence of adrenal suppression using irrigation delivery	Moderate to High	Preponderance of benefit over harm, with increased cost compared to nasal sprays	Recommended: Post-operative patients Option: Non-surgical/medical management
CRSwNP: Non-Standard Corticosteroid Delivery	B	Corticosteroid Irrigations/Atomization/Nebulization have shown benefit over INCS. Exhalation devices have shown benefit over placebo	Some evidence of systemic absorption with first generation corticosteroids especially with multiple modalities of therapy	Moderate	Benefit outweighs harm compared with oral corticosteroids but caution in patients on multiple topical therapies	If not controlled with INCS, strong recommendation for corticosteroid irrigation; recommendation for atomization/ nebulization Option: Exhalation delivery
CRSwNP: Corticosteroid eluting Implants	A	Reduction in ethmoid obstruction, polyp grade, decreased need for revision ESS, reduced nasal obstruction scores	No findings of increased risk of elevated intraocular pressure or cataracts	Moderate to High	Benefits appear to outweigh harm	Option: Corticosteroid-eluting implants can be considered as an option in a previously operated ethmoid cavity with recurrent nasal polyps
CRSwNP: Dupilumab (Biologic)	A	Decreased polyp size, improved nasal congestion, sinus imaging scores, sense of smell, and asthma control	Conjunctivitis and hyper-eosinophilia	High	Likely benefit over harm in patients with CRSwNP not responsive to medical and surgical standard of	Recommendation: May be considered for patients with severe CRSwNP who have not improved despite other medical and

					care	surgical treatment options
CRSsNP: Macrolide Antibiotics	B	Reduction in endoscopy and symptom scores	Gastrointestinal side effects, ototoxicity, hepatotoxicity, cardiotoxicity, and drug-drug interactions; See Table II-1.	Low	Benefits appear to outweigh harm	Option: Macrolides are an option for patients with CRSsNP. Optimal drug, dosage, and treatment duration are not known
CRSwNP: Macrolide Antibiotics	B	May improve symptom and endoscopic scores in CRSwNP. Macrolides appear to be comparable to INCS in selected patients	Gastrointestinal side effects, ototoxicity, hepatotoxicity, cardiotoxicity, and drug-drug interactions; See Table II-1.	Low	Benefits appear to outweigh harm	Option: Macrolides are likely beneficial in CRSwNP. Optimal drug, dosage, and treatment duration are not known
CRSwNP: Non-Macrolide Antibiotics (<3 weeks)	B (-)	Potential reduction in polyp size with doxycycline without change in symptoms	GI upset, skin rash, insomnia, and headache; See Table II-1. Potential delay of more effective interventions	Variable	Preponderance of harm over benefits	Recommendation against: Should generally not be prescribed for CRSwNP except in acute exacerbations
CRSs/wNP: Topical Antibiotics	A (-)	Systematic reviews and RCTs failed to show benefit from the use of topical antibiotics in CRS	Nasal congestion, irritation, epistaxis. Theoretical possibility of systemic absorption aminoglycosides. Possibility of bacterial resistance	Moderate to High	Relative harm over benefit	Recommendation against: Topical antibiotics are not recommended for CRSs/wNP
CRSs/wNP: Topical Antifungals	A (-)	No apparent benefit from use of topical antifungals	Potential for local irritation, epistaxis and headache less common	Low to Moderate	Minimal risk of harm but no apparent potential for benefit	Strong recommendation against: Topical antifungals are not recommended for CRSs/wNP
CRSwNP: Anti-Leukotrienes	A	Improvement in symptoms comparable to	Limited risks. Montelukast associated with	Moderate	Balance of benefits and harm	Option: Montelukast is an option for

		INCS. May have limited benefit as an adjunct to INCS	neuropsychiatric events. Zileuton associated with elevated liver enzymes requiring monitoring; See Table II-1.			CRSwNP patients either instead of or in addition to INCS
CRSs/wNP: Xylitol Irrigation	B	Symptomatic improvement in the 2 small RCTs in postoperative patients	Occasional local discomfort, stinging	Low	Preponderance of mild benefit over harm	Option postoperatively in CRSsNP and CRSwNP patients.
CRSs/wNP: Colloidal Silver	B (-)	No benefit for the use of in clinical studies	Potential increase in serum silver levels	Low to High	No benefit in light of potential harm	Recommendation against: CAg may have anti-bacterial properties in-vitro but lacks efficacy in clinical studies
CRSwNP: Furosemide	B	Reduced recurrence of nasal polyps following ESS over placebo nasal spray	No studies have been performed to assess systemic safety with nasal delivery	Low	Benefits likely outweighs harm when used on a rotating basis as studied	Option: Topical furosemide after ESS and in combination with an INCS may reduce the recurrence of nasal polyps
CRSwNP (AERD): ASA Desensitization	A	Reduced post-op polyp re-recurrence, increased QoL and reduced symptoms. Reduced need for systemic corticosteroids and surgical revisions	GI bleeding, increased morbidity in renal disease and clotting dysfunction at high maintenance doses. < 3% GI side effects with low-dose protocols	Low to Moderate (Including cost of desensitization)	Clear benefit over harm	Recommendation: Aspirin desensitization should be considered in AERD after surgical removal of NPs to prevent recurrence.

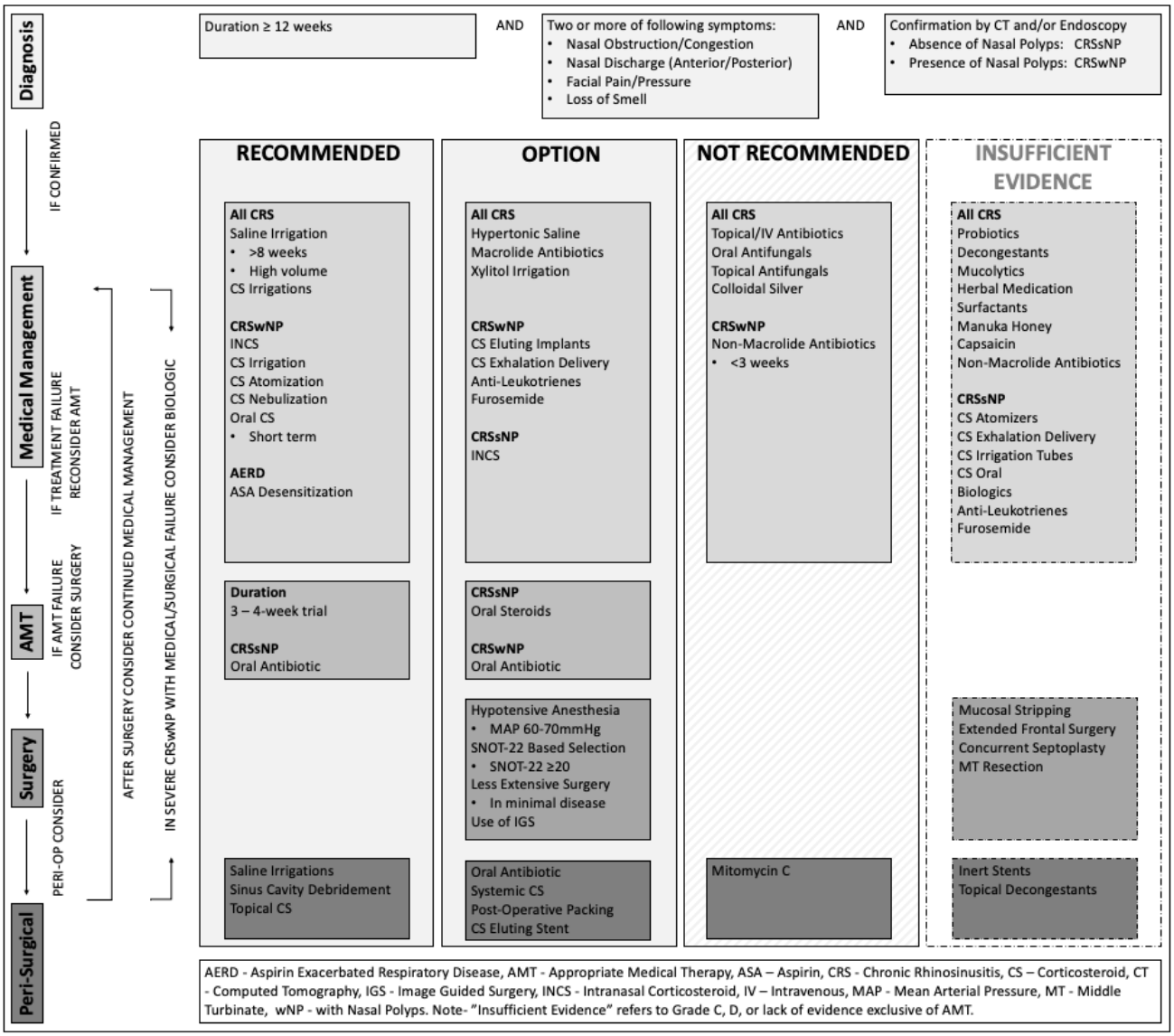


Figure I-3: Evidence based management of chronic rhinosinusitis. Evidence based reviews are based on the best available evidence. They do not define standard of care and do not define medically necessary treatments. Individual patients' condition, values, expectations and other factors must be weighed in making a treatment decision.

I.C.5.b. Evidence Based Recommendations for Surgical Timing and Indications in RS

Statements regarding indications for sinus surgery have generally cited "failure of maximal medical therapy" as a requirement before proceeding. Some evidence indicates that prolonging the time between diagnosis and surgery for CRS may negatively impact outcomes. Data from both the UK prospective audit of surgery for CRS and UK primary care electronic datasets were analyzed by Hopkins *et al.*[95,96] Patients were classified according to the duration of their CRS until their first surgical intervention for CRS. Patients in the early group (*e.g.* less than 12 months) had not only a greater percentage improvement in their symptoms, but the improvement was better maintained over five years. It has also been shown, using both UK and US datasets, that ESS was associated with

a reduction in the incidence of new asthma diagnoses following surgery, and that the risk of asthma was lowest in those having early surgery.[97] The term "appropriate" medical therapy (AMT) has therefore become preferred in order to suggest striking a balance between proceeding to surgery before appropriate nonsurgical options have been tried and delaying too long so that outcomes are negatively impacted. While high level evidence for what constitutes AMT is lacking, both in terms of composition and duration, the current best evidence is summarized below.

Table I-5. Evidence for surgical timing and indications

Intervention	Grade	Benefit	Harm	Cost	Benefit-Harm Assessment	Policy Level
AMT: CRSsNP INCS, Saline Irrigations, Antibiotics	D	Symptomatic Improvement, Avoidance of risks and costs of surgical intervention	Risk of medication adverse events, potential for increasing antibiotic resistance; See Table II-1.	Direct Cost of medications and treatment of adverse events	Differ by therapy and clinical scenario	Recommendation for AMT prior to surgical intervention. Option: Oral Corticosteroids
AMT: CRSwNP INCS, Saline Irrigations, Oral Corticosteroids (Single short course)	D	Symptomatic Improvement, Avoidance of risks and costs of surgical intervention	Risk of medication adverse events, potential for increasing antibiotic resistance; See Table II-1.	Direct Cost of medications and treatment of adverse events	Differ by therapy and clinical scenario	Recommendation for AMT prior to surgical intervention. Option: Antibiotics
AMT: Duration of 3-4 weeks	D	Symptomatic Improvement, Avoidance of risks and costs of surgical intervention	Risk of medication adverse events, potential for increasing antibiotic resistance; See Table II-1.	Direct Cost of medications and treatment of adverse events	Differ by therapy and clinical scenario	Recommendation for minimum of 3-4 week trial of AMT prior to surgical intervention

I.C.5.c. Evidence Based Surgical Management Recommendations for RS

With regards to once a surgical intervention has been embarked upon, the ICAR-RS document provides an evidence-based review with recommendations on 17 individual surgical and/or peri-surgical related therapies for RS. The following tables represent all interventions with aggregate grade A or B evidence regarding their use and their associated policy levels.

Table I-6. Grade A/B evidence-based recommendations for surgical management of CRS

Intervention	Grade	Benefit	Harm	Cost	Benefit-Harm Assessment	Policy Level
Hypotensive Anesthesia	B	Controlled hypotension with MAPs between 60 and 70 mmHg improves the surgical field	MAP < 60mmHg may result in cerebral ischemia	Low additional cost to achieve target MAP	Preponderance of benefit over harm	Option: Controlled hypotension (MAP between 60 and 70 mmHg) is safe and improves the surgical field
Patient selection to achieve a post-operative MCID	B	Use of baseline disease-specific QoL metrics (*e.g.*, SNOT-22 ≥20) as criteria can help standardize selection for patients with high likelihood of achieving a post-op MCID	Exclusion of patients based on SNOT-22 scores alone who may otherwise benefit from surgery	Ignorance of individual specific symptoms or loss of productivity at work if criteria for surgery not met	Likely benefit over harm with acknowledgement that certain patients with low SNOT-22 may still benefit from surgery	Option: Patient selection for surgical intervention should take into consideration baseline patient reported symptom burden
Extent of Surgery	B	Reduced tissue manipulation of mucosa with limited approaches (*e.g.*, balloons) has the potential to reduce surgical time	Limited techniques can result in insufficient removal of diseased tissue, persistent inflammation, reduced topical delivery, less access for postoperative care, and faster relapse of symptoms	Balloon-dilation technology is associated with increased equipment costs per case	In short term follow-up, conservative approaches do not appear to increase harm from recurrence in patients with limited sinus disease	Option: Less extensive sinus interventions are likely reasonable options in patients with minimal OMC or maxillary sinus disease
Image Guidance	B	Reduced complications, improved outcomes, more extensive surgery performed, reduced surgeon stress	Increased operating time, IGS failure leading to inaccurate localization of instruments	Costs related to longer operating time and the need for specialized equipment	Preponderance of benefit over harm in selected cases	Option: Use in patients undergoing ESS, especially in the setting of anatomic complexity or the need for more advanced procedures

I.C.5.d. Surgical Complications and Prevention Techniques in ESS

ESS outcomes have improved over the years due to advances in technology and surgical training. Despite these improvements, complications still occur during surgery due to the close proximity of the sinuses to the skull base and orbit. The reported complication rate of ESS for CRS ranges from 0.36 – 5.8%, with minor and major complications occurring in up to 5.7% and 1.5% respectively.[98-104] Up to 15% of patients will require revision surgery, with reported major complication rates of 0.46% in revision surgery.[98,105] While altered anatomy and adhesions can increase the risks of complications during revision ESS, the actual revision ESS complication rate has not been shown to be significantly different than primary ESS rates.[98,106]

Table adapted from May *et al.*[104] and Asaka *et al.*[100]

Table I-7. Anatomic relationships to consider during sinus surgery to prevent complications

Anatomic Findings	Description	Importance
Maxillary-to-Ethmoid Ratio	Ratio of the maxillary sinus height to the posterior ethmoid height (just posterior to the basal lamella) in the coronal plane	Inadvertent injury to the skull base is more likely to occur if the maxillary to ethmoid vertical height ratio is greater than 1:1.
Height of the lateral lamella (Keros Classification)	The length of the lateral cribriform lamella relative to the fovea ethmoidalis - Keros I: 1-3 mm - Keros II: 3-7 mm - Keros III: 8-16 mm	Risk for intracranial injury is positively correlated with higher Keros classification. It is critical to note for any asymmetry of the skull base or areas of bony dehiscence.
Ethmoidal Arteries	Determine if the location of the anterior and posterior ethmoid arteries are traversing through the skull base or suspended below	Arteries suspended below the skull base are more susceptible to injury during sinus surgery. Damage to the artery can result in hemorrhage, CSF leak, or orbital hematoma.
Sphenoid Sinus Pneumatization/Onodi Cell	Classify the pneumatization pattern of the sphenoid sinus (conchal, presellar, sellar). Identify the presence or absence of: - Onodi cell - Intersinus septation inserting onto carotid canal - Dehiscence over the carotid canal or optic nerve	The sphenoid sinus is helpful in identifying the anterior skull base. There is an increased risk of optic nerve injury if an Onodi cell is present or there is bony dehiscent present. Risk of carotid artery injury increases if there is an insertion of an intersinus septation or overlying bony dehiscence.

Skull base asymmetry/bony dehiscence	Evaluate for any areas of asymmetry (height and thickness) within the skull base. Examine the continuity of the bone overlying the lamina papyracea, carotid canal, and optic nerve	Inadvertent injury to the skull base is more likely in the presence of an asymmetric skull base or areas of bony dehiscence. Similarly, injury to the orbit, carotid artery, and optic nerve is increased with areas of bony dehiscence/abnormalities.

I.C.5.e. Postoperative Care Following ESS

In studies of postoperative management, one problem continues to be the heterogeneity of reported postoperative health metrics which is likely related to the need for clinicians to optimize for both short-term and long-term patient outcomes. While some evidence may assess a particular outcome, it might not address the entire clinical spectrum. The following represents the best current evidence for a range of postoperative interventions following ESS.

Table I-8. Evidence for postoperative care following ESS for CRS

Intervention	Grade	Benefit	Harm	Cost	Benefit-Harm Assessment	Policy Level
Saline irrigations	B	Well-tolerated. Improved symptoms and endoscopic appearance	Local irritation, ear symptoms	Minimal	Preponderance of benefit over harm	Recommendation for use of nasal saline irrigation
Sinus cavity debridements	B	Improved symptoms and endoscopic appearance. Reduced risk of synechia and turbinate lateralization	Inconvenience, pain, epistaxis, syncope, and mucosal injury.	In-office procedure with cost	Preponderance of benefit over harm	Recommendation for postoperative debridement
Topical corticosteroids	A	Improved symptoms and endoscopic appearance. Reduced recurrence rate of polyps	Epistaxis, headache	Moderate	Preponderance of benefit over harm	Strong Recommendation for topical corticosteroids
Oral antibiotics	B	Improved symptoms and endoscopic appearance. Reduced crusting.	GI upset, colitis, anaphylaxis, bacterial resistance.	Moderate to high	Balance of benefit and harm	Option for oral antibiotics
Topical decongestant	N/A	Potential reduced	Increased pain, possible rhinitis	Minimal	Preponderance of harm over	Recommendation against topical

s		mucosal swelling and bleeding.	medicamentosa		benefit	decongestants
Systemic corticosteroids	C	Improvement in endoscopic appearance, reduction in polyp recurrence.	Insomnia, mood changes, hyperglycemia, gastritis, increased intraocular pressure, avascular necrosis	Minimal	Balance of benefit and harm	Option for systemic corticosteroids
Mitomycin C	B	Reduction in synechia formation, improvement in maxillary ostium patency	Off-label use, systemic absorption, local toxicity	Moderate to high.	Balance of benefit and harm	Recommendation against Mitomycin C
Post-operative Packing	A	Potential reduction in post-operative adhesion and improved ostial size with some materials	Potential for increased discomfort *in situ* and on removal. Rare risk of toxic shock syndrome. Potential for an increased rate of adhesions with some materials	Costs associated with all packing materials. Absorbable materials are more costly than nonabsorbable packing	Balance of risks and benefits	Option. Although evidence does exist suggesting packing may reduce adhesion formation, it is limited and has not been compared to studies employing early and frequent debridement
Post-operative Drug-eluting Implants	A	Reduction in polyposis and adhesions which translates into a reduction in postoperative interventions	Potential for misplacement and local reaction	Variable depending on stents and medication	Preponderance of benefit over harm	Option. Corticosteroid-eluting stents can be considered in the postoperative ethmoidectomy cavity

I.C.6. CRS and COVID-19

The coronavirus disease 2019 (COVID-19) pandemic, caused by the virus SARS-CoV-2, has heightened awareness and necessitated modifications to the workup and management of sinonasal pathologies including CRS. Notably, olfactory dysfunction, a cardinal symptom of CRS, has been highlighted as a prevalent symptom of COVID-19.[3,107-110] Olfactory dysfunction is acute and profound, and may be the sole manifestation of disease. Unlike anosmia found in CRS, COVID-19-associated olfactory loss presents with no radiographic evidence of olfactory cleft disease or mucosal thickening of the sinuses.[111,112] Importantly, olfactory loss has high diagnostic value as the strongest symptomatic predictor of COVID-19 with potential for early disease screening.[107,113,114] The

prevalence of olfactory dysfunction has varied widely between 15 to 96% based on self-reported and quantitatively measured data.[115-117]

The COVID-19 pandemic has necessitated flexibility in our treatment algorithms for CRS as guided by patient preference and concerns for viral transmission. Topical intranasal corticosteroids (INCS) are recommended and maintained even during SARS-CoV-2 infection.[118,119] There is no evidence that INCS are associated with increased infectivity. Some fear discontinuing INCS may not only worsen symptoms but increase viral shedding due to coughing and sneezing. The utility and appropriateness of oral steroids remain more controversial as their effects on COVID-19 lung injury are debated,[120] though more recent studies have shown improvement in COVID-19 mortality rate.[121]

Given the high viral burden found on nasal mucosal surfaces,[2] the otolaryngologic field has carefully assessed the risks of airborne aerosol production during both diagnostic and therapeutic endonasal procedures. However, the implications of these findings on viral transmissibility, replicativity, and their designation as "aerosol generating procedures (AGPs)" remain controversial.[122-127] Both high-speed drill and bipolar electrocautery are considered aerosol-generating devices, and are often required in extended surgical approaches for recalcitrant CRS.[123,128] The use of constant suctioning during these procedures may help mitigate particle transmission.[122,125] Notably the microdebrider, with its in-line suction, does not appear to be a significant aerosol producer.[123,128] Other aerosol-generating in-office devices include bipolar RF ablation (coblation) and cryotherapy, both used for treatment of rhinitis.[128] The infectious transmission risk of diagnostic nasal endoscopy remains another area of active investigation. Both flexible and rigid nasal endoscopy have been shown to produce airborne aerosols,[127,129] require unmasking, can induce cough/sneeze, and occur within an enclosed space in close proximity to the patient. These features have all been shown to be associated with infectious transmission in community based epidemiologic studies.[130-134] Consequently, comprehensive pre-visit patient screening, environmental safety, and full PPE utilization are recommended as appropriate precautions.[129]

I.C.7. Knowledge Gaps

The breadth and quality of research into virtually all aspects of RS has advanced considerably in the past decade. The sheer scope of the ICAR-RS document is, itself, evidence of such progress. However, multiple knowledge gaps remain, particularly within the realm of developing better diagnostic and targeted therapeutic strategies to advance personalized treatment of RS.

Table I-9. Knowledge gaps in RS

Category	Research Need
Diagnosis of CRS	Validation of biosignatures of discreet CRS endotypes
Treatable Traits	Discovery of biomarkers that directly respond to targeted therapeutics and may predict efficacy
Topical Therapeutics	Development of formulations specifically designed to optimize mucosal distribution, stability, and absorption
Appropriate Medical Therapy	Define composition, duration, and response rate to AMT, through well controlled clinical trials

Interventional Strategies	Execution of sham-controlled studies using validated PROMS, clinically relevant objective endpoints, cost-benefit analyses
COVID-19	SARS-CoV-2 anosmia pathogenesis, rhinologic aerosol generating procedure risk, and how to deliver elective rhinologic care during pandemic conditions.

I.D. Discussion

This executive summary reviews many of the important new topics added to the ICAR-RS document since its first publication in 2016. Furthermore, it highlights the areas in which new evidence has been added to the existing topics, in some cases changing the overall evidence grade. Despite these advances, the knowledge gap section emphasizes the continued need to incorporate next generation research tools in order to gain deeper insights into RS etiopathogenesis and to identify treatable traits against which novel therapies may continue to be developed.

While the ICAR-RS-2021 general topic outline with its associated diagnostic and management recommendations largely followed a similar structure to the original ICAR-RS document, it is within reason to envision a future consensus statement which utilizes biosignatures to dissect out RS according to endotype while providing personalized therapeutic recommendations based on grade A clinical trial data. The laudable progress we have made since 2016 suggests this future is closer than it may appear. However, it is only through the continued aspiration towards and adherence to the type of evidence-based recommendations described in ICAR-RS-2021 that we may collectively make this future a reality.

I.E. Lay Summary

The 2021 International Consensus Statement on Allergy and Rhinology: Rhinosinusitis

The 2021 International Consensus Statement on Allergy and Rhinology: Rhinosinusitis contains the most complete and up-to-date information on what causes rhinosinusitis and how it should be treated, based on research and scientific evidence. It has been written, reviewed, and agreed upon by dozens of experts from around the world. This is one of the most important sources for doctors who treat sinus and nasal problems as it helps them understand the latest treatments that have been proven to help patients suffering from rhinosinusitis.

What is rhinosinusitis?

We use the word "rhinosinusitis" instead of "sinusitis" to include inflammation of both the sinuses and the nasal passages. The most common symptoms of rhinosinusitis are a runny nose, blockage or congestion of the nose, reduced sense of smell, and pressure or pain in the face. There are actually many types of rhinosinusitis, divided up by how long patients have symptoms. When symptoms last less than 4 weeks, we call that "acute rhinosinusitis." If symptoms last longer than 12 weeks, we call it "chronic rhinosinusitis." In order to be diagnosed with chronic rhinosinusitis patients also need to have signs of infection or inflammation on a nasal exam or CT scan. Some patients will have small growths in the nose and sinuses called "Nasal Polyps" which come from severe inflammation. Patients with nasal polyps and may be treated differently than patients without nasal polyps.

How common is rhinosinusitis?

Rhinosinusitis is very common problem. Every year about 9 out of 100 people will have acute rhinosinusitis. It is thought that about 14 out of every 100 people in the US have chronic rhinosinusitis and about 2-4 out of 100 have nasal polyps. Unless children have other medical problems, they have lower rates of chronic rhinosinusitis at about 1-2 out of 100.

How severe is chronic rhinosinusitis?

Chronic rhinosinusitis not only causes nasal symptoms but also can lower a patient's quality of life. This effect can be as severe as having other serious medical conditions like congestive heart failure, chronic obstructive pulmonary disorder (COPD), and Parkinson's disease. Patients with chronic rhinosinusitis also tend to feel very tired, have poor sleep, are more likely to be depressed, and sometimes feel they can't think or solve problems well. The treatment of chronic rhinosinusitis is very expensive and costs the medical system over 11 billion dollars every year in the US. Chronic rhinosinusitis also costs society another 13 billion dollars every year from patients not being able to go to work or not being as productive while at work.

How is rhinosinusitis treated?

Acute rhinosinusitis may first be treated with nasal steroid sprays, salt-water rinses, and sometimes a couple of days of decongestants. Doctors usually wait to give antibiotics unless symptoms don't get better after about a week. There are many treatments for chronic rhinosinusitis but the most proven ones are salt-water rinses and steroid sprays or washes. Some studies have shown a kind of antibiotic called "macrolides" and washing the nose with a special compound called "xylitol" can also be used. For patients with nasal polyps, steroid pills and medications called "anti-leukotrienes" can help.

If patients don't get better after medications are tried, their doctors may talk to them about having sinus surgery. This surgery is meant to open the sinuses so they can drain better and also to help sprayed and rinsed medications get deeper into the sinuses after surgery. Studies suggest that the worse your symptoms are and the quicker you have surgery, the better your results will be.

What is new in the treatment of chronic rhinosinusitis?

Many new treatments have been developed for patients with chronic rhinosinusitis. In some patients with less severe symptoms who don't get better with medication, the sinus openings can be stretched using balloons instead of fully opening them. Patients with nasal polyps can now also be treated with implants that release a steroid into the sinuses or an injection of a medication called a "biologic". Research continues to understand the causes and best treatments of rhinosinusitis.

II. Table of Contents

II.A. List of Abbreviations Used

3D-CTA	three-dimensional computed tomography angiography
AAOA	American Academy of Otolaryngic Allergy
AAO-HNS	American Academy of Otolaryngology - Head and Neck Surgery
AAP	American Academy of Pediatrics
ABRS	acute bacterial rhinosinusitis
ACE2	angiotensin-converting enzyme 2
AcRh	acoustic rhinometry
ACT	Asthma Control Test
ACTH	adrenocorticotropic hormone
AD	aspirin desensitization
AE	adverse event
AECRS	acute exacerbation of chronic rhinosinusitis
AERD	aspirin exacerbated respiratory disease
AFRS	allergic fungal rhinosinusitis
AGP	aerosol generating procedure
AHLs	acyl-homoserine lactones
AIFS	acute invasive fungal rhinosinusitis
AJC	apical junction complex
α-SMA	alpha smooth muscle actin
AMA-PCPI	American Medical Association Physician Consortium for Practice Improvement
AMCase	acidic mammalian chitinase
AMT	appropriate medical therapy
APDS	activated phosphoinositide 3-kinase delta syndrome
AOAH	acyloxyacyl hydroxylase
AQLQ	Asthma Quality of Life Questionnaire
AR	allergic rhinitis
ARS	acute rhinosinusitis
ASA	acetyl salacylic acid
ASL	airway surface layer
ATA	asthma tolerant to anti-inflammatory drugs
ATP	adenosine triphosphate

AVRS	acute viral rhinosinusitis
BC	black carbon
BCD	balloon catheter dilation
bFGF	basic fibroblast growth factor
BID	twice daily
BMP	bone morphogenetic protein
BSACI	British Society of Allergy and Clinical Immunology
C3	complement component 3
CAg	colloidal silver
CBC	complete blood count
CBF	ciliary beat frequency
CCAD	central compartment atopic disease
CCL1	chemokine (C-C motif) ligand 1
CD	chitosan-dextran
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator
CGD	chronic granulomatous disease
CI	confidence interval
CIFS	chronic invasive fungal rhinosinusitis
CMC	carboxymethylcellulose
CMS	Centers for Medicare & Medicaid Services
CoV	coronavirus
COX	cyclo-oxygenase
CPODS	facial congestion/fullness, facial pain/pressure, nasal obstruction/blockage, nasal drainage, and smell dysfunction
CRP	C-reactive protein
CRS	chronic rhinosinusitis
CRSsNP	chronic rhinosinusitis without nasal polyps
CRSwNP	chronic rhinosinusitis with nasal polyps
CS	conventional septoplasty
CSF	cerebrospinal fluid
CSS	Chronic Sinusitis Survey
CT	computerized tomography
CVID	common variable immunodeficiency
CYP27B1	cytochrome P450 family 27 subfamily B member 1
cysLT	cysteinyl leukotriene
DB	double blind
DBRCT	double blind randomized controlled trial
DEX	dexmedetomidine
DM	diabetes mellitus
DNA	deoxyribonucleic acid
DTH	delayed-type hypersensitivity
EBL	estimated blood loss
EBM	evidence-based medicine
EBR	evidence-based review
EBRR	evidence-based review with recommendations
ECP	eosinophilic cationic protein
EDN	eosinophil derived neurotoxin
EDS-FLU	exhalation delivery system with fluticasone
EGF	epidermal growth factor
EGPA	eosinophilic granulomatosis with polyangiitis

ELISA	enzyme-linked immunosorbent assay
EMMA	extended middle meatal antrostomy
EMRS	eosinophilic mucin rhinosinusitis
EMS	ethmomaxillary sinus
ENT	ear, nose, and throat
Eos	eosinophilic
EPOS	European Position Paper on Rhinosinusitis and Nasal Polyps
EQD-5	Euroqol 5 dimension questionnaire
ER	emergency room
ES	endoscopic septoplasty
ESR	erythrocyte sedimentation rate
ESS	endoscopic sinus surgery
FACS	fluorescence-activated cell sorting
FCP	fibrinogen cleavage product
FeNO	fractional exhaled nitric oxide
FEV1	functional expiratory volume within 1 second
FGF	fibroblast growth factor
FISH	fluorescent in situ hybridization
FLT3	fms related tyrosine kinase 3
FSP	fibroblast-specific protein
FTA	fibrin tissue adhesive
GA	general anesthesia
GA^2LEN	Global Allergy and Asthma European Network of Excellence
G-CSF	granulocyte colony-stimulating factor
GERD	gastroesophageal reflux disease
GHSI	Glasgow Health Status Inventory
GI	gastrointestinal
GIFS	granulomatous invasive rhinosinusitis
GM-CSF	granulocyte monocyte colony stimulating factor
GOSS	Global Osteitis Scoring Scale
GPA	granulomatosis with polyangiitis
GRO	growth related oncogene
H&E	hematoxylin and eosin stain
HBD	human beta defensin
HTN1	histatin 1
HLA	human leukocyte antigen
HRQoL	health related quality of life
HSNF	human sinonasal fibroblast
HU	Houndsfield unit
IA	inhalational anesthesia
ICAR-RS	International Consensus Statement on Allergy and Rhinology: Rhinosinusitis
ICD-9	International Classification of Disease, 9^{th} Revision
ICER	incremental cost-effectiveness ratio
IDT	intradermal testing
IFN-γ	interferon-γ
IFS	invasive fungal rhinosinusitis
Ig	immunoglobulin
IGS	image-guided surgery
IHC	immunohistochemistry
IL	interleukin
IL-1Ra	IL-1 receptor antagonist

ILC	innate lymphoid cell
INCS	intranasal corticosteroid sprays
ION	infraorbital nerve
IOP	intraocular pressure
IP-10	IFN-γ-induced protein 10
IV	intravenous
IVIG	intravenous immunoglobulin
KOS	Kennedy osteitis score
LK	Lund-Kennedy score
LM	Lund-Mackay score
LOE	level of evidence
LPLUNC2	Long palate, lung and nasal epithelium clone 2
LPS	lipopolysaccharide
LT	leukotriene
MAbs	monocolonal antibodies
MAD	mucosal atomization device
MAP	mean arterial pressure
MAST	maxillary antrostomy sinus tubes
MegA	mega-antrostomy
MBL	mannose-binding lectin
MCC	mucociliary clearance
MCID	minimally clinically important difference
MCP-1	monocyte chemoattractant protein-1
MDC	macrophage derived chemokine
MedMgt	medical management
MEMM	mega-antrostomy and modified endoscopic medial maxillectomy
MFNS	mometasone furoate nasal sprays
MGO	methylglyoxal
MIF	migration inhibition factor
MIP	macrophage inflammatory protein
MIST	minimally invasive sinus technique
MH	Manuka honey
MM	middle meatus
MMA	middle meatal antrostomy
MMP	matrix metalloproteinase
MMT	maximal medical therapy
MOS Sleep-R	Medical Outcomes Study Sleep Scale-Revised
MPO	myeloperoxidase
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MRSA	methicillin-resistant *Staphylococcus aureus*
MT	middle turbinate
MTL	middle turbinate lateralization
N/A	not applicable
NHA	nebulized sodium hyaluronate
NLR	nucleotide-binding oligomerization domain-like receptor
NNT	number needed to treat
NO	nitric oxide
NOD	nucleotide-binding oligomerization domain
NOS	not otherwise specified
NOSE	Nasal Obstruction Symptom Evaluation

NP	nasal polyp
NPC	non-placebo controlled
NPS	nasal polyp score
NPx	nasopharynx
NPV	negative predictive value
NRS	numeric rating scale
NSAID	nonsteroidal anti-inflammatory drug
NSAID-ERD	nonsteroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease
NSAV	nasal/sinus air volume
NSD	nasal septal deviation
NSI	nasal saline irrigation
OMC	ostiomeatal complex
OR	odds ratio
ORS	odontogenic rhinosinusitis
OSM	oncostatin M
OTU	operational taxonomic unit
PACU	post-anesthesia care unit
PAR	perennial allergic rhinitis
PAR-2	protease activated receptor-2
PARE	pharyngeal acid reflux events
PARS	pediatric acute rhinosinusitis
PC	placebo-controlled
PCD	primary ciliary dyskinesia
PCR	polymerase chain reaction
PCRS	pediatric chronic rhinosinusitis
PDGF	platelet derived growth factor
PEA	phenyl ethyl alcohol
PEFI	peak expiratory flows index
PFTs	pulmonary function tests
PG	prostaglandin
PGIC	Patient Global Impression of Change
PICC	peripherally inserted central catheter
PID	primary immunodeficiency
PLUNC	palate, lung, and nasal epithelium clone protein
PM	particulate matter
PND	postnasal drainage
PNIF	peak nasal inspiratory flow
POSE	Perioperative Sinus Endoscopy
PPI	proton pump inhibitor
PPV	positive predictive value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRR	pattern recognition receptors
PSQI	Pittsburgh Sleep Quality Index
PVA	polyvinyl acetate
PVP1	povidone-iodine
QALY	quality-adjusted life year
QI	quality improvement
QID	four times daily
QoL	quality of life
qPCR	quantitative polymerase chair reaction
qRT-PCR	quantitative real-time polymerase chain reaction

RadESS	radical endoscopic sinus surgery
RAGE	receptor for glycalation end products
RANKL	receptor activator nuclear factor κB ligand
RANTES	regulated on activation, normal T cell expressed and secreted (aka, CCL5)
RARS	recurrent acute rhinosinusitis
R-CRS	refractory chronic rhinosinusitis
RCT	randomized controlled trial
REAH	respiratory epithelial adenomatoid hamartoma
ReSI	Reflux Symptom Index
RESS	revision endoscopic sinus surgery
RNA	ribonucleic acid
ROC	receiver-operator characteristic
RQLQ	Rhinoconjunctivitis Quality of Life Questionnaire
rRNA	ribosomal ribonucleic acid
RS	rhinosinusitis
RSDI	Rhinosinusitis Disability Index
RSI	Rhinosinusitis Symptom Inventory
RSOM	Rhinosinusitis Outcome Measure
RSV	respiratory syncytial virus
RT-PCR	real-time polymerase chain reaction
RUNX2	runt-related transcription factor 2
RV	rhinovirus
S100A	S100 Calcium Binding Protein A
SA	*Staphylococcus aureus*
SAD	specific antibody deficiency
SB	single blinded
SCC	solitary chemosensory cell
SCT	saccharine clearance time
SE	Staphylococcal enterotoxins
SE-IgE	Staphylococcal enterotoxin-specific IgE
SEM	scanning electron microscopy
SF	Short Form
SN-5	Sinus and Nasal Quality of Life Survey 5
SNAQ	Sinonasal Assessment Questionnaire
SNEC	sinonasal epithelial cell
SNOT	SinoNasal Outcome Test
SNOT-20+1	Sino-Nasal Outcomes Test-20 plus olfaction
SNP	single-nucleotide polymorphism
SP	surfactant protein
SPECT	single proton emission CT
SPG	sphenopalatine ganglion
SPINK5	serine protease inhibitor Kazal-type 5
SPLUNC1	Short palate, lung and nasal epithelium clone 1
SPT	skin prick testing
T2R	taste receptor family 2
T2R38	taste receptor 2 member 38 protein
TAS2R38	taste receptor 2 member 38 gene
TC CFTR	triple combination cystic fibrosis transmembrane conductance regulator therapy (elexacaftor-tezacaftor-ivacaftor)
TFF	trefoil factor family
TGF	transforming growth factor

Th	T helper
TID	three times daily
TIVA	total intravenous anesthesia
TIW	three times weekly
TLR	toll-like receptor
TMEM16A	transmembrane member 16A
TNF	tumor necrosis factor
TNSS	total nasal symptom score
TP-1	thymostimulin
TPS	total polyp score
TRE	target registration error
TSLP	thymic stromal lymphopoietin
TSST	toxic shock syndrome toxin
UB	unblinbded
UES	upper esophageal sphincter
UPSIT	University of Pennsylvania Smell Identification Test
URI	upper respiratory infection
US FDA	United States Food and Drug Administration
VAS	visual analog scale
VCAM	vascular cell adhesion molecule
VD3	Vitamin D
VDR	vitamin D receptor
VEGF	vascular endothelial growth factor
VGDFFiM	vapors, gases, dusts, fumes, fibers, and mists
ZO-1	zona occludin-1

II.B. Possible Adverse Effects of Common Rhinosinusitis Treatments

Throughout ICAR-RS-2021, possible side effects or treatment risks of interventions are considered. In order to standardize listing of these possible side effects and treatment risks within the text, Aggregate Grade of Evidence (AGE) tables, and literature summary tables, Table II-1 defines known and typical side effects and adverse effects for commonly utilized treatment modalities that should be considered when determining policy level recommendations. Table II-1 may not include all possible risks of listed interventions.

Table II-2. Typical risks, side effects and adverse effects of common rhinosinusitis treatments*

Treatment	Possible side effects and adverse effects
Nasal saline	Nasal irritation, sneezing, cough *For high volume nasal irrigations:* ear fullness, irrigation fluid transmission to middle ear
Systemic/oral corticosteroids	Increased appetite, weight gain, fluid retention, gastritis, sleep disturbance, restlessness, anxiety, depression, aggressiveness, psychosis, adrenal suppression, cataracts, glaucoma, hair/skin changes, easy bruising, acne, delayed wound healing, muscle weakness, change in body fat distribution, immunosuppression, hypertension, hyperglycemia/diabetes, osteopenia, osteoporosis, avascular necrosis of the hip, kidney stones

Nasal corticosteroids	Discomfort/burning, epistaxis, dryness, crusting, foul taste, headache, sore throat
Systemic/oral antibiotics	Gastrointestinal upset, bloating, stomach cramping, nausea, vomiting, diarrhea, fungal infections, drug-drug interactions, photosensitivity, bone/teeth staining, allergic reaction, anaphylaxis, *C. difficile* colitis, hepatic impairment, renal impairment, antibiotic resistance, ototoxicity *For macrolides:* cardiotoxicity
Oral decongestants	Irritability, anxiety, restlessness, sleep disturbance, hypertension, tachycardia, heart palpitations, drug-drug interactions, tremors *In young children:* tachycardia, seizures, loss of consciousness, death
Nasal decongestants	Discomfort/burning, dependency, dryness, increased congestion, rhinitis medicamentosa, hypertension, anxiety, tremors
Oral antihistamines	Drowsiness, headache, dry mucous membranes, restlessness, anxiety, insomnia, tachyphylaxis, urinary retention,
Nasal antihistamines	Discomfort/burning, drowsiness, dizziness, epistaxis, dryness, crusting, foul taste, headache, sore throat, sneezing, nausea
Leukotriene antagonists	Behavior/mood alterations, agitation, depression, irritability, hallucinations, tremor, suicidal thoughts and behavior *For zileuton:* hepatotoxicity
Nasal/sinus surgery	Bleeding, infection, scarring, septal perforation, lacrimal system injury, hyposmia/anosmia, vision changes or blindness, orbital injury, cerebrospinal fluid leak, intracranial injury, major vascular injury *Table XII-26 contains an in-depth list of ESS complications.*

*May not include all possible risks of listed interventions

III. Introduction

"The body of knowledge regarding rhinosinusitis (RS) continues to expand." With that statement, we introduced the 2016 International Consensus Statement on Allergy and Rhinology: Rhinosinusitis (ICAR-RS-2016).[1] Five years later, this statement rings truer than ever. We noted that in the 15 years preceding ICAR-RS-2016, 12,847 articles had been published on the subject of RS. In the 5 years since, an additional 6,952 have been published and the annual number continues to grow (Figure III-1). This ICAR-RS-2021 evaluates and summarizes this evidence into a consumable format for the busy clinician to stay up to date on the latest advances in the field of RS.

The expanded knowledge contained in those nearly 7,000 publications mandates an update of the ICAR-RS-2016 document. This 2021 ICAR-RS document incorporates this additional evidence and, where necessary, adjusts recommendations based on the updated evidence. Every one of the more than 140 ICAR-RS-2016 sections have been updated and more than forty additional sections have been added in order to keep up with new areas of investigation as well.

While the evidence has grown dramatically, the basic methodology for this ICAR document has remained largely unchanged. The ICAR-RS-2016 statement adapted the "evidence-based review with recommendations" framework set down by Rudmik and Smith in 2011, which uses a blinded online iterative review process.[4] Internationally recognized experts contributed to the document as both section authors and blinded reviewers of others' sections, culminating in an overall consensus statement that all authors agreed upon. During the creation of ICAR-RS-2016, we found this method robustly emphasized the published, peer-reviewed evidence and minimized bias and the influence of expert opinion. Five years later we remain convinced of its effectiveness. Moreover, since the publication of ICAR-RS-2016, this same methodology has been successfully applied to the subjects of allergic rhinitis and skull base surgery, with others in development.[135,136]

In comparing this ICAR-RS-2021 update to the 2016 document, the reader will see there have been significant advances in our understanding of pathophysiology and treatment of RS. One area that will stand out, however, is this document's continued division of CRS into CRSwNP and CRSsNP. Our understanding of CRS clearly shows that division into these two phenotypes is artificially simplistic and that multiple underlying endotypes end up manifesting as these downstream groupings. Despite our collective rapid advancements in the mechanistic aspects of CRS, we have not arrived at the point where we are able to classify CRS into universally agreed upon, well-defined endotypes. Moreover, nearly all the evidence published to date relies upon the CRSw/sNP paradigm, rather than endotyping. Clearly, we must move beyond this overly simplistic paradigm in order to provide our patients with more precise and personalized treatments. The authors collectively call upon themselves and the entire rhinologic community to quickly produce the necessary evidence, agreement, and then prospective research to move past the CRSw/sNP paradigm.

Any consensus statement on so wide ranging a topic as RS will have limitations and this one is no different. The recommendations are only as good as the evidence that underlies them, which again is found to be variable and, in some areas, sorely lacking. Thus, the recommendations offered in this document should be interpreted in the context of the robustness of the evidence upon which they are based and the populations of patients studied to produce the evidence. The practice of evidence-based medicine (EBM) requires the clinician to have the best available evidence, and then combine that with individual expertise and the patient's condition, values, and expectations (Figure III-2).[137] This ICAR-RS-2021 document provides only the best available evidence. It may not, therefore, be seen as a "cookbook" for providing care for the RS patient.

While the recommendations in this document are based on the best available evidence, they do not define standard of care nor do they define medical necessity. Health care providers or any others should not assume that a particular treatment is or is not indicated in an individual patient solely based on what is written in this or any other similar document. The recommendations are based on the evidence from the study populations, which may or may not apply to the particular patient the provider is treating. The clinician must recognize the tremendous variability both between subsets of RS and within each subset, especially CRS. Patients with CRS can be mildly symptomatic or highly symptomatic; they may have limited findings on endoscopy or CT or complete involvement of all sinuses; they may be presenting for diagnosis and management for the first time or after many failed treatments or even after multiple surgeries. To assume that one patient is just like the other – and to apply the findings in this document under such an assumption – is not consistent with the practice of evidence-based medicine.

Lastly, the recommendations herein should not be viewed as static. As new and stronger evidence emerges, they will necessarily have to undergo reevaluation and possibly change. This ICAR-RS-2021 update of the ICAR-RS-2016 represents just such a reevaluation. We continue to hope that this summary will guide all who care for RS patients, empowering all of us with the knowledge we need to provide our patients with the best possible outcome.

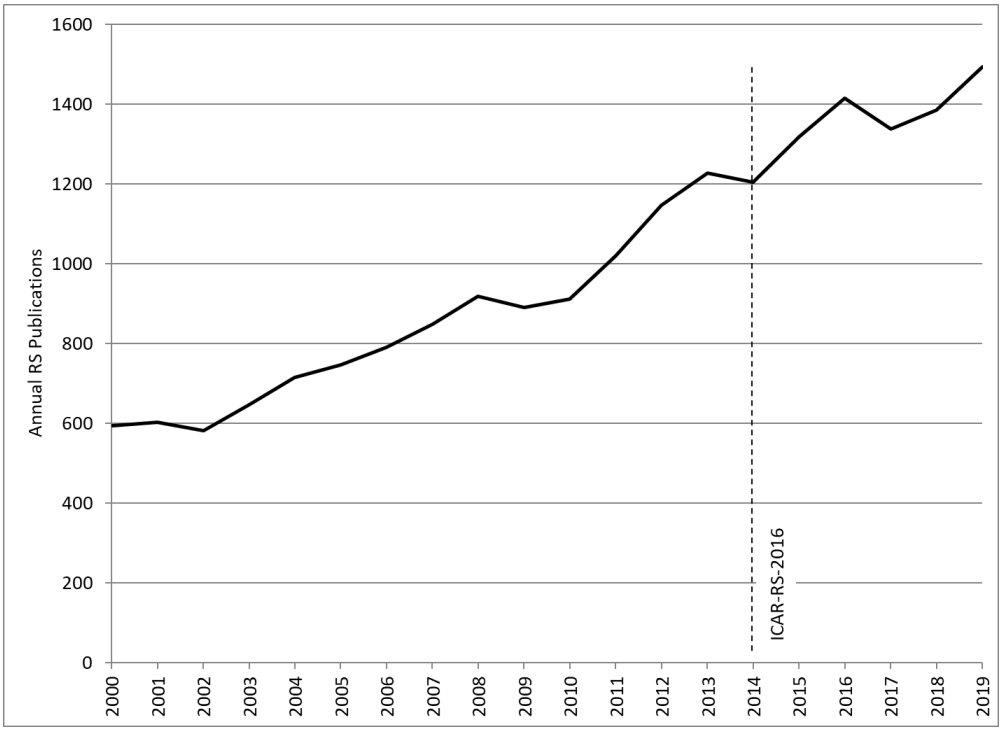


Figure III-1. Results of a PubMed search for the terms “sinusitis” or “rhinosinusitis” by year of publication. The dotted line represents the cut-off for evidence considered in the ICAR-RS-2016 document. Nearly 7,000 RS articles have been published since that time.

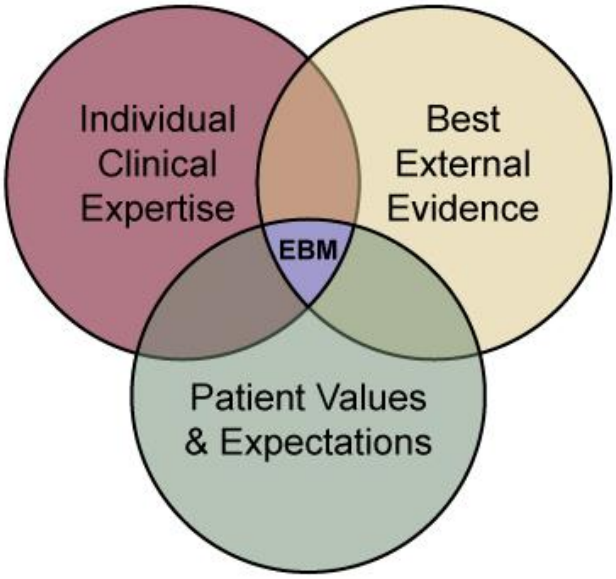


Figure III-2. The practice of evidence-based medicine. Adapted from: Armstrong EC, Harnessing new technologies while preserving basic values, *Fam Sys and Health*. 21:351-355, 2003.

IV. Methods

IV.A. Topic Development

The methodology for this consensus statement largely followed that of the ICAR-RS-2016 document. The ICAR documents are developed and written so as to have the maximal reliance on published evidence and minimal impact from expert opinion and other biases. To this end the method of writing an evidence-based review with recommendations which was described by Rudmik and Smith in 2011 has been adapted.[4] The subject of RS was initially divided into over 180 topics, more than 40 more topics than ICAR-RS-2016, reflecting the growth of evidence in the field of RS. Each topic was then assigned to a senior author who is a recognized expert in the field of rhinology, and specifically in RS. Some topics had significant evidence but did not lend themselves to providing a recommendation, such as those addressing diagnosis and pathogenesis, and these were assigned as evidence-based reviews (EBRs) without recommendations. Other topics had sufficient evidence for not only a systematic review but also for the creation of recommendations based on the evidence and were assigned as EBRs with recommendations (EBRRs). A few of the topics had little significant evidence and were assigned as literature reviews. For topics included in ICAR-RS-2016, authors were asked to update the content and recommendations based on evidence published since ICAR-RS-2016.

To provide the content for each topic, a systematic review of the literature for each topic using Ovid MEDLINE® (1947-July 2019), EMBASE (1974- July 2019) and Cochrane Review databases was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standardized guidelines.[138] The search began by identifying any previously published systematic reviews or guidelines pertaining to the assigned topic. Since clinical recommendations are best supported by randomized controlled trials (RCTs), the search focused on identifying these studies to provide the strongest level of evidence (LOE). Reference lists of all identified studies were examined to ensure all relevant studies were captured. If the authors felt as though a non-English study should be included in the review, the paper was appropriately translated to minimize the risk of missing important data during the development of recommendations.[138] In some more rapidly evolving

topics, additional studies were included after the July 2019 searches where they significantly affected the understanding on the topic and/or impacted recommendations.

To ensure complete transparency of the evidence in EBR and EBRR sections, all included studies were presented in a standardized table format and the quality of each study was evaluated to receive a level based on the Oxford levels of evidence (from level 1 to 5, Table IV-1).[139] Adjustments were made to the level of evidence due to the quality of each study based on accepted standards and changes were made transparent in the text of the section and/or the evidence summary table.[140] At the completion of the systematic review and research quality evaluation for each clinical topic, an aggregate grade of evidence was produced for the topic based on the guidelines from the American Academy of Pediatrics (AAP) Steering Committee on Quality Improvement and Management (Table IV-2).[141]

Table IV-1. Levels of evidence

Level	Diagnosis	Therapy/Prevention/Etiology
1	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Systematic review of randomized trials or *n*-of-1 trials
2	Individual cross sectional studies with consistently applied reference standard and blinding	Randomized trial or observational study with dramatic effect
3	Cohort study or control arm of randomized trial*	Non-randomized controlled cohort/follow-up study**
4	Case-series or case control studies, or poor quality prognostic cohort study**	Case-series, case-control studies, or historically controlled studies**
5	Not applicable	Mechanism-based reasoning

* Level may be graded down on the basis of study design, inconsistency between studies, indirectness of evidence, imprecision, or because the absolute effect size is very small; level may be graded up if there is a large or very large effect size or if a significant dose-response relationship is demonstrated.
** As always, a systematic review is generally better than an individual study.

Table IV-2. Aggregate grade of evidence

Grade	**Research Quality**
A	Well-designed RCTs
B	RCTs with minor limitations Overwhelming consistent evidence from observational studies
C	Observational studies (case control and cohort design)
D	Expert opinion Case reports Reasoning from first principles

For topics with more limited evidence, the EBR process was completed with the evidence table. For those topics with sufficient evidence to produce a recommendation (*i.e.*, an EBRR), a recommendation using the AAP guidelines was produced. It is important to note that each evidence-based recommendation took into account the aggregate grade of evidence along with the *balance of benefit, harm, and costs* (Table IV-3).

Table IV-3. AAP defined strategy for recommendation development[141]

Evidence Quality	**Preponderance of Benefit over Harm**	**Balance of Benefit and Harm**	**Preponderance of Harm over Benefit**
A. Well-designed RCT's	*Strong Recommendation*	*Option*	*Strong Recommendation Against*
B. RCT's with minor limitations; Overwhelmingly consistent evidence from observational studies	*Recommendation*		
C. Observational studies (case control and cohort design)			*Recommendation Against*
D. Expert opinion, Case reports, Reasoning from first principles	*Option*	*No Recommendation*	

Determination of LOE for an individual publication is not always straightforward. In certain cases, individual studies do not fit neatly into one of the Oxford LOE categories. Oxford LOE grading has also changed over time, which adds complexity to evidence grading. This issue is more complicated for certain documents that employ advanced evidence searches and systematic literature evaluation to create recommendations, practice parameters, and guidelines (e.g., Clinical Practice Guidelines, ICAR, EPOS, etc). For such publications, even methodological experts may disagree on evidence levels – some seeing these documents as systematic reviews with higher evidence levels, and others seeing them as consensus statements/expert opinion or guidelines and assign lower evidence levels. Moreover, these large reviews assess diferent levels of evidence for different subsections. As a result, when these large reviews are cited for particular subjects, they may be graded as different LOEs. In ICAR-RS-2021, we have honored the author/reviewer LOE grading for each individual topic in order to remain true to the ICAR methodology. Therefore, the reader may notice some fluctuation in LOE for certain frequently-cited documents throughout the ICAR text, depending on the individual topic area.

Following the development of the initial topic LR, EBR, or EBRR, the manuscript underwent a 2-stage online iterative review process using two blinded independent reviewers. The purpose of these steps was to evaluate the completeness of the identified literature and ensure any recommendations were appropriate. Following the first review, the reviewer was unblinded and any necessary changes were agreed upon by both reviewer and initial authors. The topic content was then reviewed by a second blinded reviewer and changes were agreed upon by the initial authors and all reviewers.

IV.B. ICAR-RS Statement Development

Following the completion of all topics, the principal editors (RRO, TTK, and TLS) compiled them into one ICAR-RS statement. This draft document was then reviewed by all contributing authors. The final ICAR-RS manuscript was produced once consensus was reached among all authors regarding the literature and final recommendations.

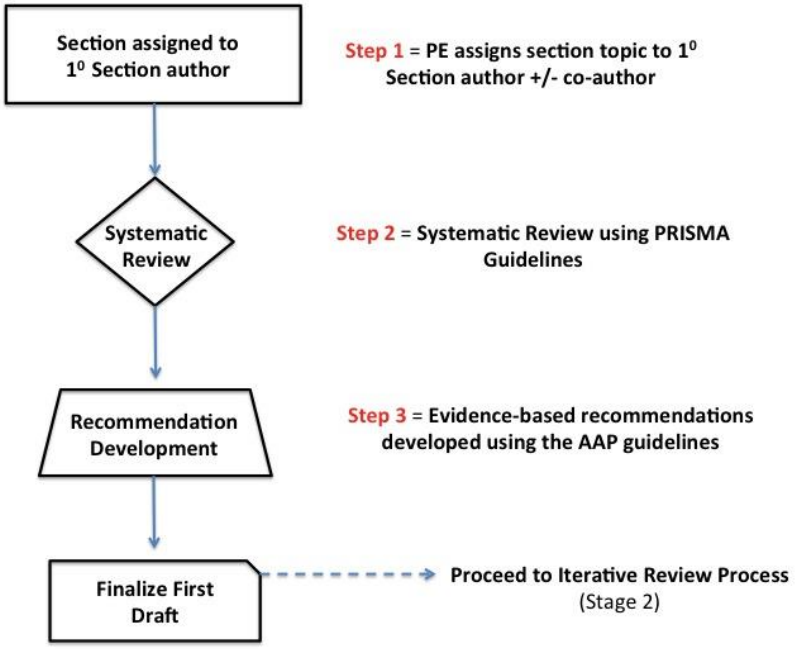


Figure IV-1. Topic Development (PE=principal editor; 1^0=primary).

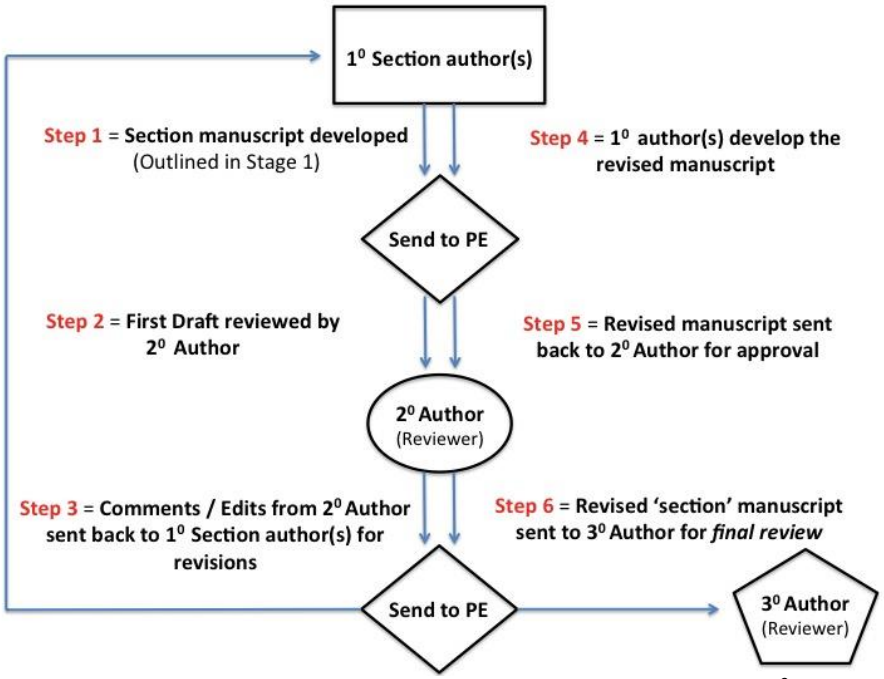


Figure IV-2. Topic EBRR Iterative Review Process (PE=principal editor; 1^0=primary; 2^0=secondary; 3^0=Tertiary).

V. Definitions

V.A. Acute Rhinosinusitis (ARS)

The definition of acute rhinosinusitis (ARS) is based on expert opinion and consensus. There has been no significant change to this definition in the recent literature.[1] ARS is defined as sinonasal inflammation lasting less than four weeks associated with the sudden onset of symptoms.[31,88,142,143] Symptoms must include purulent nasal drainage (anterior/posterior) and nasal blockage/obstruction/congestion or facial pain/pressure or both.[31,88,142]

The distinction between viral ARS and bacterial ARS (ABRS) is largely based on illness pattern and duration, with viral illnesses lasting fewer than 10 days.[31,88,142] The American Academy of Otolaryngology – Head and Neck Surgery defines ABRS as: a) symptoms/signs of ARS without evidence of improvement for at least 10 days beyond the onset of symptoms, or b) symptoms/ signs of ARS that worsen within 10 days after an initial improvement (double worsening).[88] The European Position Paper on Rhinosinusitis and Nasal Polyposis (EPOS) also recognizes *acute post-viral rhinosinusitis,* defined as worsening symptoms after five days, or persistent symptoms after 10 days.[31] Fever, elevated erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP) are also included in their diagnostic criteria.[31] The Canadian guidelines define ABRS as symptoms persisting beyond 7 days.[88,142]

The definition of pediatric disease is discussed in section V.G.

Definition of Acute Rhinosinusitis
Sinonasal inflammation lasting less than 4 weeks associated with sudden onset of symptoms.
Symptoms must include:
- purulent nasal drainage (anterior/posterior) and
- nasal blockage/obstruction/congestion or facial pain/pressure or both

Definition of Acute Rhinosinusitis

Aggregate Grade of Evidence: B (Level 2: 2 studies; level 3: 5 studies; level 4: 2 studies)

Table V-1. Evidence for the definition of acute rhinosinusitis

Study	Year	LOE	Study Design	Study Groups	Conclusion
Fokkens[31]	2012	2	Systematic Review	Rhinosinusitis patients	Acute post-viral rhinosinusitis is defined as: increase of symptoms after 5 days or persistent symptoms after 10 days with less than 12 weeks duration. ABRS is suggested by the presence of at least 3 of the following symptoms/signs: discolored discharge, severe local pain, fever (>38 degrees C), elevated ESR/CRP, 'Double sickening'.

Rosenfeld[88]	2015	2	Systematic Review	Adults with ABRS	ARS symptoms include purulent nasal discharge and nasal obstruction, facial pain/pressure/fullness, or both. ABRS likely if symptoms persist without evidence of improvement for at least 10 days or symptoms worsen within 10 days after an initial improvement.
Hansen[144]	2014	3	Systematic Review	Adults with ABRS	Acute post-viral rhinosinusitis: increase of symptoms after 5 days or persistent symptoms after 10 days with less than 12 weeks duration. ABRS: At least 3 of: discolored discharge and purulent secretions, severe local pain (with unilateral predominance), fever > 38, elevated ESR/CRP, double sickening (deterioration after an initial milder phase of illness).
Hauer[145]	2014	3	Systematic Review	Adults suspected of ABRS. Either or both fever (>38.0 C) and (facial and dental) pain.	The value of fever and facial pain could not be assessed in adults with ABRS and these symptoms should not be used in clinical practice to distinguish between a bacterial and viral source
Kaplan[142]	2014	3	Systematic Review	Adults with ABRS	Diagnosis of ABRS is based on symptoms and symptom duration. Symptoms must include nasal obstruction or purulence/discharge and at least one other: facial pain/pressure, hyposmia/anosmia. ABRS is symptoms worsen in 5-7 days after initial improvement, persist for more than 7 days without improvement, or if purulence is present for 3-4 days with high fever.
Meltzer[146]	2004	3	Literature Review	Rhinosinusitis patients	ABRS probable if 2 or more major symptoms or 1 major symptom and 2 or more minor symptoms are present.
Benninger[143]	2003	3	Literature Review	Adults with ARS	A strong history suggestive of ARS includes 2 major factors or 1 major factor with 2 minor factors, or nasal purulence on exam. Fever and facial pain in the absence of nasal symptoms is not suggestive of ARS.

Lanza[147]	1997	4	Literature Review	Rhinosinusitis patients	ABRS probable if 2 or more major symptoms or 1 major symptom and 2 or more minor symptoms are present.
Shapiro[148]	1992	4	Literature Review	Rhinosinusitis patients	ABRS probable if 2 or more major symptoms or 1 major symptom and 2 or more minor symptoms are present. ABRS probable if CT or radiographic evidence of RS.

V.B. Chronic Rhinosinusitis (CRS)

Chronic rhinosinusitis (CRS) is defined as sinonasal inflammation persisting for more than 12 weeks.[1,31,88,143,146,149,150] The diagnosis is based on global consensus and has been consistent for the last three decades. Diagnosis requires a combination of subjective and objective findings. Recognized symptoms of CRS are nasal obstruction/congestion/blockage, anterior or posterior (mucopurulent) nasal drainage, loss or decreased sense of smell, and facial pressure/pain/fullness.[1,31,88,143,146,149,150] These are sometimes referred to using the mnemonic CPODS: facial Congestion/fullness, facial Pain/pressure, nasal Obstruction/blockage, nasal Drainage, and Smell dysfunction (hyposmia/anosmia).[151] Symptoms alone have high sensitivity but low specificity, which is why the symptoms must be accompanied by objective evidence of disease. Objective evidence is defined either by radiographic evidence of sinonasal inflammation or by mucopurulent mucus, edema or polyps on examination.[1,31,88,143,146,149,150]

Phenotypic subgroups, including CRSwNP and CRSsNP, are well-recognized clinical entities, as are allergic fungal rhinosinusitis (AFRS), aspirin exacerbated respiratory disease (AERD), and cystic fibrosis. Odontogenic sinusitis is an increasingly recognized variant of CRS. Additionally, our understanding of classification by endotype is emerging, with some research suggesting ten or more inflammatory subtypes may exist.[49] While the global definition of CRS remains stable, it is important to recognize the significant variability present within this condition.

Refer to section V.G for pediatric disease definition.

Definition of Chronic Rhinosinusitis

Sinonasal inflammation persisting for more than 12 weeks, with a combination of at least two of the following symptoms and confirmed by endoscopic or radiographic findings:
- nasal obstruction/congestion/blockage
- anterior or posterior (mucopurulent) nasal drainage
- loss or decreased sense of smell
- facial pressure/pain/fullness

Definition of Chronic Rhinosinusitis

Aggregate Grade of Evidence: B (Level 1: 1 studies; level 2: 4 studies; level 3: 2 studies)

Table V-2. Evidence for the definition of chronic rhinosinusitis

Study	Year	LOE	Study Design	Study Groups	Conclusion
Kaper[150]	2019	1	Systematic Review	Consensus statements on CRS	Consensus on endoscopic and computed tomography in the diagnosis of CRS. Symptoms present for minimum of 12 weeks. Majority of international diagnosis rely on combination of symptoms and objective findings.
Orlandi[1]	2016	2	Systematic Review	Patients with CRS	Diagnosis of CRS based on 2 of CPODS symptoms for minimum of 12 weeks with objective evidence of inflammation.*
Rosenfeld[88]	2015	2	Systematic Review	Patients with CRS	Diagnosis of CRS based on 2 of CPODS symptoms for minimum of 12 weeks with objective evidence of inflammation.*
Bachert[149]	2014	2	Systematic Review	Patients with CRS	Consistent adoption of "rhinosinusitis" versus "sinusitis" in the literature. Diagnosis of CRS based on 2 of CPODS symptoms for minimum of 12 weeks with objective evidence of inflammation.*
Fokkens[31]	2012	2	Systematic Review	Patients with CRS	Diagnosis of CRS based on 2 of CPODS symptoms for minimum of 12 weeks with objective evidence of inflammation.*
Meltzer[146]	2004	3	Systematic Review	Patients with CRS	Diagnosis of CRS based on sinonasal symptoms for minimum of 12 weeks with objective evidence of inflammation.*
Benninger[143]	2003	3	Systematic Review	Patients with CRS	Strong history for diagnosis of CRS based on 2 major, 1 major plus 2 minor or purulence on nasal exam

*Objective findings: positive nasal endoscopy (purulence, polyps, or edema) or positive imaging findings consisting of inflammation or mucosal changes within the sinuses

V.B.1. CRS: Disease or Syndrome?

In view of different clinical phenotypes and inflammatory endotypes, CRS can be considered an umbrella term covering several inflammatory disease states of the sinonasal cavities.[1] The challenge for every clinician is to characterize and describe the clinical phenotype and endotype as well as possible, within the possibilities of diagnostic work-up in a routine clinical setting.[152] Given the multitude of underlying etiologic factors, it is not surprising to find multiple phenotypes or mixtures of phenotypes in CRS.

On the basis of history and nasal endoscopic and/or CT scan findings, CRS is generally divided into CRSsNP and CRSwNP. Apart from the latter two major clinical phenotypes, other phenotypes relate to the variety of presenting symptoms in CRS patients and the presence or absence of concomitant bronchial disease.[26,153,154] Recognizable clinical phenotypes include aspirin-exacerbated respiratory disease, fungal rhinosinusitis (RS), of which there are several subtypes, and CRS associated with other systemic diseases including vasculitic, rheumatologic, and genetic processes. Also severity, level of control and response to treatment differ amongst CRS patients, which are all key determinants of the phenotype.[155]

A wide range of inflammatory patterns may act together with mucociliary and/or structural abnormalities to give rise to the development of CRS. The multifactorial etiology of CRS, involving genetic factors, environmental influences, occupational factors, infection, allergy, immune dysfunction, and systemic diseases, has led to definition of endotypes of disease.[154] CRS has been classified into different inflammatory clusters, including Th1 driven or neutrophilic inflammation, Th2 driven or eosinophilic inflammation, neurogenic, epithelial, and mixed endotypes.[156]

In view of different clinical phenotypes and inflammatory endotypes of CRS, this condition encompasses multiple disease states of the sinonasal cavities. In a single CRS patient, pin-pointing the different etiologic factors responsible for the development of the disease remains the challenge for the future.

V.B.2. CRS: Endotyping

Phenotypic stratification of CRS based on the presence (CRSwNP) or absence (CRSsNP) of nasal polyps may be overly simplistic for the purposes of treatment selection, as there is substantial inflammatory heterogeneity within each conventionally phenotyped category as well as a continuum of pathophysiology between CRSwNP and CRSsNP patients.[41-45] Aided by advances in molecular and statistical techniques, several research groups have worked toward defining endotypes, or biological inflammatory subtypes of CRS, based on mucus and tissue biomarkers.[46-50] This effort has been further accelerated by the development of several novel therapeutic monoclonal antibodies targeting potential inflammatory mediators of CRS,[56-58] as there is a need to determine which patients will benefit from these treatments.[14] Overall, endotype research in CRS has drawn inspiration from a similar effort in the management of asthma,[51] which has led to improved understanding of the underlying pathophysiology and better outcomes in treatment refractory patients.[52,53]

Along with the advances in understanding endotypes, some of the nomenclature around inflammatory patterns has evolved. Th1, Th2, and Th17 inflammatory patterns are now often referred to as Type 1, Type 2, and Type 3 patterns, respectively (Figure I-2). Much of the evidence reviewed throughout this ICAR-RS-2021 document uses the previous terminology while some includes the newer classification pattern. Inasmuch as this nomenclature is in evolution, both are used throughout the document.

A number of studies have identified putative endotypes in phenotypically heterogenous CRS populations using unsupervised cluster analysis of tissue and mucus biomarkers. The first study defining potential endotypes of CRS was published in 2016 by Tomassen *et al.*[49] The study assayed inflammatory markers in 173 European patients and reported 10 distinct CRS clusters or endotypes using 11 tissue biomarkers. Six clusters were noted to have high tissue levels of type 2 inflammatory markers (Th2). These 6 clusters were IL-5 positive, with a "moderate" IL-5 group characterized by

mixed CRSsNP/CRSwNP with asthma phenotype, and a "high" IL-5 group predominantly consisting of patients with nasal polyposis and asthma that also had concomitant high levels of *S. aureus* specific IgE. Within the four low Th2 clusters, IL-5 was negative, and most groups were CRSsNP without asthma, with one cluster demonstrating a mixed phenotype and high IL-17 levels. Overall, about 56% of patients clustered into a moderate/high Th2 endotype, including a majority of patients with CRSwNP.

Divekar *et al.*[47] utilized a commercial immunoassay of 41 inflammatory markers and MPO to examine sinonasal tissue from 26 patients. The study identified three inflammatory endotypes: a Th1/Th17 group, a Th2 dominant group, and a growth factor dominant group. In a larger cohort of 90 CRS patients, Turner *et al.*[46] identified 6 disease clusters using a panel of 18 soluble mucus cytokines. This study offered a less invasive method of endotyping than studies using tissue, and the authors proposed that mucus could be used for longitudinal analysis.[157] The majority of CRS patients had elevation of Th2 markers, but only a limited subset had a Th2 dominant profile. Two clusters were noted to have a relatively low inflammatory burden comparable with controls, with a final group demonstrating a high level of IL-1b and more neutrophilic disease. Another study conducted by Liao *et al.*[48] in 246 Chinese patients identified 7 unique clusters using tissue inflammatory biomarkers as well as clinical variables. In contrast to studies in Western countries, only 13% of Chinese patients with CRSwNP had a type 2 dominant inflammatory signature, and neutrophilic inflammation groups were associated with a higher percentage of "difficult-to-treat" patients. A similarly subdued pattern of type 2 inflammation relative to studies in the U.S. and Europe was noted in an endotyping study of 93 CRS patients in New Zealand.[50] Notably, this study also incorporated bacterial community data to assess variances between endotypes, but did not find any significant differences.

Despite these promising initial findings, endotypic classifications are still in their infancy. Although there is a lack of consensus on the use of biomarkers for endotyping, it is evident that Th1, Th2 and Th3 markers (also referred to as type 1, 2 and 17 immune reactions) should be included. Additionally, there is increasing evidence that differentiating type 2 versus non-type 2 endotypes is clinically meaningful, as type 2 immune reactions are associated with asthma,[49] an increased risk of recurrence after surgery,[55] and are the basis for the use of innovative type 2 biologics.[56-60] There appear to be substantial global variations in the distribution of CRS endotypes as well, likely driven by undefined environmental factors which merit further study.[54] Finally, treatment stratifications based on endotypes have been proposed, but prospective data associating endotypes with long-term disease outcomes remain limited.[48,59] As work in this field evolves, however, it is likely that future evidence-based recommendation statements will increasingly utilize classification schemes based on endotypes.

CRS Endotyping

Aggregate Grade of Evidence: C (Level 4: 5 studies)

Table V-3. Studies identifying putative CRS endotypes

Study	Year	LOE	Study Design	Study Groups	Main Biomarkers	Endotypes
Tomassen[4][9]	2016	4	Case-control	173 patients, 89 controls in Europe	Tissue: IL-5,IFN-γ, IL-17A,TNF-α,IL-22, IL1β,IL-6,IL-8,ECP, MPO,TGF-β, IgE, SE-IgE, Albumin	10 total: 6 IL-5 positive, 4 IL-5 negative. IL-5+ clusters with higher % of polyps and asthma; with high IL-5 clusters notable for high levels of SE-IgE.
Divekar[47]	2017	4	Case-control	26 patients, 6 controls in the U.S.	Tissue: IL-1Rα, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-12p40 and 70, IL-13, IL-15, IL-17A, IFN-γ, MCP, MIP, G-CSF, GM-CSF, PDGF, FGF, EGF, MDC, Fractalkine, GRO, FLT3, IP10, IFN, VEGF, Eotaxin	3 total: Th1/Th17, Th2, and PDGF/VEGF dominant
Liao[48]	2018	4	Case-control	246 patients, 16 controls in China	Tissue: IL-1β, IL-1Rα, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8. IL-9. IL-10, IL-12. IL-13, IL-15, IL-17A, IL-22, IL-25, Eotaxin, bFGF, C-CSF, IFN-γ, IP-10, MCP-1, MIP-1a, PDGF-BB, MIP-1b, TNF-α, VEGF, IgG1-4, IgM, IgE, eosinophils, neutrophils, plasma cells, mononuclear cells, mucosal glands	7 total; 1 – Th2 dominant, eosinophilic CRS. 2 – mild inflammation, atopic CRS. 3 – high IL-1b, IL-6, IL-8, neutrophilic CRS. 4 – High IgG3, mild inflammation, moderate eosinophils. 5 – High IL-10, IL-17A. 6 – Moderate IL-8, neutrophilic, difficult to treat. 7 – Mild inflammatory load with nasal polyps.

Turner[46]	2018	4	Case-control	90 patients, 17 controls in the U.S.	Mucus: IL-1β, IL-2, IL-3. IL-4. IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-13, IL-17A, Eotaxin, IFN-γ, TNFα, RANTES	6 total; Low inflammation: 1 –high IL-5 2 –low IL-1b and IL-12 High inflammation: 3 – Th2 dominant; high IL-5, 6, 9, 10, 13, eotaxin, IFN-γ 4 – Th2 dominant; high IL-2, IL-3, IL-4, IL-17 5 – low IL-5, high IL-1b 6 – high IL-4, 5, 6, 7, 8, 12, 13, 17-A, 21, TNFa
Hoggard[50]	2018	4	Case-control	93 patients, 17 controls in New Zealand	Tissue: $CD3^+$ T cells, $CD20^+$ B cells, $CD68^+$ macrophages, plasma cells, eosinophils, neutrophils, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-13, IL-17A, IFN-γ, and TNF	8 total; 1 – low inflammation, controls 2 – IL-17A, IFN-γ, TNFα 3 – IL-2, 4, 6, 17A, IFN-γ, TNFα 4 – IL-2, IL-10, TNF 5 – IL-8, macrophages 6 – IL-5, 6, eosinophils, neutrophils, macrophages 7 – AERD 8 – IL-6, 8, neutrophils, T cells, B-cells, macrophages

V.B.3. CRS: Unified Airway Concept and Comorbid Asthma

CRS and asthma are both common manifestations of an inflammatory process within the contiguous upper and lower airway system. The prevalence of asthma is around 25% in patients with CRS compared to 5% in the general population.[158] The etiology or pathogenic mechanisms underlying the development and progress of these two conditions are not fully understood, since both CRS and asthma are highly heterogeneous with respect to genetic background, environmental factors and the specific host reaction of the airway mucosa. However, it is well known that the upper and lower airways share continuous airway anatomy, cell and humoral immunity, and experience common stimulations and risk factors.[31] Moreover, eosinophilia and airway remodeling, two major histological hallmarks of both diseases, have been suggested as the same pathologic disease process.[159-162] Therefore, asthma and CRS are associated with one another in the concept of the unified airway.[163]

Indeed, epidemiological and clinical evidence has consistently revealed the coexistence of CRS and asthma. A number of studies have shown that CRS and asthma frequently coexist in the same patient,[20,160,164] and comorbid asthma has been associated with atopy and increased severity in CRS than controls. [165-168] CRS patients with asthma require significantly more health care for CRS and more revision sinus procedures overall than patients without asthma.[158,169] Treatment of CRS, medical or surgical, benefits concomitant asthma.[170,171] In a recent Korean population-based survey,

a history of asthma increased the risk of developing CRS up to 2.06-fold (95% CI 2.00-2.13).[172] Another cross-sectional population-based study in Iran also showed that CRS was more frequent among the participants with asthma (57.3%, OR = 2.3; 95% CI 2.1–2.5), and there was a significant association between CRS and current, early and late-onset of asthma (P < 0.001; OR = 4.4, 3.2 and 6, respectively).[173]

CRS has been postulated as a risk factor contributing to the development and severity of asthma. The presence of CRS is associated with more severe asthma symptoms, particularly cough and sputum,[174] and appears to increase the risk of exacerbations in asthmatic patients.[174,175] A random sample survey study, with over 52,000 adults aged 18-75 years in 12 European countries, showed that asthma was found to be strongly coupled with CRS appropriate symptoms (adjusted OR: 3.47; 95% CI: 3.20-3.76).[164] The reported incidence of asthma varies from 2% to 38% in patients with CRS,[165-167,169,176,177] 2-66% in CRSwNP,[159,165-167,169,176-184] and up to 68-91% in refractory CRSwNP.[160,167] Among these reports, the prevalence of asthma in patients with CRSsNP or CRSwNP appears to be lower in Asians than Caucasians.[172] In patients with CRS, the coexistence of asthma is associated with a higher incidence of CRSwNP (56%) than CRSsNP (36%).[185] Asthma is often underdiagnosed in CRS patients but is more common in patients who subsequently are diagnosed with CRS.[17,30,165,183,186]

The "unified airway" concept suggest that treatment of one disease could potentially improve the coexisting condition. The association of comorbid asthma with lower QoL, more atopy and increased risk of revision surgery in CRS is related to the clinical status (*e.g.*, exacerbation) of asthma.[187-191] Endoscopic sinus surgery for CRS in asthmatic patients has been reported to improve multiple clinical asthma parameters with improved overall asthma control, reduced frequency of asthma attacks and number of hospitalizations, and decreased use of oral and inhaled corticosteroids.[189-192] Early ESS in the disease continuum also helped patients with recalcitrant CRS to decrease the risk of developing asthma.[97]

Asthma as a CRS Comorbidity

Aggregate Grade of Evidence: C (Level 3: 14 studies; levellevel 4: 2 studies)

Table V-4. Evidence for asthma as a CRS comorbidity

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Kaper[193]	2020	3	Population-based survey	56,825 adults patients with RS in the Netherlands	CRS and its comorbidities	29% had co-morbidities (usually COPD/asthma).
Kim[172]	2020	3	Population-based survey	14,762 patients with CRS and 29,524 patients without CRS in Korea	CRS and its comorbidities	The adjusted HR of asthma was 2.06 in CRS versus non-CRS patients.
Nyennhuis [194]	2020	3	Population-based survey	28,508 patients with asthma	Asthma and its comorbidities	Patients seen by specialists versus those by primary care physician had more comorbid RS (p<0.01).
Ostovar [173]	2019	3	Cross-sectional, population-based study	5201 patients in the province of Bushehr, Iran	The prevalence of asthma by using the (GA2LEN)	CRS was more frequent among the participants with

				completed the GA2LEN questionnaire	questionnaire and examine its association with CRS	asthma and there was a significant association between CRS and current, early and late-onset of asthma.
Phillips[30]	2019	3	Cross-sectional study	Patients with CRS (N = 209)	Characteristics associated with exacerbations in CRS	An exacerbation-prone phenotype was positively associated with comorbid asthma.
Sella [188]	2019	3	Nonconcurrent cohort study	201 patients with CRS who underwent ESS were followed for an average period of 12 years in a nonconcurrent cohort.	Factors associated with recurrence of CRS	Asthma was the only factor that was significantly related to recurrence both in patients with CRSsNP (HR: 5.54) and in patients with CRSwNP (HR: 3.27).
Smith[189]	2019	3	Population-based survey	A total of 29,934 patients were identified, with a mean length of follow-up of 9.7 years.	Long-term revision rates for ESS	Comorbid asthma, increased the risk of requiring revision surgery.
Campbell [190]	2018	3	Cross-sectional cohort study	350 participants with CRS were recruited (28.3% were asthmatic)	Determine if asthma is associated with lower QoL in CRS	The association of comorbid asthma with lower QoL in CRS is related to the clinical status (*e.g.*, control) of asthma.
Khan [195]	2018	3	Multicenter cross-sectional case-control study	237 CRSsNP; 445 CRSwNP; 187 controls	Impact of CRS on HRQoL, comorbidity incidence, objective disease measures, and medical and surgical treatments were collected	Asthma was significantly more frequent in CRS patients.
Philpott [196]	2018	3	Prospective case-control multicenter study	Included 1470 study participants: 221 controls, 553 CRSsNP, 651 CRSwNP and 45 allergic fungal rhinosinusitis (AFRS)	Identify the prevalence of asthma	The prevalence of asthma was 9.95, 21.16, 46.9 and 73.3% in the four groups respectively.
Won [197]	2018	3	Cross-sectional	A cross-sectional	To investigate	CRSwNP was

			study	data set of 17,506 adult participants (≥18 years old) in the Korean National Health and Nutrition Examination Survey	relationships between CRSwNP and asthma characteristics	significantly associated with adult-onset asthma or late-onset asthma (onset after 40 years), whereas CRS without nasal polyps was related to childhood-onset asthma or early-onset asthma (onset before 40 years).
Schlosser [192]	2017	3	Prospective, multi-center, observational cohort study	86 patients with CRS comorbid asthma	The impact of CRS or ESS upon asthma QoL and asthma control using validated outcome metrics	Patients undergoing ESS reported improved miniAQLQ and ACT scores at 6 months postoperatively.
Stevens [198]	2017	3	Case series study	459 patients with CRSwNP alone, 412 with both CRSwNP and asthma, 171 with AERD, and 300 with asthma only	Compared the clinical characteristics of patients with AERD to those with CRSwNP alone, asthma alone, or both CRSwNP and asthma.	Atopy was significantly more prevalent in patients with asthma (85%) than in CRSwNP patients without asthma (66%).
Chen [199]	2016	3	Population-based survey	81,462 patients with a mean ± SD follow-up period of 5.8 ± 2.4 years.	Association between asthma and the risk of CRS	Asthma was associated with increased risks of CRSwNP and CRSsNP.
Benjamin [185]	2019	4	Retrospective clinical data review study	507 patients with CRSsNP and 874 with CRSwNP	Demographics, comorbid conditions, and radiologic sinus severity	The prevalence of asthma was 36% in CRSsNP versus 56% in CRSwNP. Comorbid asthma was associated with severity in CRSwNP.
Hoehle [200]	2018	4	Retrospective review	572 CRS patients in a single rhinology clinic	Prevalence of CRS characteristics and their associations with CRS symptom severity	Prevalence of asthma was 27.8%, and more severe CRS symptomatology was associated with comorbid asthma.

V.C. Recurrent Acute Rhinosinusitis (RARS)

Recurrent acute rhinosinusitis (RARS) is defined as four or more episodes of ARS (defined in section V.A) per year with distinct symptom-free periods between acute episodes.[1] During symptom free periods, patients typically have normal endoscopic or radiologic examinations. The threshold of four episodes in a year was selected to reduce the risk of misdiagnosing or over diagnosing RARS.[201] However, some literature has suggested that five episodes per year should be considered as a threshold to maximize the value of surgical intervention.[202,203]

There is growing concern surrounding the over or misdiagnosis of RARS. Acute exacerbations characterized by symptoms are not necessarily associated with objective (endoscopic or radiologic) evidence of sinonasal inflammation.[204,205] Surgical appropriateness criteria for RARS suggest a diagnosis should include at least four episodes per year as well as objective evidence (endoscopic or radiologic) of an acute exacerbation.[206] There are also conflicting reports on whether sinonasal anatomic variations are associated with or predispose patients to RARS.[207,208] Despite the growing literature, RARS is still an under-examined entity and has been identified as one of the top priorities for rhinology-specific quality improvement in the future.[209]

Definition of Recurrent Acute Rhinosinusitis:
Four or more episodes of ARS per year with distinct symptom-free periods between acute episodes.

The definition of pediatric disease is discussed in section V.G.

Definition of Recurrent Acute Rhinosinusitis

Aggregate Grade of Evidence: C (Level 3: 2 studies; level 4: 4 studies)

Table V-5. Evidence for the definition of recurrent acute rhinosinusitis

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoints	Conclusion
Beswick[204]	2019	3	Retrospective outcomes research	RARS patients	SNOT-22 scores Endoscopy scores	Acute episodes (AE) associated with worse QoL scores. Patients with AE had worse endoscopy scores than patients not in AE. Not all patients with subjective AE had endoscopic evidence of sinonasal inflammation. In light of absent objective evidence of sinonasal inflammation, RARS AE may be over-diagnosed.
Costa[208]	2015	3	Cohort study/cross-over study	RARS-medical therapy RARS-surgical RARS-cross over	SNOT-22 scores CT anatomic variation	RARS patients can benefit from both medical and surgical treatment options. Surgical treatment may have greater symptomatic improvement vs medical treatment. Endoscopic and CT scores are

						low in RARS patients and do not necessarily correlate with response to medical therapy or need for surgery. Infraorbital ethmoid cell, concha bullosa, accessory ostia, reduced infundibular width associated with RARS.
Rudmik[206]	2019	4	RAND-UCLA Appropriateness methodology	RARS clinical scenarios	Appropriateness for ESS	Appropriateness criteria for surgery include 4 or more annual episodes of ABRS, objective evidence of at least 1 acute episode by endoscopy or CT, failed trial or INCS, or presence of significant productivity losses.
Barham[205]	2017	4	Case Series	Suspected RARS	RARS diagnosis	CT findings rarely abnormal during acute exacerbations of symptoms. RARS rare diagnosis. Given possible alternate diagnoses and lack of CT evidence of sinonasal inflammation, antibiotics and surgery inappropriate in this population.
Rudmik[209]	2017	4	RAND modified Delphi methodology	N/A	Quality indicator prioritized ranking	Within top 2 disease category priorities for rhinology-specific quality improvement
Loftus[207]	2016	4	Case Series	RARS patients	CT anatomic variation	Anatomic variants are not a risk factor for RARS. No correlation between presence of specific anatomic variants and severity of inflammatory changes on CT.

V.D. Acute Exacerbation of Chronic Rhinosinusitis

An acute exacerbation of chronic rhinosinusitis (AECRS) is described as an acute worsening of pre-existing CRS symptoms, with subsequent return to baseline symptoms spontaneously or following treatment.[1] In the previous ICAR:RS, a definition of AECRS was proposed which included worsening nasal blockage, congestion or stuffiness, nasal discharge or postnasal drip, facial pain, pressure or headache, and reduction in sense of smell. This may be accompanied by endoscopic evidence of purulence, crusting, edema or polyps supporting the diagnosis of AECRS in a patient previously diagnosed with CRS.[1] Since these criteria were introduced, there has been limited work on AECRS. There have been three studies utilizing the suggested definition from the 2016 ICAR document, including one literature review and two cohort studies which used but did not assess the definition.[29,210,211]

One additional study examined three different definitions of AECRS.[212] Of these, the most sensitive definition was a worsening in sinonasal symptoms ≥1 week in duration. The definition with the highest positive predictive value was a worsening in sinonasal symptoms ≥1 week and green/yellow discharge.[212] While the literature on AECRS is growing, additional research is needed to create a precise consensus definition of AECRS.

Definition of Acute Exacerbation of Chronic Rhinosinusitis:
An acute worsening of pre-existing CRS symptoms, with subsequent return to baseline symptoms spontaneously or following treatment.

Definition of Acute Exacerbation of Chronic Rhinosinusitis

Aggregate Grade of Evidence: D (Level 3: 1 study; level 4: 2 studies)

Table V-6. Evidence for the definition of acute exacerbation of chronic rhinosinusitis

Study	Year	LOE	Study Design	Study Groups	Clinical End-point	Conclusion
Kuiper[212]	2018	3	Prospective cohort study, survey based	Patient with CRS	Survey responses every 4 months with self-reported exacerbations Three definitions of AECRS operationalized and assessed	The most sensitive definition of AECRS was a worsening in sinonasal symptoms ≥1 week in duration. The definition with the highest positive predictive value of AECRS was a worsening in sinonasal symptoms ≥1 week and green/yellow discharge.
Wu[210]	2019	4	Literature Review	N/A	Definition of AECRS	AECRS sudden worsening of symptoms in a patient previously diagnosed with CRS, with a return to baseline symptoms after treatment. Consensus definition and diagnostic criterion are still lacking.
Orlandi[1]	2016	4	Literature Review (AECRS section)	N/A	Definition of AECRS	AECRS includes worsening nasal blockage, congestion or stuffiness, nasal discharge or postnasal drip, facial pain, pressure or headache, and reduction in sense of smell. AECRS may be accompanied by purulence, crusting, edema or polyps on endoscopic exam.

V.E. Subacute Rhinosinusitis

Subacute RS is a term that has been used to describe clinical presentations of sinonasal disease that fall between the timeframe of ARS and CRS (symptoms of 4 to 12 weeks duration).[1,143] There continue to be few clinical reports on which to delineate these patients as a distinct clinical entity and those that do define the process based on consensus. The previous iteration of ICAR:RS included subacute RS, which has been largely absent from consensus statements and guidelines for several years.[1] It is thought that patients who fall into this group either have slow to resolve ARS or an early presentation of evolving CRS. In some papers, subacute RS is defined in part as resolving completely following treatment.[143] However, it is possible that these poorly defined patients may be experiencing the onset of CRS and may go on to develop persistent symptoms.

Of note, in the European Position Paper on Rhinosinusitis and Nasal Polyps 2012, the term subacute RS was eliminated as the number of patients who fell into this category was extremely small, and were thought to represent other disease processes.[31]

Of the few studies that have set out to examine subacute RS in the recent literature, the duration of patient symptoms is unclear, as are the patient outcomes.[213,214] Unfortunately, there is no additional clarity on the definition or classification of subacute RS in these studies. Use of this definition or classification should be limited until a better understanding of this condition is achieved.

The definition of pediatric disease is discussed in section V.G.

Definition of Subacute Rhinosinusitis

Aggregate Grade of Evidence: D (Level 2: 1 study against; level 3: 1 study; level 4: 3 studies)

Table V-7. Evidence for the definition of subacute rhinosinusitis

Study	Year	LOE	Study Design	Study Groups	Clinical End-point	Conclusion
Fokkens[31]	2012	2	Systematic Review	N/A	Definition of subacute RS	Subacute rhinosinusitis terminology removed, as thought to represent other (ARS or CRS) disease processes
Benninger[143]	2003	3	Systematic Review	Patients with CRS	Definition of subacute RS	Patients with a strong history for diagnosis based on 2 major, 1 major plus 2 minor or purulence on nasal exam AND Symptoms resolve completely after treatment
Hsu[214]	2018	4	Prospective cohort study	Patients with sinonasal symptoms for less than 12 weeks*	Ability to diagnose ARS with sinus ultrasound	Sinus ultrasound and endoscopy had moderate agreement in diagnosing ARS.

Bahtouee[213]	2017	4	Prospective cohort study	Patients with sinonasal symptoms for 3 to 12 weeks**	Efficacy of Acetylcysteine in the treatment of subacute RS	No added benefit from acetylcysteine.
Orlandi[1]	2016	4	Expert Opinion (Subacute RS Section)	N/A	Definition of subacute RS	Patients with sinonasal symptoms lasting 4 to 12 weeks in duration.

*not restricted to a strict definition of subacute RS, outcomes unknown after treatment, duration of symptoms not reported
**not restricted to a strict definition of subacute RS, duration of symptoms not reported

V.F. Coexistence of Rhinitis with Sinusitis: What Evidence Supports Using the Term "Rhinosinusitis"?

Historically, there has been a broad debate on the best terminology to represent the inflammatory conditions that may afflict the paranasal sinuses. Since 1996, the Task Force on Rhinosinusitis (sponsored by the AAO-HNS) has suggested the replacement of the term “sinusitis” by “rhinosinusitis”.[215] The main argument is that the majority of inflammatory diseases affect both the paranasal mucosa and the nose, in variable degrees of pathological involvement and clinical presentation.

However, the evidence to support the terminology “rhinosinusitis” instead of “sinusitis” is still scant in the literature. Gwaltney *et al.*[216] evaluated 31 self-diagnosed patients with common cold using computed tomography (CT). They demonstrated that within 96 hours after onset of clinical manifestation, most patients presented sinus mucosal alteration (*e.g.*, 77% of cases with thickening of the ethmoid infundibulum) and nasal mucosal lining involvement (42% of cases with nasal lateral wall thickening, 22% with inferior turbinate engorgement). This study was the first to demonstrate that in patients with common cold, there is a frequent simultaneous involvement of the nose and sinus mucosa. Another piece of evidence was introduced by Bhattacharrya,[217] who compared the density of inflammatory cells in the ethmoidal mucosa with the nasal septum mucosa in patients with CRS. Bhattacharya showed that the density of eosinophils in the ethmoid correlates with the number of cells in the nasal septum, but not with other inflammatory cells or the total number of cells. Finally, Van Crombruggen et. al.[218] studied the levels of inflammatory markers in the inferior turbinate mucosa plus the mucosa of the ethmoid sinus and nasal polyps from the same individual diagnosed with CRS, comparing results with healthy controls. CRS patients demonstrated increased inflammatory mediators in both sinus and inferior turbinate mucosa in relation to controls.

After the recommendation of the Task Force, many guidelines involving multidisciplinary specialties have recognized and adopted the term rhinosinusitis.[31,149,151] However, there are still some critiques on the universal use of rhinosinusitis for all types of sinusitis.[219] The main criticism is that rhinitis and sinusitis are just two different diseases which coexist in most cases, but do not necessarily reflect the same pathophysiological process.

In the clinical practice, there is a wide range of clinical presentations regarding rhinitis leading to sinusitis and vice-versa. It is a fact that ‘rhinosinusitis’ reflects the majority of cases because it shows the coexistence and a continuum of the inflammatory process affecting the paranasal sinuses and the nose. Nevertheless, it is important to recognize that the term “sinusitis” still may be the most appropriate for some conditions, such as fungus ball, odontogenic sinusitis, or mucopyocele.

V.G. Definition Differences for Pediatric Rhinosinusitis

Pediatric ARS (PARS) is defined as the new onset of two or more of the following symptoms in children that occur for less than 12 weeks: nasal obstruction, discolored nasal discharge, and cough.[31] In bacterial PARS, the most commonly isolated pathogens are similar to adult ARS (*S. pneumoniae, H. influenzae*, and *M. catarrhalis)*. Isolation of *S. aureus* occurs in adults but is rare in children.[88]

Pediatric CRS (PCRS) is defined as two or more of the following symptoms that are present in children for 12 or more weeks: nasal obstruction, nasal discharge, facial pain/pressure, and cough. Further, the diagnosis of PCRS requires either nasal obstruction or nasal discharge to be present as well as endoscopic or radiologic confirmation of sinonasal inflammation.[31] Nasal polyps in children are diagnosed similarly to adults.[31,88]

Subacute RS in the pediatric population had been previously defined as RS lasting from 4-12 weeks,[220,221] however EPOS and AAO-HNS guidelines note that this classification is no longer required and RS lasting up to 12 weeks in children is classified as PARS [31,88]. RARS has been described in children but is not a commonly employed classification.[222]

Diagnoses of PARS and PCRS rely more heavily on cough than in the adult population. In a study of 154 pediatric patients with RS, cough was the most common principal symptom, noted by 54% of subjects with PARS and 45% of subjects with PCRS.[223] Another study of 50 patients with PCRS found that 40% had nocturnal or daytime cough, with other symptoms being more common.[224] Prior evidence also suggests that cough is among the four most common symptoms in children with rhinosinusitis.[225]

Defintion of Pediatric Acute Rhinosinusitis
Sinonasal inflammation for less than 12 weeks in children with two or more of the following symptoms: - nasal obstruction - discolored nasal discharge - cough

Definition of Pediatric Chronic Rhinosinusitis
Sinonasal inflammation for 12 or more weeks in children with two or more of the following symptoms: - nasal obstruction - nasal discharge - facial pain/pressure - cough The diagnosis of PCRS requires either nasal obstruction or nasal discharge to be present as well as endoscopic or radiologic confirmation of sinonasal inflammation.

Cough as a Presenting Symptom in Pediatric Chronic Rhinosinusitis
Aggregate Grade of Evidence: C (Level 4: 3 studies).

Table V-8. Evidence for the definition of pediatric rhinosinusitis

Study	Year	LOE	Study Design	Study Groups	Clinical End-point	Conclusion
Ilhan[224]	2012	4	Case series	50 children with PCRS	Symptoms Allergy testing and serum studies testing	Nasal obstruction was the most common symptoms (90%), followed by nasal drainage (48-62%) and cough (40%).
Poachanukoon[223]	2012	4	Case series	103 children with RS for < 4 weeks (PARS). 51 children with RS for > 8 weeks (PCRS)	Main symptoms Examination findings Treatment details	Cough followed by rhinorrhea were the most common symptoms in both groups and the prevalence of these symptoms did not differ between groups.
Rachelefsky[225]	1978	4	Case series	70 children with chronic respiratory symptoms	History and physical exam Sinus radiographs CBC, Ig, ESR	Subjects with abnormal sinus radiographs had more frequent cough, sore throat, and postnasal drainage than those with normal radiographs. Serum studies did not differ based on radiographic inflammation.

VI. General Concepts of Rhinosinusitis.

VI.A. Societal Burden of Rhinosinusitis

VI.A.1. Direct Costs of Rhinosinusitis

Rhinosinusitis (both acute and chronic forms) affects approximately 12-15.2% of the adult population in the United States, annually.[9,87] This prevalence exceeds that of other common respiratory conditions such as hay fever (8.9%), acute asthma (3.8%) and chronic bronchitis (4.8%).[87] The direct costs of managing acute and chronic RS are thought to exceed USD$11 billion per year.[88] These figures, however, do not distinguish between acute and chronic forms of RS and further stratification is presented below. Furthermore, how we define "cost" vs. "charges" has been difficult to extrapolate from the current literature as cost has been loosely defined as the difference between the true costs and published costs from a payer perspective which are actually "charges" from the perspective of healthcare systems.

Acute Bacterial Rhinosinusitis (ABRS)

Direct cost estimates attributable to the diagnosis and treatment of ABRS are sparse in the literature. The disease burden of ABRS has been primarily assessed using utilization measures such as office visits and antibiotic prescription rates. For example, there are approximately 5.1 million ambulatory office visits per year with a coded diagnosis of ARS and approximately 86% of these visits result in an oral antibiotic prescription.[226] ABRS is the fifth most common diagnosis associated with antibiotic therapy.[88] Data regarding the direct costs of ABRS are limited, although studies from Europe suggest direct costs of ABRS of €97 to €266 (approximately USD$115-USD$315) *per episode*, depending on treatment model and antibiotic resistance rates.[227,228]

Chronic Rhinosinusitis (CRS)

Analyses of the direct costs of CRS may include the costs for both recurrent acute rhinosinusitis (RARS) and the traditional form of CRS. The direct costs of CRS have been ascertained on multiple levels based on single-institutional cohorts, analyses of claims databases and analyses of nationally representative healthcare cost data sets. For example, individual patient cohorts, most commonly from academic medical centers, have quantified the direct medical costs at USD$921-1220 per patient-year.[229,230] These data may, however, may represent a bias towards more diseased patient populations and also rely on some extrapolation of costs.

More recent claims-based studies have provided more refined and generalized cost data for CRS. In a study of 4.4 million patients, Bhattacharyya et. al. identified 4460 patients undergoing ESS.[89] The healthcare costs for CRS in the year leading up to ESS (therefore, medically refractory patients) were USD$2449, USD$1789 of which were attributable to facility and physicians' charges. Finally, a population-based assessment has determined incremental costs of CRS relative to those without CRS. Bhattacharyya determined significantly increased *incremental* healthcare utilization costs of USD$772, USD$346 and USD$397 for total healthcare expenses, office-based expenditures in prescription expenditures ($p \leq 0.01$ versus those adults without CRS) for CRS in a nationally representative healthcare economics database.[90] A similar population-based assessment suggested that these incremental costs may be rising to as much as USD$1152 per afflicted individual annually.[231] From an international perspective, also utilizing a national healthcare insurance database, Chung, *et al.*, found that patients with CRS diagnoses incurred significantly higher outpatient costs (USD$953 versus USD$665; $p<0.001$) and total healthcare costs (USD$1318 versus USD$946; $p<0.001$).[91] Examining CRSwNP specifically, Bhattacharyya *et al.* found an incremental increase in annual direct medical costs of USD$1067 per patient versus controls without CRS.[92] Although less commonly studied, recent claims-based data indicate an annual direct cost of

treatment attributable to RARS of USD$1091 per patient-year.[232] With the increasing availability of over-the-counter and adjunctive remedies for the management of CRS, the patient's out-of-pocket expenses is significant. For example, Yip *et al.* derived a yearly out-of-pocket expense in a Canadian cohort of patients of approximately USD$614 per year.[233] The current overall direct cost burden of CRS in the United States has been estimated at USD$10-13 billion per year.[234]

Surgical Costs in CRS

In CRS cases found to be medically refractory, endoscopic sinus surgery (ESS) has proven to be a clinically and economically effective management option, but the overall costs of ESS do warrant consideration.[235,236] In a systematic review, Smith *et al.* reviewed 10 studies specific to ESS and found that the cost of outpatient ESS ranges from $8200 to $10,500 per procedure in 2014 USD. In a large claims-based study, Purcell *et al.* found that although the mean surgical cost of ESS was USD$7,782, direct healthcare costs decreased steadily in the 3 years after surgery with greater than half of the patients resolving direct costs attributable to CRS.[93] Cost for ESS may vary widely and the component extent of surgery (*e.g.*, anterior ESS versus full ESS) as well as the geographic location of the procedure influence this.[237] Finally, costs of ESS will also vary based on international geography and healthcare system. For example, Au and Rudmik found that the overall cost for routine outpatient ESS approximated $3510 in Canadian dollars from the perspective of the Canadian government payer.[238]

VI.A.2. Indirect Costs of Rhinosinusitis

The indirect healthcare costs of RS include societal costs related to absence from work (absenteeism), decreased work productivity while at work (presenteeism) and other forms of lost productivity (*e.g.*, leisure time lost). Such costs can be measured in terms of time, such as workdays lost, or in terms of dollar equivalents based on prevailing wages. In a nationally based household study, among the 15.2% of those reporting acute or chronic RS annually, 5.7 workdays were missed versus 3.7 for those without RS ($p<0.001$).[87] This translates into 61.2 million potential workdays missed per year among adults in the United States and an estimated work productivity loss of USD$3.79 billion per year.[87,94] Data for presenteeism and other forms of lost productivity due to RS as a whole are sparse, but data for several subtypes of RS are available.

Acute Bacterial Rhinosinusitis (ABRS)

Data for the indirect costs of ABRS are somewhat limited, with most data coming from control arms of interventional studies for ABRS. Recently, Spanish investigators found the indirect cost of an ABRS episode to range from €224-€439 (approximately USD$264-USD$520) depending on treatment intervention.[239] If patients are assumed to be absent from work during the symptomatic days of an ABRS episode, the indirect costs increase to USD$747-USD$820, depending on whether antibiotic treatment is offered.[94]

Chronic Rhinosinusitis (CRS)

The indirect cost burden of CRS is substantial and relates to the underlying severity of the CRS. A recent national healthcare expenditure database investigation found that patients with CRS experienced 1.0±0.4 incremental workdays lost per year due to CRS.[240] This figure includes both non-refractory and refractory patients and directly compares those with and without CRS diagnoses. Examining CRS cohorts presenting specifically for disease management, larger costs are noted. European investigators found 57% of CRS patients reported absenteeism from work due to CRS.[241] In patients with relatively limited CRS planning balloon dilatation, Stankiewicz *et al.* found proportions of time lost with absenteeism, presenteeism and productivity loss of 6.5%, 36.2% and 38.3%, respectively via a validated work specific survey.[242]

Several other recent cohort studies have quantified the temporal and monetary productivity losses associated with CRS. Chowdhury *et al.* found mean annual productivity costs of USD$11,820 per patient with an additional USD$8000-USD$12,000 in incremental losses with comorbid immunodeficiency, tobacco use or steroid dependency.[243] Smith *et al.* investigated CRS-related facial pain and productivity losses and found that facial pain had a strong correlation with presenteeism, which is a main driver of productivity losses and indirect costs associated with CRS, with an overall lost productivity at USD$20,300 per patient per year.[244] In a multi-institutional study from rhinology clinics, Rudmik *et al.* found mean annual rates of absenteeism to be 24.6 days and presenteeism to be 38.8 days, with an overall annual productivity cost of USD$10,077 per patient.[245] Yip *et al.* found that employed Canadian patients demonstrated an average days lost of 12.9 days due to CRS symptoms, 3.3 days for medical appointments, and 2.4 workdays for emergency department visits. Furthermore, even in patients undergoing active continued medical management for CRS, work-related productivity losses approximate USD$4510 per 90 days.[246]

The indirect costs of CRS are not only work-related. Stankiewicz identified a 40.0% rate of impairment of activity with CRS and Bhattacharyya determined activity, work, social and cognitive limitations in 13.3%, 12.0% 9.0% and 6.0%, respectively. [240,242] In a comprehensive review, DeConde and Soler found that the indirect costs related to decreased productivity from CRS were estimated at USD$12.8 billion per year in the US.[14]

Recurrent acute rhinosinusitis (RARS)

The indirect costs of RARS primarily relate to workdays lost and productivity decreases due to the acute phase of each episode of RS. Although relatively limited RARS data are available, investigators found an average of 4.4 workdays missed per year specifically due to RARS.[247] Economic studies of RARS have identified absenteeism and presenteeism rates of 1.7 and 0.66 days per acute episode, respectively.[203] Steele *et al.* noted that RARS patients reported at baseline 12.6 days that were "missed or impacted due to sinus-related symptoms" in the 90 days prior to assessment. Interestingly, these losses were similar to those reported by patients with CRSsNP (11.7 days).[248]

VI.B. Individual Burden of Rhinosinusitis

By definition, patients with CRS will suffer with some combination of cardinal sinonasal symptoms, including nasal congestion, nasal drainage, facial pressure/pain, and loss of smell. However, the impact of CRS often extends beyond the sinonasal region and can have profound effects on functional well-being and general health-related quality of life (QoL). Numerous studies have explored the burden of CRS using either general health-related QoL or health-state utility scores and compared these findings to scores from patients with other chronic diseases[62,65,68]. Health-state utility scores are particularly useful for comparing the burden of different diseases because these instruments measure disease impacts using a single, common metric. Using transformations of the Short Form 6D instrument (SF-6D), health states of 230 patients with CRS were found to average 0.65 (0=death, 1=perfect health), a valuation that was worse than what has been reported for congestive heart failure, chronic obstructive pulmonary disorder, and Parkinson's disease.[62] Similar studies have been performed showing severe impairment in general QoL and wellbeing using the Short-Form 36 (SF-36) and Euroqol 5 Dimension (EQD-5) questionnaires.[63-65] When responses of CRS patients are examined in detail, the most common extra-sinus disease manifestations include fatigue and bodily pain, sleep dysfunction, cognitive function, and depression. Importantly, these extra-sinus manifestations are often the drivers of overall health-state utility scores and patient decision-making[66].[65,67,68]

Severe fatigue is commonly reported by patients with CRS. A systematic review with meta-analysis, including data on 3427 patients from 28 studies, examined fatigue in patients with CRS.[69] The baseline median prevalence of fatigue was 54%, ranging from 11-73% across studies. Another systemic review with meta-analysis examined bodily pain in 11 studies with 1019 patients.[249] Using primarily the SF-36 instrument, pooled mean bodily pain scores were 0.89 standard deviations below national or local population norms ($p<0.001$), exceeding bodily pain scores reported in patient populations aged 25 years older. Both fatigue and bodily pain were shown to significantly improve after sinus surgery, with combined effects sizes of 0.77 (95% CI: 0.59-0.95) for fatigue and 0.55 (95%CI: 0.45-0.64) for bodily pain.

Poor sleep quality is a frequent complaint of patients with CRS and this impact has been the focus of recent investigations. Using the PSQI, subjective sleep quality was assessed in a multi-institutional cohort of 268 patients with CRS.[70] The PSQI is a self-reported questionnaire (range: 0-21 with higher scores indicating worse sleep) measuring sleep quality and disturbance over the preceding 1-month period. The mean PSQI score in this group was 9.4, with 75% reporting "poor" sleep based on accepted cut-offs (*i.e.*, abnormal is >5). In this group, PSQI scores significantly correlated with sinus-specific QoL scores on both the SNOT-22 and RSDI instruments ($r=0.55$ and $r=0.53$ respectively).[71,72] Similarly, a large population-based study in Europe found that sleep problems were 50-90% more common among subjects with CRS as compared with the general population[73]. A recent multi-institutional, case-control study explored objective sleep changes, finding that patients with CRS have increased number of awakenings during a night's sleep, increased rapid eye movement sleep latency, and spent a greater portion of the night snoring at >40 dB[250]. Potential mechanisms of sleep dysfunction in CRS include alterations in nasal airflow and direct effects of antisomnogenic cytokines, but these hypotheses remain speculative and further research is required to understand the association between CRS and sleep.[251]

The impact of CRS on cognitive function is a newer area of inquiry. A case-control study found that patients with CRS report significantly worse scores on the Cognitive Failures Questionnaire as compared with controls[74]. Additionally, CRS patients had worse simple reaction time scores compared to controls on computerized neurocognitive testing, a difference that persisted regardless of polyp status. Since this initial report, several studies have found improvements in patient-reported and objective cognitive function after both medical and surgical treatment of CRS[75-77].

Another prominent factor that impacts overall QoL and wellbeing in patients with CRS is the increased prevalence of depression. A systematic review found prevalence rates for depression in CRS ranging from 11-40%.[78-84] This wide range likely reflects differences in patient populations and the diagnostic accuracy for depression (*i.e.*, patient-report, physician diagnosis, validated questionnaire). Regardless, the frequency of depression in patients with CRS is above population norms of between 5-10% with a recent population study from Asia estimating an adjusted hazard ratio of 1.56 (95% CI: 1.43–1.70).[85,86] The comorbid presence of depression is associated with worse sinus-specific and general QoL compared to CRS patients who are not depressed.[80,81,83] Not surprisingly, those CRS patients with depression have higher healthcare utilization, including increased antibiotic usage and physician visits, as well as more missed workdays than CRS patients without this comorbidity.[82,252] A number of studies have examined the impact of depression on outcomes after sinus surgery.[78,80,81,83] Universally, patients with comorbid depression and CRS have worse sinus-specific QoL at both baseline and postoperative time points compared to those without depression even after controlling for other factors. Importantly, however, patients with depression do appear to have a similar degree of overall improvement after surgery compared to those without depression. Further studies are required to understand whether depression is simply a common comorbid disease or whether the presence of CRS contributes to depression.

VI.C. Disease Measurement

In both clinical practice and research, CRS is frequently characterized with clinical evaluation and patient based assessment, including endoscopic examinations, radiologic studies, and patient-reported, disease-specific QoL assessments. These data are integrated to establish the diagnosis of CRS, guide intervention, and assess treatment outcomes. Interestingly, objective endoscopic and radiographic findings have not been shown to correlate strongly with subjective, patient-reported outcomes. Rather than a weakness of these measures, it more reflects that different aspects of the disease are being measured. In the assessment and treatment of CRS, it is important to quantify both objective findings and how the patient's QoL is affected.

A hallmark of both diagnosis and post-treatment disease monitoring in CRS is the endoscopic examination. Multiple grading systems such as the Lund Kennedy, modifications thereof, the Perioperative Sinus Endoscopy (POSE), and the Davos nasal polyp score have been created in an attempt to standardize results of this examination.[253-257] Inter-rater and test-retest reliability varies depending on the domain assessed (polyp, discharge, crusting, etc.) and the specific scoring system.[258] These endoscopic scoring systems typically correlate only weakly with QoL measures.[259,260] However, the correlation between certain endoscopic (polyps, edema) and QoL subdomains (rhinological symptoms) is stronger than overall aggregate scores.[261] CT is also widely used clinically in the diagnosis of CRS. Similar to endoscopy, findings are often abstracted with various scoring systems such as the Lund Mackay, but correlation with QoL measures and patient symptoms is limited. [262-264] One radiographic finding, neo-osteogenesis, has been found to correlate with other objective measures of disease severity (endoscopic score, olfactory function) as well as diminished improvement following intervention for CRS.[265] Sinonasal inflammation is paramount to the diagnosis of CRS. Objective assessment with standardized reporting is necessary both clinically and in research.

Numerous patient-reported, disease-specific QoL assessments such as the SNOT-22, RSDI, and Chronic Sinusitis Survey (CSS) can be used individually or in conjunction with other disease-, or health-related outcome measures to assess patient QoL.[266-268] Individual measures may be designed to assess a patients' physical symptoms while others measure emotional wellbeing, productivity, or other domains. With a range of lengths, they represent varying degrees of survey burden which can impact patient experience and clinical workflow. Overall, patients' responses on these tools can assist with evaluation of disease impact, decision to pursue surgery and quantification of treatment outcomes.[269,270]

Objective findings of sinonasal inflammation with nasal endoscopy and CT are essential for the diagnosis of CRS and treatment planning. Disease-specific QoL is the primary clinically relevant outcome measure that drives patient decision making. Assessment of both, with reliable and valid measures, is key for the diagnosis and management of CRS. In the future, more fundamental objective measures of pathophysiology such as genetic, microbiome, or immune function may better predict QoL outcomes.

Table VI-1. Common rhinosinusitis disease measurement tools

	Abbreviation		Score Range	MCID	Reference
Patient Reported QoL Tools					
22-item Sinonasal Outcome Test	SNOT-22		0 – 110	8.9, 12*	71,266,271
Chronic Sinusitis Survey	CSS		0 – 100	9.75	64
Rhinosinusitis Disability Index	RSDI		0 – 120	10.35	72
Endoscopic Tools					
Lund-Kennedy	LK		0 – 10**	-	253
Modified Lund-Kennedy	mLK		0 – 6**	-	272
Nasal Polyp Score	NPS		0 – 3**	-	257
Radiographic Tools					
Lund Mackay	LM		0 – 12**	-	262

*Several observational studies have used different treatment cohorts to evaluate MCID values for the SNOT-22. A change in total SNOT-22 score of 8.9 and 12 have been defined as the MCID among patients receiving surgical versus medical therapy, respectively.

**Each nasal cavity is scored independently.

VI.D. CRS Quality Metrics

There is a dearth of evidence regarding quality metrics for assessment of physician practice patterns for CRS. While some RS-specific quality metrics have been developed, none have been tested or shown to improve patient outcomes or alter physician practices. The majority of these metrics appear to either be used for reporting to the Merit-based Incentive Payment System (MIPS) of the Centers for Medicare and Medicaid Services (CMS), or are not tracked at all. All currently available metrics are process metrics, which serve to only provide data on the actions providers take rather than how patients fare as a result of those actions. For example, in 2018 the American Academy of Otolaryngology – Head and Neck Surgery (AAO-HNS), supported only one CRS-specific metric.[273] This involved measuring whether a provider ordered more than one CT sinus within a 90-day period. However, in the 2019 and 2020 quality metrics publication of the AAO-HNS, this CRS metric is no longer listed, and the only RS metrics currently supported by the AAO-HNS relate strictly to ARS.[274,275] Other measures relevant to CRS exist, and these have mostly been developed as a result of a partnership between the AAO-HNS and the American Medical Association Physician Consortium for Practice Improvement (AMA-PCPI).[276] All of these remain process metrics, and while one of these metrics deals with patient-reported outcomes measures (PROMs), it simply asks whether or not a PROM was administered.

The Quality Improvement (QI) Committee of the American Rhinologic Society compiled all available quality metrics for RS in 2017 outlining these shortcomings.[277] In that study, several quality metrics for CRS were identified as established by the AMA-PCPI and AAO-HNS. These metrics primarily focused on efficiency; and specifically assessed (1) appropriate diagnostic testing (percentage of adult CRS patients who had either a CT or nasal endoscopy at the time or within 90 days of diagnosis), (2) unnecessary imaging (percentage of adult CRS patients who had more than 1 sinus CT within 90 days of diagnosis), and (3) QoL measurements (percentage of adult CRS patients who completed a validated QoL instrument at time of diagnosis and follow-up).[277] None of these metrics were outcomes-based RS quality metrics that evaluated patient response to treatment (*i.e.*, symptom improvement, work productivity, etc.), safety, or timeliness of care.[277] In 2018, the QI committee of the ARS developed a framework for quality measurement in the presurgical care of

CRS termed "CRS Appropriate Presurgical Algorithm (CAPA)." Based on the available evidence, the following quality metrics were supported as part of the presurgical care for CRS: (1) a guideline-based diagnosis should be verified, (2) appropriate medical management should be attempted, (3) a CT scan should be obtained, and (4) a patient-centered discussion should take place encompassing risks and benefits of available treatment options, long-term medical compliance, and patient preferences and expectations.[278] However, actual implementation and validation of this framework is still yet to be determined.

The above review highlights the need to implement outcomes-based metrics to evaluate physicians treating CRS. However, several logistical obstacles will need to be overcome before this next step becomes a reality. First, agreement would have to coalesce around a single outcome measure, or perhaps a core set of outcome metrics. Next, individual physicians would need a means of accurately and efficiently collecting individual-level patient data and submitting it to a centralized registry in a manner that safeguards patient privacy. Finally, methods would need to be developed to regularly analyze and share this data in order to provide benchmarking and inform individual physicians on how their outcomes compare to the larger group.

Table VI-2: Evidence for quality measurement of physician practices in chronic rhinosinusitis

Study	Year	LOE	Conclusions
Mattos [278]	2018	4	Defining metrics that assess key components to CRS care prior to offering surgery has the potential to further improve upon an already successful treatment paradigm, reduce unwarranted practice variation, and to ensure that patients are receiving a similar level of high-quality care.
Rudmik [277]	2017	4	The current status of quality measurement for RS has focused primarily on the quality domain of efficiency and process measures for ARS. More work is needed to develop, validate, and track outcome-based quality metrics along with CRS-specific metrics. Major gaps and challenges remain that need to be considered during the development of future metrics.

VI.E. Necessity of and Approach to Evaluating the Cost-Effectiveness of CRS Treatments

As the number and breadth of treatment options for CRS continues to expand, treating physicians are faced with increasingly complicated decisions regarding treatment choices. While factors such as clinical effectiveness and patient preference play important roles in treatment choices, the cost-effectiveness of treatments should also be considered. Cost-effectiveness analysis allows one to weigh the benefit/cost ratio of one treatment relative to an alternative option, most often using the incremental cost-effectiveness ratio (ICER) which describes the cost per additional improvement of outcome that a treatment offers over the alternative.[279] The benefit, or outcome measure, of treatment options that is often used in cost-effectiveness analysis is the quality-adjusted life year (QALY) which is defined as the additional year(s) of life gained secondary to the intervention weighted by the quality of the additional year(s).[279,280] Thus ICER is often described as cost per additional QALY. These analyses have been previously used in CRS to study ESS vs. continued medical management for medically refractory disease.[281,282] With the increasing number of therapeutic options available, more cost-effectiveness analyses are needed to determine when and for which patients new CRS treatment options should be used.

Cost-effectiveness analysis requires development of a clinical decision-making model that clearly delineates possible treatment choices such as what constitutes the alternative treatment, against which a new treatment is compared. Presently for CRS, the current standard of care treatments

include a trial of appropriate medical treatment followed by ESS for those with medically refractory disease. [281-283] However, clear definition of medical management and ESS is inherently fraught with difficulty due to complexity of what constitutes appropriate medical therapy and what is the appropriate extent of sinus surgery. While ESS has been shown to be cost-effective by multiple studies,[281,282] one recent study has found the cost-effectiveness of adding frontal sinus surgery to ESS may be questionnable.[284] These difficulties are highlighted in cost-effectiveness studies of recently-developed treatment modalities. The cost-effectiveness of steroid-eluting implants compared to non-steroid eluting implants following ESS has been reported in relation to preventing additional post-operative interventions such as provision of oral steroids or lysis of adhesions.[281,285] However, cost-effectiveness analyses of these steroid-eluting stents has not yet been performed in comparison to more realistic alternative treatments, such as no implant placement or a steroid irrigation, or by using QALYs as the outcome measure. Similarly, the cost-effectiveness of balloon sinus dilation has been studied in pediatric CRS where upfront adenoidectomy with balloon sinus dilation was found to be 0.03% more effective but with an incremental cost of USD$81,431, compared to a graduated approach starting with adenoidectomy alone.[286] These studies show that while new CRS treatments may be clinically effective, their cost-effectiveness may be affected by the clinical scenario and outcome measure considered.

Separate consideration should be given to patients with recalcitrant disease despite appropriate medical and surgical treatment, who may need further treatment such as revision surgery, in-office procedures or additional medical treatment.[1] Cost-effectiveness study of these CRS patients is nascent. The need for revision ESS is estimated to occur in 15-20% in all types of CRS[189,287] and is associated with increased health care expenditure.[288] Another treatment option for recalcitrant disease includes in-office placement of drug eluting implants.[289] Most recently, biologics have shown promising results for the treatment of recalcitrant CRS, although long term follow-up studies are ongoing.[290,291] The cost-effectiveness studies for revision surgery, implants and biologics for these CRS patients with recalcitrant disease is needed.[292]

This is particularly true for biologics which have annual costs in the tens of thousands of US dollars and studies showing an indefinite need for their use in responders. In asthma, a recent study of the cost effectiveness of biologics found that the price of these medications exceeds cost-effectiveness thresholds for willingness to pay and that the pricing would need to decrease by 60% to meet these measures.[293] It has therefore been proposed in both asthma and CRS, that to make biologics most cost-effective at their current prices, disease subtypes (*e.g.*, endotypes) must be identified which predict good response to biologic therapy and then patients must be monitored once on biologics to ensure adequate response to continue to justify the cost of treatment.[279,280,293] In this way, the need to establish cost-effectiveness for biologics may also help to drive discovery and innovation in the field of CRS to better implement personalized treatment based on the *a priori* knowledge of increased likelihood of response to biologics.

As new research, device innovation and therapies arise, physicians have a responsibility to assess the improved outcomes relative to the current standard of care and also evaluate the associated costs. The balance of these factors is needed to decide what is ultimately best for patient care while being respectful of growing health care costs. Consideration for this need is especially important now with the rapid proliferation of new treatments for CRS.

VII. Acute Rhinosinusitis (ARS)

VII.A. Incidence and Prevalence of ARS

ARS is one of the most commonly diagnosed diseases in the primary care setting, accounting for 2-10% of primary care and otolaryngology visits.[5,6] The estimated incidence of ARS ranges from 1.39%-9% annually depending on the study methodology and population being studied.[7-9]

However, ARS symptoms can overlap considerably with other URI symptoms, making an accurate diagnosis challenging.[294,295] It is estimated that adults will experience between 1-3 episodes of viral ARS per year.[9,294,295] Furthermore, the diagnostic criteria for ARS may vary depending on country, affecting the calculated prevalence and incidence of ARS between countries.[296]

While both viral and bacterial pathogens can cause ARS, the majority of cases probably begin with a viral URI. The incidence of ABRS is unknown, but it is estimated at 0.5-2.0% of all viral infections.[10] Classification of ARS into a bacterial versus nonbacterial source is clinically important in determining whether to prescribe antibiotics for treatment.[88] In patients with clinically suspected ARS, the prevalence of bacterial growth on antral puncture or endoscopically-guided cultures ranged from 31%-61.1% based on recently published meta-analyses.[297,298] However, the cohorts in these studies only included patients who sought and received medical attention, thus not capturing episodes of ARS for which patients did not seek care.

VII.B. Diagnosis of ARS

The diagnosis of ARS is clinical and based on multiple symptoms including nasal congestion or blockage, drainage or postnasal drainage (PND), and facial pressure/pain.[297,299-303] ARS may also be associated with regional upper airway symptoms such as sore throat, hoarseness, and cough, as well as non-specific systemic complaints such as malaise, fatigue, and fever.[297,303] Objective evidence of ARS on nasal endoscopy, antral puncture, or radiographic imaging (X-ray, ultrasonography, or CT) is not required for the diagnosis in uncomplicated cases.[304,305] In patients with suspected ARS based on symptoms, the prevalence of confirmed ARS through imaging, culture, or antral puncture is around 50% in adults.[297,304] Anterior rhinoscopy is recommended and may reveal evidence of inflammation, mucosal edema, and discharge.[306] Clinical decision models have been developed to diagnose ARS but lack prospective validation.[297] ESR and CRP are inflammatory markers found to be elevated during ARS, but they are not routinely used for diagnosis because of their limited specificity.[301,304,307]

Diagnosis of Acute Rhinosinusitis

Aggregate Grade of Evidence: C (Level 2: 3 studies; level 3: 2 studies; level 4: 4 studies)

Table VII-1. Evidence for diagnosis of ARS

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Ebell[297]	2019	2*	Systematic Review	ARS ABRS	Association between clinical findings and diagnosis of ARS and ABRS	Overall clinical impression and purulent secretions in the middle meatus best predict ARS. Overall clinical impression, cacosmia,

						and pain in the teeth best predict ABRS
Ebell[304]	2016	2*	Systematic Review	ARS	Association between laboratory, imaging studies and the diagnosis of ARS	Normal radiography helps rule out ARS when negative. Elevated CRP and ESR help rule in ARS when positive.
Lindbaek[301]	2002	2**	Systematic Review	ABRS ARS	Purulence on maxillary sinus tap correlated with symptoms	Purulent rhinorrhea, maxillary/dental pain, pain when bending forward, and two phases of illness correlated with presence of maxillary sinus purulence
Hansen[307]	1995	3	Prospective cohort study	Acute maxillary sinusitis	ESR, CRP association with acute maxillary sinusitis	Elevations in ESR and CRP significantly associated with acute maxillary sinusitis
Berg[303]	1988	3	Validating cohort study	Maxillary empyema No maxillary empyema	Association between sinus symptoms and empyema	High reliability of local pain, purulent rhinorrhea, especially when unilateral, with maxillary sinus empyema
Autio[305]	2016	4***	Prospective inception cohort	ARS ABRS	Association between abnormal CT findings, time course of ARS/ABRS, and symptoms	Paranasal mucosal abnormalities and occlusion of OMC are present early (2-3 days), and remain constant (9-10 days) during ARS/ABRS episode. There is a weak correlation between CT findings and symptom scores.
Autio[306]	2015	4***	Prospective inception cohort	ABRS ARS	Association between symptoms, clinical exam findings and ABRS diagnosis	Length of symptoms not associated with ABRS. Clinical exam findings of secretions in the nasal cavity, posterior pharynx, or middle meatus at 9 to 10 days associated with ABRS
Klossek[299]	2011	4	Cross sectional survey	ARS	Symptom prevalence	Most common symptoms were nasal obstruction, pain, rhinorrhea, and headache

Hueston[300]	1998	4	Retrospective case series	ARS URI	Association between symptoms and ARS diagnosis	Sinus tenderness, pressure, postnasal drainage, and discolored nasal discharge were highly associated with ARS diagnosis
* Level of evidence was downgraded because of heterogeneity of studies included. These also included many studies with a high risk for bias. ** Level of evidence was downgraded because the limited number of studies included. *** Level of evidence was downgraded because of the limited number of patients.						

VII.B.1. Establishing the Diagnosis of ARS

Acute rhinosinusitis (ARS) as a general entity is both underdiagnosed and overly treated, which can lead to missed opportunities in both providing patients with validation of their symptoms as well as non-antibiotic supportive sinus treatment.

Thus, correctly diagnosing patients with ARS is the first and most important step in correctly treating them. The diagnosis is a clinical one, based on history and examination. There are many symptoms and signs possible associated with ARS, including sneezing, malaise, fever, cough, nasal discharge, nasal obstruction, cough, sore throat and headache, however many of these are nonspecific and can also be seen in isolated nasal infection or inflammation as well as with allergy flares.[299,301,303,307-309] The three cardinal symptoms and signs that otolaryngology, rhinology and infectious disease experts have agreed upon to diagnose ARS are: up to 4 weeks of purulent nasal drainage, accompanied by nasal obstruction, facial pain/pressure/fullness, or both.[26,31,88,146,310] These cardinal symptoms and signs do not have high level of evidence backing them up but instead have been agreed upon multiple times over many years by various task forces and consensus groups. Nasal endoscopy is not necessary for diagnosis, but anterior rhinoscopy is indicated to evaluate for the nasal drainage, and other findings on rhinoscopy may include mucosal inflammation and edema.[300]

It is important to note here that nasal obstruction on its own without purulent nasal drainage is not enough for this diagnosis and facial pain or pressure on its own without purulent nasal drainage is also not enough for diagnosis. Inquiry should also be made about typical allergy symptoms such as itchy and watery eyes and nose to distinguish ARS from an allergy flare and about other syndromes such as primary headache etiologies that can cause facial pressure and pain.

Use of Clinical History and Physical Examination to Establish the Diagnosis of ARS

Aggregate Grade of Evidence: C (Level 2: 2 studies; level 3: 3 studies; level 4: 6 studies)
Benefit: Distinguish non-RS (especially non-infectious) conditions from ARS
Harm: Risk of misclassifying ARS as something else
Cost: Minimal.
Benefits-Harm Assessment: Benefit very likely to outweigh harm.
Value Judgments: Importance of avoiding inappropriate treatment, importance of decreasing delay to appropriate treatment.
Policy Level: Recommendation
Intervention: Use clinical history and physical exam to appropriately diagnose ARS, and distinguish infectious RS from other diagnoses such as allergy or primary headache syndromes.

Table VII-2. Evidence for using clinical history and physical examination to establish the diagnosis of ARS.

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Klossek [299]	2011	2	Cross-sectional survey	ARS	Symptom prevalence	Most common symptoms were nasal obstruction, pain, rhinorrhea, and headache
Lindbaek [301]	2002	2	Systematic review	ABRS ARS	Purulence on maxillary sinus tap correlated with symptoms	Purulent rhinorrhea, maxillary/dental pain, pain when bending forward, and two phases of illness correlated with presence of maxillary sinus purulence
Shaikh [309]	2013	3	Validating cohort study	ARS URI	Symptom prevalence	Mild symptoms, absence of green discharge or disturbed sleep more likely viral
Hansen [307]	1995	3	Prospective cohort study	Acute maxillary sinusitis	ESR, CRP association with acute maxillary sinusitis	Elevations in ESR and CRP significantly associated with acute maxillary sinusitis
Berg [303]	1988	3	Validating cohort study	Maxillary empyema; No maxillary empyema	Association between sinus symptoms and empyema	High reliability of local pain, purulent rhinorrhea, especially when unilateral, with maxillary sinus empyema
Arnstead [310]	2020	4	Expert consensus statement with recommendations	ARS	Defining forms of RS	Two of the four symptoms of facial pain/pressure, nasal obstruction, decreased or absent smell, or nasal discharge
Fokkens [26]	2020	4	Expert consensus statement	ARS	Defining forms of RS	2 or more symptoms of nasal obstruction and nasal drainage +/- facial pressure, +/-reduction in smell and either directly visualized or CT changes c/w ARS are diagnostic
Rosenfeld [88]	2015	4	Clinical guideline	ARS	Association between symptoms and signs and ARS	Up to 4 weeks of purulent nasal drainage, along with nasal obstruction, facial pain/pressure/fullness or both is highly diagnostic of ARS
Fokkens [31]	2012	4	Expert consensus statement	ARS	Association between symptoms and signs of ARS	2 or more symptoms of nasal obstruction and nasal drainage +/- facial pressure, +/-reduction in smell and either directly visualized or CT changes c/w ARS are

						diagnostic
Meltzer [146]	2004	4	Expert consensus statement	ARS	Defining forms of RS	Established that the sinuses are commonly involved in the "common cold" and that duration of these cold symptoms is the way to further establish diagnosis
Hueston [300]	1998	4	Retrospective case series	ARS URI	Association between symptoms and ARS diagnosis	Sinus tenderness, pressure, postnasal drainage, and discolored nasal discharge were highly associated with ARS diagnosis

Finally, radiographic imaging is not indicated for the diagnosis of ARS, unless evaluating for a complication or searching for alternative diagnosis. There are multiple studies, including a meta-analysis, demonstrating that clinical criteria had similar diagnostic accuracy, and that radiographic imaging is not cost-effective.[311-313] Figure VII-1 depicts a diagnostic algorithm for suspected ARS.

Using Radiographic Imaging to Establish the Diagnosis of ARS

Aggregate Grade of Evidence: B (Level 2: 1 study; level 3: 1 study; level 4: 2 studies)
Benefit: Avoid unnecessary radiation dose to patients, avoid cost of unnecessary test, avoid delay in diagnosis from waiting for results of unnecessary test, avoid incidental radiographic findings leading to patient concern and further testing which may or may not be warranted
Harm: Risk of delayed diagnosis if alternative underlying condition exists
Cost: Minimal.
Benefits-Harm Assessment: Benefit very likely to outweigh harm.
Value Judgments: Importance of avoiding unnecessary radiation and cost in diagnosis of ARS
Policy Level: Recommendation against obtaining imaging
Intervention: Do not use radiographic imaging studies in the diagnosis of uncomplicated ARS, instead use history and physical exam and established clinical criteria.

Figure VII-1. Algorithm for the diagnosis of ARS

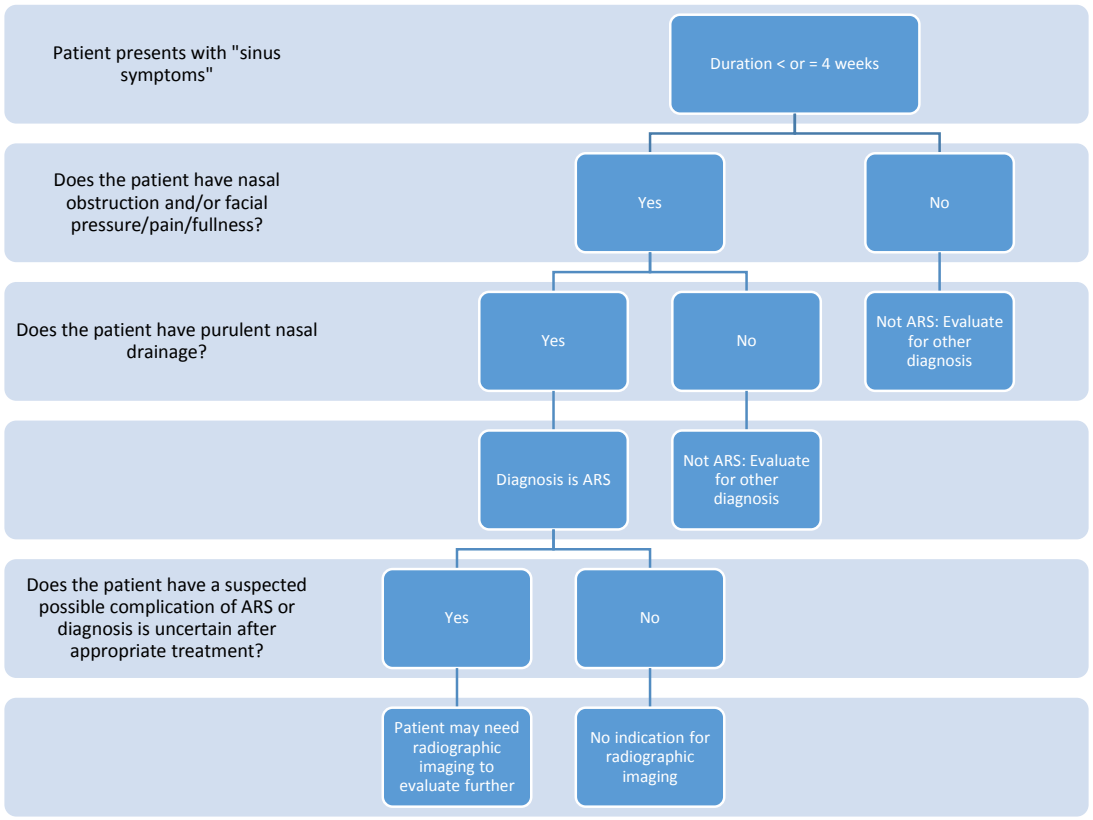


Table VII-3. Evidence for using radiographic imaging to establish the diagnosis of ARS

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Balk[313]	2001	2	Meta-analysis via modeling	Patient with 14 days of sinus symptoms with 1. No antibiotics 2. Empiric antibiotics 3. Clinical-criteria guided treatment 4. Radiography guided treatment	Cost-effectiveness	Sinus radiography treatment was never cost-effective for initial treatment in this patient population
Gwaltney [216]	1994	3	Prospective cohort study	Patients with the "common cold"	Abnormality within the sinuses on CT scan	The majority of patients with the "common cold" had multiple abnormal findings within the sinuses on CT scan, thus CT cannot distinguish between URI and ABRS.
Setzen [311]	2012	4	Clinical consensus statement	ARS	Need for CT imaging in ARS	CT imaging is not indicated in clinically diagnosed uncomplicated cases of ARS
Cornelius [312]	2013	4	Clinical consensus statement	ARS	Need for CT imaging in ARS	CT sinus is only recommended if atypical symptoms and diagnosis is uncertain or suspecting complications

VII.B.2. Differentiating Viral from Bacterial ARS

Distinguishing between bacterial and viral ARS can be challenging as the symptoms associated with these conditions greatly overlap.[145,314] Duration is thought to be a key factor differentiating ABRS from a common cold, with persistence of symptoms beyond 10 days or worsening of symptoms after 5 days being indicators of development of post-viral ABRS.[88,314-316] Unfortunately, little evidence exists to support this widely held belief.

Clinical factors associated with ABRS include purulent discharge,[88] localized unilateral pain,[317] and a period of worsening after an initial milder phase of illness.[309,318,319] Nasopharyngeal or sinus cultures are not necessary for ABRS diagnosis, but may help with antibiotic guidance in the primary care setting.[320]

Some groups recommend assuming bacterial ARS is present if diagnostic criteria for ARS are m*et al.*ong with two additional findings such as timing of the disease, severe pain over the teeth and maxilla, purulent secretions on rhinoscopy, and fever > 38˚C; whereas others suggest there is no data to support symptom severity or purulence as differentiators and suggest relying on the disease time course. Unfortunately, the data supporting these various positions are low in both quality and quantity.

CRP is elevated in bacterial infection and therefore, advocated as a marker of bacterial respiratory tract infection to limit unnecessary antibiotic use[321]. CRP levels are significantly correlated with changes on CT scans,[322] a raised CRP is predictive of a positive bacterial culture on sinus puncture or lavage[307,323] and CRP-guided treatment has been associated with a reduction in antibiotic use without any impairment of outcomes.[304]

Similarly, procalcitonin has been advocated as a potential biomarker for more severe bacterial infection. A review of two RCTs using procalcitonin as a marker[324] showed reduced antibiotic prescribing without detrimental effects on outcomes. Markers of inflammation such as ESR are also raised in ABRS. ESR levels correlate with CT changes in ARS with an ESR of >10 predictive of sinus fluid levels or sinus opacity on CT scans.[307] Another analysis of laboratory indices indicated they have poor specificity and questionable sensitivity in ABRS, limiting their utility.[325]

In summary, differentiating between bacterial and viral ARS can be challenging even in the setting of endoscopy and cultures. Close follow-up of patient symptomology can often help in making the diagnosis, especially for patients that do not improve with supportive care. The evidence related to differentiating acute viral from acute bacterial RS is variable and is summarized in Table VII-4.

Differentiating Viral from Bacterial ARS

Aggregate Grade of Evidence: B B (Level 1: 1 study, level 2: 5 studies, level 3: 4 studies)

Table VII-4. Evidence for differentiating viral from bacterial ARS

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Smith[298]	2014	1	Systematic Review	Radiographic evidence Purulence	Correlation of radiographic findings or purulence with sinus culture	Diagnosis based on radiographs or purulent drainage only has a 50% correlation with positive cultures
Ebell[297]	2019	2*	Meta-analysis	ABRS and ARS	Correlation of clinical impression and diagnostic studies	Clinical impression, cacosmia, and pain in the teeth are predictors of ABRS
Hauer[145]	2014	2**	Systematic review	ABRS and ARS	Fever, facial pain	Cannot distinguish viral from bacterial based on fever or facial pain
Van Den Broek[314]	2014	2**	Systematic review	RS URI	Symptom duration, purulent rhinorrhea	Cannot distinguish viral from bacterial based on symptom duration or purulent rhinorrhea
Young[326]	2003	2	RCT	Amoxicillin-Clavulanate Placebo	Symptom improvement by diagnostic predictors	History of purulent discharge and visible pus in nasal cavity were more predictive of antibiotic improvement than radiography or labs
Lacroix[317]	2002	2	Validating cohort study	Rhinosinusitis URI	Discolored discharge, facial pain, radiograph compared to NPx culture	Discolored drainage, facial pain, radiological maxillary sinusitis were associated with positive culture.
Lee[327]	2013	3	Validating cohort study	NPx Culture MM Culture	Concordance between culture locations	Good concordance for the culture sites makes them a viable diagnostic tool.
Berger[328]	2011	3	Prospective cohort	ABRS no ABRS	Correlation of fiberoptic endoscopy, radiography with ABRS diagnosis	Fiberoptic endoscopy is valuable for diagnosis of ABRS
Hansen[323]	2009	3	Validating cohort study	Positive or negative maxillary sinus cultures	Symptoms, blood labs	Elevated ESR and CRP were sensitive but not specific for positive bacterial cultures
Savolainen[325]	1997	3	Validating cohort study	Positive or negative maxillary	ESR, CRP, WBC	None of the blood tests were sensitive

				sinus cultures		indicators of ABRS

* Level of evidence was downgraded because of heterogeneity of studies included. These also included many studies with a high risk for bias.
**Level of evidence was downgraded due to the small number of studies included.

VII.C. Pathophysiology of ARS

VII.C.1. Contributing Factors for ARS: Anatomic Variants and Septal Deviation

Evidence that anatomical variants are associated with the development of ARS is lacking. This is due in large part to the fact that radiographic imaging is not indicated in the diagnosis of uncomplicated ARS making retrospective studies difficult. Instead, inferences have been made from studies of complex cases including RARS, complications of ARS, AECRS, or collective cases of undefined RS.

There is mixed evidence supporting the association of ARS (definition based on clinical suspicion and mucosal thickening on imaging) and anatomical variants specific to concha bullosa,[305,329-331] nasal septal deviation,[305,329,331,332] infraorbital ethmoid cell,[305,329-331,333] infundibulum stenosis, [305,329,330,333] or agger nasi cell.[329,331] There is also limited evidence of association with radiographic mucosal thickening and findings of intralamellar cells,[329] middle turbinate hypertrophy,[329] aerated uncinate process,[329,330] and asymmetry of the ethmoid roof.[330] Collectively, there is very weak evidence that these anatomical structures are a potential cause of ARS.

In 2010, Orlandi published a systematic analysis of the association between septal deviation and RS.[332] Over 300 references were initially identified, and 13 articles comprised the basis of the analysis. The review found conflicting results and poorly powered studies. Overall, there appeared to be a small association between septal deviation and the presence of RS, with increasing degree of septal deflection correlating with increasing risk of RS. However, the studies comprising this systematic review did not adequately differentiate ARS from RARS or CRS. Moreover, a search of the literature since that review, using the terms “septal deviation and acute rhinosinusitis/sinusitis” fails to identify any new studies on this topic. Thus, from the available published evidence, it is not possible to determine the pathophysiologic impact of septal deviation on ARS. No definitive guidance can be provided whether correcting a septal deviation will result in reduced frequency of ARS episodes.

Since ICAR-RS-2016, several studies have evaluated the effect of anatomy on the specific diagnosis of ARS. A focused study on refractory ARS in 32 patients by Hirshoren *et al.* found a significant association with nasal septal deviation but no other anatomic variants, including agger nasi cell, infraorbital ethmoid cell, concha bullosa, or paradoxical middle turbinate.[331] On the contrary, Autio *et al.* evaluated sinus disease progression through a single episode of ARS in 51 patients using cone-beam CT.[305] Patients diagnosed with ARS, including 16% with a history of recurrent maxillary sinusitis, underwent imaging at enrollment, 5-6 days after onset of symptoms, and around the 10th day of symptoms. They evaluated the prevalence of multiple anatomic variants including, nasal septal deviation, and found no association of culture-proven bacterial ARS with any of these anatomical variations. A 2015 retrospective study that reviewed 192 CT images of patients referred for symptoms of active RS comparing those with minimal versus significant disease on CT imaging also did not find any difference in prevalence of anatomic variants. However, there was no distinction in the subtype of RS.[334] In summary, there is conflicting data that ARS is associated with nasal septal deviation, and there continues to be a lack of data associating ARS with other anatomical variants.

Non-osteomeatal complex related causes of ARS include oro-antral fistula and odontogenic sinusitis. One retrospective case series showed that patients with a periapical abscess of a maxillary tooth are 9.75 times ($p<0.001$) more likely to have substantial reactive maxillary sinus mucosal thickening on cone beam CT.[335] Additionally, another study demonstrated that periodontal disease with tooth roots emerging into the antrum and oro-antral fistulas can cause the symptoms and signs of ARS.[336] However, Hirshoren *et al.* noted that intrusion of healthy teeth into the maxillary sinus is a common finding and not associated with ARS.[331] More recently, a series assessed unilateral symptoms in ARS patients and found that an odontogenic origin was suspected in 15% of patients, with significant association of oral microbial findings in maxillary sinus cultures, indicating that odontogenic sinusitis is a source of ARS.[337]

In summary, the evidence for association between ARS and anatomic variants is conflicting and limited and largely inferred from a small number of studies.

Anatomic Variants as a Contributing Factor for ARS

Aggregate Grade of Evidence: C (Level 2: 1 study; level 4: 15 studies)

Table VII-5. Evidence for anatomic variants as a contributing factor for ARS

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Orlandi [332]	2010	2	Systematic review of cohort studies	RS patients	CT evidence of sinus disease	Increasing degrees of septal deviation were associated with an increased risk of RS
Wuokko-Lande[337]	2019	4	Retrospective Case Series	Clinical history of ARS	CT evidence of unilateral sinus disease and dental observations and microbial findings on sinus culture	15% of ARS suspected to be associated with odontogenic source, significant association between unilateral symptoms and oral microbial findings in maxillary sinus cultures
Khojastepour [333]	2017	4	Retrospective Case Series	Preoperative imaging for rhinoplasty	CT evidence of sinus disease	Ipsilateral maxillary sinus mucosal thickening associated with presence and surface area of infraorbital ethmoid cells
Kaya [329]	2017	4	Retrospective Case Series	Clinical suspicion of RS	CT evidence of sinus disease	Anatomical variations associated with radiologic mucosal thickening: agger nasi cell, MT

						hypertrophy, concha bullosa, lamellar concha bullosa, infraorbital ethmoid cell, uncinate bulla and deviation
Roman [330]	2016	4	Retrospective Case Series	Clinical suspicion of RS Normal (control)	CT evidence of sinus disease	Anatomical variations associated with radiologic mucosal thickening: infraorbital ethmoid cell, concha bullosa, uncinate process bulla and deviation, ethmoid roof asymmetry
Autio [305]	2016	4	Prospective Cohort Study	ARS including recurrent maxillary sinusitis	CT evidence of sinus disease	Anatomical variants were not associated with culture-proven bacterial ARS
Shpilberg [334]	2015	4	Retrospective Case Series	Active RS symptoms Minimal versus clinically significant disease	CT evidence of sinus disease	No significant association of anatomic variants between radiographic minimal and clinically significant groups
Shanbhag [335]	2013	4	Retrospective Case Series	CT with maxillary sinusitis	Fluid filling sinus (by 1/3rds) Mucosal thickening	Oro-antral fistula, periodontal disease and projected root or abscess predict maxillary sinusitis
Hirshoren [331]	2012	4	Prospective Cohort Study	ARS refractory to medical management	CT evidence of sinus disease	NSD was associated with refractory ARS
Alkire [341]	2010	4	Diagnostic Case-Control	RARS symptoms Normal	CT evidence of sinus disease	RARS associated with Infraorbital ethmoid cell and smaller infundibular width.
Bomeli [336]	2009	4	Retrospective Case Series	CT with mucosal thickening	Periapical tooth lucencies	Periapical lucencies increase presence of sinus

					Periodontal disease	inflammation by 9.75 times (odds ratio)
Caughey [342]	2005	4	Diagnostic Case-Control	CT evidence of mucosal thickening Normal CT	CT evidence of sinus disease	Concha bullosa, NSD, and Infraorbital ethmoid cell increases risk of sinus disease.
Stallman [344]	2004	4	Diagnostic Case-Control	CT with mucosal disease with concha bullosa CT with mucosal disease without concha bullosa	CT evidence of sinus disease	In cases of mucosal thickening, no increased chance of concha bullosa.
Stackpole [345]	1997	4	Diagnostic Case-Control	CT evidence of mucosal thickening and Infraorbital ethmoid cells	CT evidence of sinus disease	Infraorbital ethmoid cell size predicts mucosal thickening on CTs.
Nadas [347]	1995	4	Diagnostic Case-Control	Concha bullosa: absent, small, medium, and large	CT evidence of sinus disease	Concha bullosa appears unlikely to have an effect on CRS
Calhoun [349]	1991	4	Diagnostic Case-Control	Any sinus symptoms No sinus symptoms	CT evidence of sinus disease	Concha bullosa and NSD increased risk of sinus disease. Paradoxical MT showed no effect.

VII.C.2. Contributing Factors for ARS: Allergy

Some studies demonstrate an association between allergic rhinitis (AR) and ARS, though this is a not a uniform finding. An early investigation by Savolainen [350] identified a 25% prevalence of allergy in a group of 224 patients with acute maxillary sinusitis versus 16% in the disease-free control group. More recently, in a nationwide survey of the Netherlands citizenship, the risk of ARS was increased in respondents with a physician's diagnosis of AR[351] and a cross-sectional study of the Finnish population demonstrated increased risk for RS in patients with atopic disease.[352] Increased risk for ARS was also found in pediatric patients with AR in a nationwide cohort study of Taiwanese children.[353]

The pathophysiology of ARS is not well-characterized, with studies investigating AR's contribution to the development of ARS or modification of disease course. Regarding the latter, Holzmann *et al.* reported an increased prevalence of AR in children with orbital complications of ARS and that these complications were seen more commonly during pollinating seasons.[354] Conversely, a 2014 systematic review found no evidence to support a prolonged course of ARS in the setting of AR.[355] Furthermore, a randomized controlled trial of the effect of loratadine as an adjunct to antibiotic and

corticosteroid therapy in patients with comorbid AR and ARS demonstrated improvement in individual symptoms of sneezing, nasal obstruction, and cough, as well as total symptom scores; ARS cure rate was not assessed.[356]

Only one prospective study exists examining AR as a risk factor for ARS, and this study was performed in a pediatric population. Leo *et al.* followed a group of 242 children with grass pollen induced AR and 65 normal controls for 3 months during the grass pollen season and found no significant difference in the incidence of ARS between groups.[357]

Several pathologic mechanisms have been proposed to facilitate an interaction between AR and ARS including increased inflammation and narrowing of sinus ostia. To this end, allergen stimulation of nasal mucosa in allergic individuals was shown to generate increased eosinophils in the maxillary sinus[358] and a study of subjects with ragweed-sensitive AR found 60% had sinus mucosal abnormalities on CT imaging during ragweed season.[359] The exact contribution of allergic inflammation in sinus inflammation is not clear as the mucosal abnormalities persisted in the CT scans after the ragweed season despite symptomatic improvement.

A murine model was also employed to study the relationship of AR and ARS. Allergen-sensitized mice that were induced with ARS and exposed to intranasal allergen demonstrated increased mucosal inflammation mediated by Th2 cells.[360,361] These studies suggest that local allergic inflammation may play a role in the expression of ARS.

In summary, population-based studies seem to support an association between AR and ARS. Additionally, a murine model demonstrates comorbid AR and ARS leads to Th2-driven increased mucosal inflammation. In human subjects, allergic individuals demonstrate increased mucosal inflammation during peak allergy season, but this has not been shown to lead to increased incidence of ARS in a prospective study of pediatric patients. While there is some evidence that AR may increase the incidence of orbital complications in children with ARS, there is no evidence to support a prolonged course of ARS in patients with AR. In the treatment of comorbid AR and ARS, loratadine decreases symptoms of cough, sneezing, nasal obstruction and overall symptom scores. While intranasal corticosteroids have clear benefit for AR,[135] no studies have investigated the utility of these medications in allergic adults with ARS. Moreover, there is no evidence that treatment of AR reduces the incidence of ARS.

Allergy as a Contributing Factor for ARS

Aggregate Grade of Evidence: C (Level 2: 5 studies; level 3: 4 studies; level 4: 2 studies)

Table VII-6. Evidence for allergy as a contributing factor for ARS

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Lin [351]	2019	2	Cross sectional cohort (n= 43588)	Taiwanese children with- and without AR	Incidence of ARS	Risk of ARS higher in allergic patients than non-allergic patients (adjusted hazard ratio 3.03)
Frerichs [355]	2014	2	Systematic review	Allergic and nonallergic patients	Prolonged course (>4 weeks) of RS	No significant increase in prolonged RS
Rantala [352]	2013	2	Cross-sectional (n = 1008)	Atopic and nonatopic adults age 21-63	Upper and lower respiratory tract infections	Individuals with atopic disease had higher risk of developing URIs including RS
Baroody [358]	2008	2	DB randomized placebo controlled crossover (n = 20)	Allergic subjects who underwent nasal challenge; controls	Eosinophils in maxillary sinus	Nasal challenge with allergen causes increased eosinophils in the maxillary sinus
Braun [356]	1997	2	DBPC parallel group RCT (n = 139)	Comorbid AR and ARS; treated with amoxicillin-clavulanate plussteroid or amoxicillin-clavulanate plus steroid plus loratadine	Overall and individual symptom scores improvement at 28 days	Adjunctive loratadine improved sneezing at 14 days, and cough and nasal congestion at 28 days
Hoffmans [353]	2018	3*	Questionnaire (n = 8347, representing 50% response rate)	Dutch adults	Risk factors for AR, ARS, and CRS	Risk of ARS was significantly higher with a physician diagnosis of AR (OR 1.70)
Leo [357]	2018	3	Observational case-control study (n = 242; control n = 65)	Children with AR vs. non-allergic control group	Incidence of ARS during allergen season	No significant difference in incidence of ARS among children with AR and non-allergic controls

Chen [362]	2001	3*	Questionnaire (n = 8723)	Children in Taiwan	Rhinosinusitis	Children reporting allergy more likely to have RS
Naclerio [359]	1997	3	Observational (n = 10)	Allergic subjects at peak allergy season	Sinus CT abnormality	60% had CT abnormalities
Holzmann [354]	2001	4**	Retrospective review (n = 102)	Children with orbital complications of ARS	Prevalence of AR	Orbital complications more common during high pollen season
Savolainen [350]	1989	4	Case control (n = 224)	Acute maxillary sinusitis with and without allergy compared to controls without maxillary sinusitis	ARS	Prevalence of AR 25% in acute maxillary sinusitis and 16.5% in controls

* LOE downgraded due to study design (self-reported ARS)
** LOE downgraded due to sample size (n=102)

VII.C.3. Contributing Factors for ARS: Viruses

It has been hypothesized that viral URI predisposes to development of ARS. Autio *et al.* noted 84% nasopharyngeal viral prevalence by multiplex PCR in ARS patients.[363] Maxillary infundibulum occlusion in viral infection[216] and increased nasal or ostiomeatial complex (OMC) bacterial loads in viral URI compared to healthy controls[364,365] have also been suggested as contributing factors.

Several lines of evidence have been published, including epidemiologic studies, prospective viral challenges, and *in vitro* experiments.

Epidemiologic studies. There have been several studies estimating the prevalence of RS and co-occurrence of viral infection as a complication of URI in children and adults. In cohort studies by Demuri *et al.*, 7.1% of children with URI symptoms developed ARS.[366] Rhinovirus (RV: 45%), coronavirus (CoV: 6%), and respiratory syncytial virus (RSV: 3%) were detected in patients with uncomplicated URI. In patients with ARS, 76% showed early PCR evidence of virus (35% RV, 13% CoV, 10% RSV). One limitation of this study is that diagnoses of ARS were based solely on clinical criteria alone. RV is the predominant virus detected in the majority of epidemiologic studies.[363,366,367]

Prospective RV challenges. Prospective viral challenges have examined the impact of experimentally-induced RV inoculation. Hofstra *et al.* utilized 16s rRNA sequencing to evaluate bacterial populations in 6 healthy participants with confirmed, experimentally-induced RV-16 infections.[368] Trends were observed toward increased *H. parainfluenzae, S. aureus*, and *N. subflava*, suggesting increased bacterial populations after RV infection. Allen *et al.* inoculated 10 healthy volunteers with RV-39. No increase in bacterial load was found.[369] Both studies were underpowered to demonstrate a statistically significant change.

Koch *et al.* and Heymann *et al.* evaluated changes in inflammatory cytokine levels in healthy volunteers upon RV inoculation.[370,371] Both studies found early increases in interleukin-10 in controls

exposed to rhinovirus. Koch *et al.* also showed increases in interleukin-6 and interferon gamma-induced protein-10.[370] These studies suggest viral infection induced alteration of the immunologic homeostasis of the sinonasal mucosa, which could promote secondary bacterial infection. Interestingly, Koch *et al.* also found repeated inoculation with RV one week after initial exposure had attenuated cytokine response.[370] This is consistent with anti-inflammatory and immunosuppressive functions for IL-10 seen in overexpression experiments by Stanic *et al.* and could provide a mechanism for ABRS following RV infection.[372]

In vitro RV models. In vitro experiments have focused on the effect of RV inoculation on markers of immunoregulation, as RV accounts for most viral URIs.[373] These studies suggest that viral infection provokes alterations to immunologic homeostasis, consistent with *in vivo* studies. Wang *et al.* determined that RV infections *in vitro* resulted in increased bacterial adhesion on subsequent exposure to common bacterial pathogens, likely explained by RV-induced expression of enhanced bacterial host cell adhesion molecules.[374] This finding is consistent with the trend toward increased bacterial load noted in Hofstra *et al.*[368]

In summary, the epidemiologic studies show that a subset of patients with viral URI will develop clinical ARS. Viral challenge experiments with RV support previous data showing increased bacterial populations in naturally occurring viral infection. *In vitro* studies provide evidence that viral infection (particularly RV) leads to altered immunologic homeostasis that could underly previously proposed mechanisms of ostial obstruction or disrupted mucociliary clearance. Further longitudinal studies are needed to evaluate why only a small percentage of patients with viral infection develop ARS, and if there are specific virome-genome interactions that result in these susceptible populations.

Viruses as a Contributing Factor for ARS

Aggregate Grade of Evidence: C (Level 3: 4 studies; level 4: 8 studies; level 5: 6 studies)

Table VII-7. Evidence for viruses as a contributing factor for ARS

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Koch [370]	2018	3	Prospective viral challenge	Healthy adults; rhinovirus challenge	Rhinovirus infection; cytokine induction	RV challenge increases inflammatory cytokines but lowers cytokine response to subsequent RV infection
Hofstra [368]	2015	3	Prospective viral challenge	Healthy adults; rhinovirus challenge	Patient symptoms scores; bacterial load	Non-significant trends toward increased load of pathogenic bacteria following challenge
Jackson [375]	2015	3	Prospective viral challenge	Healthy and asthmatic adults; rhinovirus challenge	Symptoms, nasal IL-18 levels	RV increased nasal IL-18, with attenuated response in asthmatic

						patients
Allen [369]	2014	3	Prospective viral challenge	Healthy adults; rhinovirus challenge	Bacterial load and species; symptom scores	Bacterial profiles did not change with rhinovirus inoculation
DeMuri [376]	2019	4	Case-control	Longitudinal follow-up, child served as own control	Viral detection; bacterial culture	essentially unchanged from interim data below
DeMuri [377]	2018	4	Case-control	Longitudinal follow-up, child served as own control	Viral detection; bacterial culture	Total 55% viral detection in ARS (day 10 symptoms); RSV at day 3 associated with ARS; 1/3 had different virus at day 3 & day 10
Landry [378]	2018	4	Cases-series	Adults with acute uri	Viral detection, cytokine production	alterations in cytokine production could predict viral infection
Autio [379]	2017	4	Cohort study	Adults; clinical ARS	Inflammatory markers; viral PCR or positive bacterial culture	increased systemic and local inflammation in ABRS, influenza, adenovirus, or multi-viral infection
Heymann [371]	2017	4	Case-control	Adult asthmatics and healthy controls	Nasal epithelial gene expression, symptom diary	Upregulation of early immune response (IL-6 pathway) in control and asthmatics; differential IL-10 expression between groups
Kloepfer [380]	2017	4	Cohort study (uncontrolled)	Asthmatic children followed prospectively	Rhinovirus infection, bacterial cultures of nasal secretions	rhinovirus associated with increases in pathogenic bacteria
DeMuri [366]	2016	4	Case-control	Longitudinal follow-up, child served	Clinically diagnosed sinusitis	8.8% of URI developed sinusitis;

				as own control		rhinovirus most common virus
Nino [381]	2014	4	Case-control	Children hospitalized for acute respiratory illness	TSLP, CCL11/eotaxin1	increased airway secretion of TSLP and CCL11/eotaxin-1 with rhinovirus infection
Tan [382]	2018	5	*In vitro* rhinovirus challenge	Included sinonasal cells from healthy controls	CXCL9/10/11, RANTES	significant cytokine elevation after rhinovirus inoculation
Essaidi-Laziosi [383]	2017	5	*In vitro* rhinovirus challenge	Included sinonasal cells from healthy controls	IL-8, IP-10, RANTES, IFN-γ, IL-1, IL-6, GM-CSF	significant cytokine increases after rhinovirus inoculation
Globinska[384]	2017	5	*In vitro* rhinovirus challenge	Included sinonasal cells from inferior turbinate of healthy controls	IFN-γ, IFN-alpha, IFN-β, RANTES	significant cytokine increases after rhinovirus inoculation
Alves [385]	2016	5	*In vitro* rhinovirus challenge	Included sinonasal cells from middle turbinate healthy controls	IFN-β, IFN-γ, IL-6, IL-8	significant cytokine change after rhinovirus inoculation
Kim [386]	2015	5	*In vitro* rhinovirus challenge	Included sinonasal cells from inferior turbinate of healthy controls	IL-6, IL-8, IFN-β	significant change after rhinovirus inoculation
McErlean [387]	2014	5	*In vitro* rhinovirus challenge	Included sinonasal cells from healthy controls	DNA methylation profile	no significant change after rhinovirus inoculation

VII.C.4. Contributing Factors for ARS: Odontogenic Infections

Odontogenic rhinosinusitis (ORS) results from diseases arising from the dental or dentoalveolar structures. During development, the adult maxillary sinus expands towards the maxillary alveolar ridge resulting in the maxillary tooth roots to be in close proximity or even penetrate through the floor of the maxillary sinus. This anatomic proximity of the tooth root apices to the maxillary sinus likely underlies the development of ORS in patients with maxillary dental pathology, such as tooth extraction and other dento-alveolar lesions including dentigerous cysts, dental caries, and radicular cysts.[388]

Patients with ORS can present with dental symptoms such as dental pain and hypersensitivity or sinonasal symptoms including facial pain and pressure, congestion, nasal obstruction, purulent rhinorrhea, loss of smell, and post nasal drip. A common misperception, 29% of patients do not present with tenderness/pain to palpation over the affected sinus.[389] Nasal endoscopy most commonly demonstrates purulence in the middle meatus.[390] Imaging can be helpful in further delineating symptomology. ORS is particularly likely when there is severe maxillary sinus opacification (50-75%).[390,391] It is not uncommon to have ORS extend beyond the maxillary sinus (up to 88% involvement of the anterior ethmoid and 36% of the frontal sinus),[390] although bilateral disease is less likely (16-19%).[392] Additional findings on CT imaging indicative of ORS most commonly include periapical lucencies,[390] as well as thinning of the maxillary sinus floor and presence of foreign bodies.[392] However, Turfe *et al.* demonstrated that these CT findings are missed in up to 66% of radiology reports.[390] Furthermore, if only plain films are relied upon, ORS findings can be missed 55-86% of the time.

Historically, the overall prevalence of ORS has been quoted to be 10-15%.[393] However, this percentage may be much higher. In a recent series examining 134 patients with unilateral sinus disease, Turfe *et al.* demonstrated that 45% of unilateral sinus disease was odontogenic in origin; the remainder was either non-odontogenic inflammatory (35%), or neoplastic (19%).[390] The most common cause of ORS is iatrogenic.[391,394] Bomeli *et al.* evaluated the frequency of acute maxillary RS and found oro-antral fistulas to be the only independent predictor of RS.[336] Other etiologies assessed included periodontal disease, projecting tooth roots, and apical abscess were not independent predictors, but there were interaction effects. However, the presence of periodontal disease along with either a projecting tooth root or an abscess was predictive of ORS using regression analysis. It has been hypothesized that endosseous implant placement that projects into the maxillary sinus may also be a nidus for infection resulting in acute maxillary sinusitis,[395,396] while some authors refute this concept.[397] In addition, a recent 20-year retrospective study suggests that implants with less than 3 mm sinus penetration are not associated with clinical or radiological signs of RS.[398] A recent review on ORS demonstrated that about 80% of teeth with periapical osteitis have mucosal thickening of the maxillary sinus, commenting on the association between the two entities.[399] The authors postulate that bacteria from the diseased dental roots spread through of the bone to the maxillary sinus.[399]

The microbiology of ORS is unique in that anaerobic microorganisms are more commonly prevalent.[400] Data reliably demonstrate that the polymicrobial nature of ORS (*i.e.,* Peptostreptococcus, Prevotella, Staphylococcus, Streptococcus, and Actinomyces spp.) overlaps in microbiological findings with intraoral/periapical flora[400] and that a lack of these typical bacteria is highly predictive of a non-odontogenic source.[401]

The current literature demonstrates an absence of a well-designed and published investigation into the role of odontogenic infections in ARS. Currently, our understanding of odontogenic ARS is based on low level evidence.

Odontogenic Infections as a Contributing Factor for ARS

Aggregate Grade of Evidence: C (Level 2: 1 study; level 4: 7 studies)

Table VII-8. Evidence for odontogenic infections as a contributing factor for ARS

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Turfe [390]	2019	2	Prospective	Primary dental	SNOT 22,	Faster resolution of

			cohort (n=134)	treatment vs ESS	symptoms, endoscopy	endpoints with primary ESS compared to primary dental treatment
Abi Najm [398]	2013	4	Observation Case series (n=70)	Patients with dental implants	Maxillary sinus imaging	Implant penetration is not associated with odontogenic sinusitis
Tabrizi [397]	2012	4	Observation Case series (n=18)	Patients with dental implants	Maxillary sinus imaging	No increased risk
Longhini [389]	2011	4	Observation case series (n=21)	Patients with odontogenic maxillary sinusitis	Clinical aspects of disease	Dental pathology commonly missed on imaging. Dental pain and foul smell are common symptoms.
Bomeli [336]	2009	4	Observation Case series (n=124)	Acute maxillary sinusitis patients	Maxillary sinus imaging	Odontogenic infections associated with opacification in 17-86%
Jung [396]	2007	4	Observation Case series (n=23)	Patients with dental implants	Maxillary sinus imaging	Implant projection of 4 mm associated with mucosal thickening
Abrahams [402]	1996	4	Observation Case series (n=84)	Patients presenting with periodontal disease	Maxillary sinus imaging	38% positive detection rate for maxillary opacification
Regev [395]	1995	4	Observation Case series (n=8)	Patients with dental implants	Presence/absence of maxillary sinusitis symptoms	Maxillary sinusitis associated with implants

VII.D. Management of ARS

VII.D.1. ARS Management: Antibiotics

While antibiotics have traditionally been prescribed for ARS, routine use has recently been questioned given the high spontaneous resolution rate and unknown cost-benefit ratio.[137,403] Six systematic reviews of RCTs show small benefit of antibiotics compared to placebo for ARS with cure rates at 7-15 days in 91% and 86%, respectively.[318,403-407] Number needed to treat ranged from 10 to 19, greater when diagnosed on clinical grounds alone. A higher proportion with CT evidence of fluid levels and complete sinus opacification demonstrated faster cure. Burgstaller *et al.*[404] analyzed RCTs of patients with ≥7 days of symptoms managed with either antibiotic or placebo. Treated patients had increased rates of improvement at days 3 and 7, but there was no significant difference after day 10. In addition, a recent Cochrane review from Lemiengre *et al.*[318] did not find that antibiotics reduced either time to pain relief or general feeling of illness, but instead increased the rate of adverse events, with the number needed to treat before harm being 8.1 (Table VII-9).

Rosenfeld *et al.* recommended a "watchful waiting" approach where prescriptions are given at the initial visit with instructions to fill if there is no improvement after 7 days or worsening at any time.[889] Multiple systematic reviews,[405,406] reviews with recommendations,[31,151] and clinical practice

guidelines[32,88] have thoroughly compared different antibiotics, dosages, and therapy durations. Consensus is that amoxicillin ± clavulanate is first line in treating suspected ABRS. Whether to include clavulanate is controversial,[31,32,88,151] although this combination has 88-97% response rate in penicillin-resistant pneumococcus and beta-lactamase positive infections.[408] High dose (4g/day) amoxicillin + clavulanate appears to have greater efficacy of reducing nasopharyngeal carriage of pneumococcus and resistant isolates compared to lower dose (1.5g/day).[409] Resistance of common bacteria is an increasing concern. Middle meatal swabs from a mixed adult/pediatric group showed penicillin-resistant pneumococcus in 72%, and ampicillin-resistant *H. influenzae* and *M. catarrhalis* in 60% and 58.3%, respectively.[410] Options after failing amoxicillin ± clavulanate or for penicillin allergy include trimethoprim-sulfamethoxazole, doxycycline, or a fluoroquinolone. Concomitant use of the latter with systemic steroids should be undertaken with great caution.[411] Duration is typically recommended for 10 days or less, with shorter courses favoring fewer adverse events and higher compliance.[31,88]

A Cochrane review[405] showed adverse effects were greater in amoxicillin-treated patients than placebo (31% vs. 22%) and that discontinuation rates were highest with amoxicillin-clavulanate (3.4%). No significant differences have been observed between amoxicillin and placebo with regard to missed work days or inability to do non-work activities (Table VII-10).[405,412]

Antibiotic Therapy for ARS

Aggregate Grade of Evidence: B for antibiotics with some small benefit (Level 1: 6 meta-analyses of RCTs but with some conflicting observations); C for amoxicillin-clavulanate being superior to amoxicillin (Level 1b: 2; level 2b: 2; level 4: 3).
Benefit: Potential for shorter duration of symptoms; reduced pathogen carriage.
Harm: Gastrointestinal (GI) complaints greater than observed in placebo for both drugs, more pronounced for amoxicillin-clavulanate. Potential for resistance and for anaphylaxis (see Table II-1).
Cost: Low to moderate. Similar among options available as generics.
Benefits-Harm Assessment: Benefit of treatment over placebo is small.
Value Judgments: Decision to treat and timing thereof should also consider mitigating circumstances including severe symptoms, immunocompromised state, concern for impending complications, and suspected odontogenic source.
Policy Level: Option.
Interventions: Consider initial watchful waiting in uncomplicated cases, with institution of antibiotic therapy if no improvement after 7 days or worsening at any time, or for mitigating circumstances as noted above.

Table VII-9. Evidence for antibiotic therapy in ARS.

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Lemiengre [318]	2018	1	Systematic review of RCTs (15 total studies)	Antibiotic vs. placebo for ARS	Cure when diagnosed based on symptoms Cure when diagnosed radiologically	Purulent secretion resolved faster with antibiotics Cure rates with antibiotics were higher when fluid level or total opacification was found on CRT Confirmed prior report[403]
Burgstaller	2016	1	Systematic	Antibiotic vs.	Cure or	Antibiotic compared to

[404]			review of RCTs (only 6 met criteria)	placebo for ARS symptoms lasting for 7 or more days	improvement at days 3, 7 and 10 post antibiotic or placebo	placebo relieves symptoms in a higher proportion of ARS patients, only earlier in the course of treatment
Ahovuo-Saloranta [405]	2014	1	Systematic review of RCTs and meta-analysis	Antibiotic vs. placebo for ARS Differing classes of antibiotics	Clinical symptoms at 7 to 15 days Drop-outs due to medication side efects	When clinical failure was defined as a lack of full recovery, antibiotics decreased risk of failure. Amoxicillin+clavulanate had significantly more drop-outs due to adverse effects than cephalosporins and macrolides
Lemiengre[403]	2012	1	Systematic review of RCTs (10 studies)	Antibiotic vs. placebo for ARS	Symptom resolution Adverse events	Five per 100 will cure faster between 7 -14 days if they receive antibiotics 27% who received antibiotics vs. 15% who received placebo experienced adverse events
Falagas[406]	2008	1	Meta-analysis of RCTs	Short-term therapy (up to 7 days) for ARS Longer- term therapy for ARS (9 or more days)	Improvement of symptoms	No difference between short- and long-term courses of antibiotics
Young[407]	2008	1	Meta-analysis of RCTs	Antibiotics vs. placebo for ARS	Symptom resolution	15 patients need to be treated before 1 benefits from antibiotics

Table VII-10. Evidence for amoxicillin vs. amoxicillin-clavulanate in ARS.

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Garbutt[412]	2001	2	RCT in pediatric patients	Amoxicillin Amoxicillin + clavulanate Placebo	Telephone interviews at 3 to 60 days	Day 14 improvement rate was similar between groups. Similar relapse/ recurrence rates
Wald[413]	1986	2	RCT in pediatric patients	Amoxicillin Amoxicillin + clavulanate Placebo	Telephone questionnaire at 1 to 10 days	Both antibiotics were superior to placebo at days 3 and 10
Anon[408]	2006	3	Cohort study	Amoxicillin-clavulanate	Bacterial eradication or no clinical evidence	Success in 87.8%

					of infection	
Brook[409]	2005	3	Cohort study	Amoxicillin + clavulanate with two different amoxicillin doses (4 g/d v. 1.5 g/d)	Bacteria isolated by nasopharyngeal swab pre- and post-therapy	Bacteria were isolated pre- and post-therapy
Olwoch[414]	2010	4	Case series	Patients with complicated RS treated with antibiotics and surgery	Bacterial isolates and resistance	Pneumococcal prevalence low (2.6%); penicillin resistance high (64.3%);
Brook[415]	2008	4	Retrospective series without control	Culture data from two different time periods	Prevalence of *S. aureus* and MRSA	Prevalence of MRSA was greater in the latter time period
Huang[410]	2004	4	Case series	Middle meatal discharge cultured during ARS episode	Prevalence of antibiotic resistance	First line penicillin class resistance in 58-72% for common pathogens

VII.D.2. ARS Management: Corticosteroids

Treatment with corticosteroids is hypothesized to reduce mucosal inflammation (nasal and meatal) to restore aeration of the sinuses and allow for natural mucociliary clearance (MCC) for symptom resolution.[416,417]

VII.D.2.a. ARS Management: Intranasal Corticosteroids (INCS)

INCS offer anti-inflammatory benefits and potential edema reduction with negligible systemic bioavailability.[418,419] Randomized placebo controlled trials have examined different INCS (fluticasone, mometasone, budesonide) with variable doses (110, 200, 400 mcg) administered either daily or twice daily to manage ARS symptoms. Randomized placebo controlled clinical trials demonstrate that for patients with mild to moderate symptoms, treatment with monotherapy INCS is better than antibiotic treatment alone[420] and may be useful as an adjunctive therapy in those treated with antibiotics for presumed bacterial RS.[419,421] High dose INCS improve ARS symptoms, in particular congestion and rhinorrhea as compared to lower dose INCS, standard antibiotic therapy or placebo sprays.[4161,7,8] Symptom duration has also been shown to be shortened with INCS as compared to placebo sprays.[419-424] A Cochrane review meta-analysis, which included 1943 participants from four studies, similarly found that ARS patients receiving INCS were more likely to resolve or improve than in placebo treated patients.[416] However, these effects were modest, requiring INCS treatment of 100 patients to provide 7 patients with complete or marked symptom relief.[416]

With rare adverse events and limited systemic uptake,[416] INCS use in ARS is a strong recommendation with grade A aggregate quality of evidence, showing a modest effect. Additional studies comparing ideal INCS formulation, dose, and duration will provide insight to optimize INCS treatment in ARS.

Intranasal Corticosteroids for ARS

Aggregate Grade of Evidence: A (Level 1: 6 studies; level 2: 8 studies)

Benefit: INCS improved patient symptoms as monotherapy in mild or moderate cases and as adjuvant to antibiotics in severe cases and may shorten recovery.
Harm: Minimal harm with rare mild adverse event (see Table II-1).
Cost: Low.
Benefits-Harm Assessment: Benefit of treatment over placebo small, but tangible; minimal harm with INCS.
Value Judgments: INCS improved patient symptoms with low risk for adverse event.
Policy Level: Use of INCS: Strong recommendation.
Intervention: INCS should be used as monotherapy in mild to moderate ARS or as adjuvant to antibiotic therapy in severe cases of ARS.

VII.D.2.b. ARS Management: Systemic Corticosteroids

The majority of trials have focused on the role of INCS in CRS, however, five trials (two unavailable in English[425,426]) have evaluated the role of systemic corticosteroids in treatment of ARS. Each study used different corticosteroid formulations in varying doses and duration, thus limiting direct comparison of results.[427,428] Studies by Gehanno *et al.*[427] and Ratau *et al.*[429] offered early support for the use of systemic corticosteroids for management of ARS associated symptoms, particularly facial pain. However, Venekamp *et al.* report the only study performed without confounding antibiotics. It failed to find significant symptomatic improvement in patients taking corticosteroid monotherapy.[428] A Cochrane review meta-analysis failed to find significant evidence to support systemic corticosteroids in ARS, despite reviewing trial results from 1193 participants.[430] It is possible there may be a role for oral steroid treatment as an adjunct in severe RS, but evidence is currently lacking.

Given the conflicting evidence, there is no recommendation for systemic corticosteroids in cases of uncomplicated ARS, with a grade D aggregate quality of evidence.

Oral Corticosteroids for ARS

Aggregate Grade of Evidence: D (Level 1: 1 study; level 2: 3 studies; conflicting evidence).
Benefit: Systemic steroids may have minimal short-term benefit, no clear benefit as monotherapy.
Harm: Minimal harm with rare mild adverse event (see Table II-1).
Cost: Low.
Benefits-Harm Assessment: Benefit of systemic steroids over placebo small when used as adjuvant therapy, minimal risk of harm.
Value Judgments: Systemic steroids may improve patient symptoms with low risk for adverse event.
Policy Level: Use of systemic corticosteroid: No recommendation.
Intervention: Systemic corticosteroids may be useful with severe facial pain or headaches secondary to ARS, otherwise no tangible benefit. No role as monotherapy for ARS.

Table VII-11. Evidence for intranasal corticosteroids in ARS.

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
van Loon [431]	2013	1	Systematic review (n=539)	INCS review in RARS	Time to clinical cure (duration of symptoms)	INCS not recommended as monotherapy in RARS
Zalmanovici [416]	2013	1	Analysis of 4 RCTs (n=1,943)	INCS Placebo	Resolution of symptoms, adverse events, rates of	INCS improved resolution of symptoms; higher doses may have

					relapse, etc.	stronger effect
Hayward [432]	2012	1	Systemic review (n=2,495)	ARS patients	Symptom improvement, adverse events, relapse rates, etc.	Small symptomatic benefit in ARS; higher effect with longer duration and higher doses. NNT=13
Meltzer [433]	2008	1	Systemic review	ARS patients		INCS useful as adjunct or as monotherapy to reduce symptoms
Keith [424]	2012	2	RCT (n=737)	Fluticasone 110mcg BID (n=240) Fluticasone 110mcg daily (n=252) Placebo spray (n=245)	Symptom improvement	Both doses of INCS reduced symptoms and shortened duration of symptoms.
Meltzer [423]	2012	2	RCT (n=981)	Mometasone 200mcg BID (n=235) + placebo antibiotic Mometasone 200mcg daily (n=243) + placebo antibiotic Amoxicillin 500mg TID (n=251) + placebo spray Placebo spray + placebo antibiotics (n=252)	Minimal-symptom days and minimal-congestion days	High dose INCS had more minimal-symptom days and more minimal congestion days
Bachert [422]	2007	2	RCT (n=981)	Mometasone 200mcg BID (n=235) + placebo antibiotic Mometasone 200mcg daily (n=243) + placebo antibiotic Amoxicillin 500mg TID (n=251) + placebo spray Placebo spray + placebo antibiotics (n=252)	SNOT-20, QoL	Higher dose INCS had clinically significant improvement in SNOT-20
Williamson [434]	2007	2	RCT (n=240)	Amoxicillin 500mg TID + Budesonide 200umcg daily (n=53) Amoxicillin 500mg TID + placebo spray daily (n=60) Budesonide 200mcg daily + placebo antibiotic (n=64) Placebo antibiotic + placebo spray (n=63)	Improvement in Total Symptom Severity Score by >4 points	No synergistic effect between INCS and antibiotics Milder cases benefited from the INCS while more severe cases did not

Meltzer [420]	2005	2	RCT (n=981)	Mometasone 200mcg BID (n=235) + placebo antibiotic Mometasone 200mcg daily (n=243) + placebo antibiotic Amoxicillin 500mg TID (n=251) + placebo spray Placebo spray + placebo antibiotics (n=252)	Symptom severity and resolution	INCS BID was significantly better than all other groups
Nayak [419]	2002	2	RCT (n=967)	Amoxicillin/ clavulanate 875mg BID plus: 1. Mometasone 400 mcg BID (n=324) 2. Mometasone 200 mcg BID (n=318) 3. Placebo (n=325)	Change from baseline symptoms and CT normalization	High and low dose INCS improved symptoms with no significant change in CT score
Dolor [421]	2001	2	RCT (n=95)	Fluticasone propionate 200mcg daily (n=47) Placebo (n=48)	Symptoms improved at 10-56 days Time to success Number of ARS recurrences	INCS pts have higher rates of resolution, shorter time to success (6 vs 9 days); and trend toward fewer recurrences
Meltzer [435]	2000	2	RCT (n=407)	Mometasone furoate 400mcg BID + Amox/clav 875mg BID (n =200) Placebo spray + Amox/clav 875mg BID (n=207)	Symptom improvement	INCS improved congestion, facial pain, and headache significantly No difference in purulent rhinorrhea, PND or cough.
El-Hennawi [436]	2015	3	RCT (n=40)	Ofloxacin 0.26% + dexamethasone 0.053% nasal drops (n=20) Amoxicillin (90mg/kg) (n=20)	VAS subjective symptom improvement	Delay in clinical improvement with topical antibiotic and steroid at 48hrs, but similar results at 10days.
Inanli [417]	2002	3	Cohort (n=60)	Amoxicillin/ clavulanate 875mg BID plus: No topical therapy (n=12) Fluticasone 100microg daily (n=14) 0.05% oxymetazoline TID (n=9) 3% NaCl (n=12) 0.9% NaCl (n=13)	Nasal MCC	No difference in basal MCC with INCS.

Table VII-12. Evidence for systemic corticosteroids in ARS.

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Venekamp [430]	2014	1	Meta-analysis of 5 RCTs (n=1,193)	Systemic corticosteroid Placebo	Symptom improvement, time to resolution, bacteriological cure/relapse, adverse events	Oral corticosteroids are ineffective as monotherapy; oral corticosteroids may be beneficial as adjunct to antibiotics
Venekamp [428]	2012	2	RCT (n=185)	Prednisolone 30mg daily (n=93) Placebo (n=92)	Resolution of facial pain/ pressure and other symptoms	No differences seen in any outcomes.
Gehanno [427]	2000	2	RCT (n=417)	Amoxicillin/clavulanate 500mg TID plus: 1. Methylprednisolone 8mg TID (n=208) 2. Placebo (n=209)	Regression of clinical symptoms or radiologic signs by day 14	Oral corticosteroids may help in short term relief, particularly facial pain, but effect diminishes by 14 days
Ratau [429]	2004	2	RCT (n=42)	Amoxicillin/ clavulanate 625mg TID plus: 1. Betamethasone 1 mg daily (n=21) 2. Placebo daily (n=21)	Reduction in symptom severity by day 6	Headache, facial pain, nasal congestion and dizziness improved with steroid

VII.D.3. ARS Management: Topical Saline Spray and Irrigation

There were 7 RCTs and one meta-analysis assessing the effects of saline in adult patients with ARS.[417,437-441] Of the seven, two trials studied patients with presumed ABRS[417,437] The reason for exclusion were: acute viral rhinosinusitis (AVRS),[440] mixed population of ABRS with AVRS,[438] mixed population of ARS and CRS[441,442] and suspected RS by symptoms without confirmatory examination.[439] Results from a meta-analysis were not included because data were pooled from RCTs studying common colds and AVRS.[443]

Inanli *et al.*[417] assessed patients with presumed ABRS. Diagnostic criteria were worsening of RS symptoms for longer than 1 to 3 weeks and an abnormal nasal examination. Nasal saline treatment using a syringe (10ml) was given as an adjunct with oral amoxicillin/clavulanic acid. Mucociliary clearance (MCC) time was compared among study groups, including the saline groups: 0.9% saline (n=13) and 3% saline (n=12) and the group without topical treatment (n=12). At three weeks, the changes in MCC time among 3 groups were not different. Safety was not assessed.

Gelardi *et al.*[437] treated presumed ABRS patients (n=20) with levofloxacin and compared the effects of two types of devices for delivering saline irrigation. They showed the benefit of large volume (250ml) irrigation over the syringe (10ml) in improvement for rhinorrhea and post-nasal drip. When

compared to baseline, nasal resistance was decreased in the large-volume irrigation group but not in the syringe group. Safety was not assessed.

Nasal saline treatment as an adjunct therapy along with antibiotics may have a role in symptom reduction in ABRS.[88] The sole effects of saline spray/irrigation in the ABRS population cannot be concluded. Beneficial effects of saline irrigation using a 10ml syringe over no saline treatment were not shown. However, large-volume irrigation (250ml) showed superior effects over a low volume syringe (10ml). Safety of saline spray/irrigation for treating ABRS cannot be concluded due to limited studies. In general, saline treatment is considered safe without reported major adverse effects.[444] Minor adverse effects, including ear fullness, or irritation, are more common in patients receiving hypertonic versus isotonic saline solution.[445]

Topical Saline Spray and Irrigation for ARS

Aggregate Grade of Evidence: B (Level 3: 2 studies).
Benefit: Not shown when using a low volume syringe (10ml) but possible improvement in nasal patency, rhinorrhea and post-nasal drip when using a larger volume device (250ml).
Harm: Unclear but possible ear fullness, or irritation (see Table II-1).
Cost: Minimal.
Benefits-Harm Assessment: Balance of benefit and harm.
Value Judgments: Saline treatment may improve symptoms when using a large-volume device despite possible minor adverse effects and its minimal cost.
Policy Level: Option.
Intervention: Saline irrigation may be used in adjunct with antibiotics for ABRS.

Table VII-13. Evidence for nasal saline treatment in ARS

Study	Year	LOE	Study design	Study groups (n)	Device	Clinical endpoint	Conclusion
Gelardi [437]	2009	3	RCT, UB, NPC	ABRS 1. Syringe (10) 2. Irrigation bag (10)	Syringe 10ml Irrigation bag 250ml	Nasal obstruction, rhinorrhea, and post-nasal drip (visual analog scale) and anterior rhinomanometry at 3 weeks	The irrigation bag group had significantly greater symptoms reduction than syringe group for rhinorrhea and post-nasal drip. No significant difference in nasal obstruction and anterior rhinomanometry between groups.
Inanli [417]	2002	3	RCT, UB, PC	ABRS 1. Hypertonic saline (12) 2. Isotonic saline (13) 3. No saline (12)	Syringe 10ml	Change in MCC at 3 weeks	No significant difference in MCC between the groups.

V.D.3. ARS Management: Decongestants and Other Adjunctive Treatments

VII.D.3.a. Decongestants

Decongestants are used in ARS with the presumed benefit of reducing nasal congestion and hence improving patient symptoms. Topical and oral decongestants have shown to increase ostial patency in healthy individuals and in patients with acute rhinitis and CRS [446-448] There is minimal evidence regarding the use of topical or oral decongestants in adult ARS. Inanli performed an RCT of ABRS addressing this topic.[417] The primary outcome measure was MCC (MCC) measured by saccharin transit time. MCC was slower initially in patients with ARS and faster 20 minutes following use of oxymetazoline or hypertonic saline. The study utilized MCC as a measure of a defense mechanism against pathogens and noxious stimuli in patients with respiratory infections although this may not be a very relevant clinical outcome in practice. Ultimately however, no significant difference between active treatment groups and controls was observed at the conclusion of the study with respect to improvement in MCC. Wiklund *et al.*, performed a double-blind RCT on patients with acute maxillary sinusitis.[449] They compared oxymetazoline versus placebo delivered either as a conventional nasal spray or with a bellows device. The outcome measures were patient reported symptoms and radiographic improvement. Neither form of oxymetazoline delivery was shown to have significant benefit over placebo at the study conclusion.

Several international guidelines on this topic have been published.[26,32,88,450,451] None have found sufficient data for an evidenced-based recommendation to be made.

Decongestants for ARS

Aggregate Grade of Evidence: C (Level 2: 1 study; level 3: 1 study; level 5: 4 studies).
Benefit: Theoretical relief of nasal congestion and restoration of patency of blocked sinus ostia.
Harm: Risk of rhinitis medicamentosa (topical) with prolonged use or hypertension (oral), irritability, palpitations, and insomnia (see Table II-1)
Cost: Low direct cost.
Benefits-Harm Assessment: Preponderance of benefit over harm has not been demonstrated.
Value Judgments: Patient's comorbidities and age need to be considered due to risk of adverse effects.
Policy Level: Option.
Intervention: Decongestants are an option in ABRS. Decongestants can reduce congestion in patients with ABRS however side effects should be considered.

Table VII-14. Evidence for decongestants in ARS treatment.

Study	Year	LOE	Study Design	Study Groups	Clinical End-point	Conclusion
Wiklund[449]	1994	2	DBRCT	Patients with acute maxillary sinusitis treated with phenoxymethyl-penicillin and: Oxymetazoline Placebo	Clinical examination through 28 days Sinus X-ray VAS entries in patient diary	No difference between groups
Inanli[417]	2002	3	RCT	ABRS patients (ages 12-75) treated with amoxicillin/clavulanic acid and: No topical treatment INCS	Mucociliary clearance	No significant difference among the groups

				Oxymetazoline Hypertonic saline Normal saline		
Rosenfeld[88]	2015	5	Guideline			Discourage decongestant use in ABRS based on Grade D evidence, first principles
Peters[451]	2014	5	Guideline			No evidence for use of decongestants ARS (option, Grade D)
Fokkens[26]	2020	5	Guideline			No Recommendation
Chow[32]	2012	5	Guideline			Recommend against use of oral/topical decongestants in ABRS (strong recommendation, low-moderate evidence)

V.D.3.b. Antihistamines

Antihistamines are prescribed in ARS on the basis that they reduce nasal secretions. There is a theoretical concern that the increased viscosity could decrease MCC and worsen ABRS. Systematic reviews have looked at their efficacy in the treatment of adult ARS [26,32,88,151,451]. No evidence to support their use in this setting was demonstrated. In patients with confirmed AR however, an RCT by Braun *et al.* demonstrated improvement in patient symptoms scores when loratadine was added to antibiotics for treatment of ARS [356].

Antihistamines for ARS

Aggregate Grade of Evidence: C (Level 2: 1 study; level 5: 4 studies).
Benefit: Relief of AR symptoms associated with ARS.
Harm: Some antihistamines may cause sedation (see Table II-1).
Cost: Low direct cost.
Benefits-Harm Assessment: Preponderance of benefit over harm has not been demonstrated.
Value Judgments: None.
Policy Level: Option.
Intervention: Antihistamines are an option in ABRS with comorbid AR and can be used to decrease symptoms of AR.

Table VII-15. Evidence for antihistamines in ARS treatment.

Study	Year	LOE	Study Design	Study Groups	Clinical End-point	Conclusion

Braun[356]	1997	3	DBRCT	Patient with ARS (ages 15-65) and comorbid AR treated with amoxicillin/clavulanic acid, prednisone and: - Loratadine - Placebo	Symptom score cards Clinical exam including rhinoscopy	Significant improvement in total symptom scores
Rosenfeld[88]	2015	5	Guideline			Discourage antihistamine use in ABRS based on Grade D evidence, first principles
Peters[451]	2014	5	Guideline			No evidence for use of antihistamines in ARS (option, Grade D)
Fokkens[26]	2020	5	Guideline			No recommendation.
Chow[32]	2012	5	Guideline			Recommend against use of antihistamines in ABRS (strong recommendation, low-moderate evidence)

V.D.3.c. Mucolytics

Although commonly prescribed by practitioners for ARS, evidence for or against the use of mucolytics in this condition is lacking.[88,451] In an RCT of subacute RS patients, Bahtouee *et al.* found that adding acetylcysteine 600 MG orally once daily to the treatment regimen did not have any benefit when measured radiographically or via symptom scores.[213]

Mucolytics for ARS

Aggregate Grade of Evidence: D (Level 3: 1 study, Level 5: 2 studies).
Benefit: Thinning of mucus theoretically leading to increased MCC
Harm: Costs of medication.
Cost: Low direct cost.
Benefits-Harm Assessment: Preponderance of benefit over harm has not been demonstrated.
Value Judgments: None.
Policy Level: No recommendation.
Intervention: Based on the current evidence, no recommendation can be given for mucolytics in ABRS.

Table VII-16. Evidence for mucolytics in ARS treatment.

Study	Year	LOE	Study Design	Study Groups	Clinical End-point	Conclusion

Bahtouee[213]	2017	3	DBRCT	Subacute rhinosinusitis patients treated with amoxicillin/clavulanic acid, saline and oral pseudoephedrine and: Acetylcysteine Placebo	Sinus CT changes Lund-Mackay score SNOT-20 score	No benefit to adding acetycysteine
Rosenfeld[88]	2015	5	Guideline			No evidence to support use of mucolytics in ABRS
Peters[451]	2014	5	Guideline			No evidence for use or lack of sufficient prospective studies of mucolytics in ABRS

V.D.3.d. Herbal Remedies

A number of herbal interventions for ARS have been published in the literature [452-454] with some systematic reviews showing some promise of benefit without sufficient evidence for recommendations.[26,455-457] In a DBPCT of acute upper respiratory tract infection by Gabrielian *et al.*,[452] patients were treated with *Andrographis paniculata/Eleutherococcus senticosus* herbal for 5 days. Patients treated with the herbal had greater improvement in mean symptom scores at the end of treatment including in the subset of patients with ARS. Bachert *et al.* found that *Pelargonium sidoides* extract provided superior improvement of sinonasal symptoms compared to placebo after 7 days of treatment.[453]

Although extract of *Pelargonium sidoides* and cineole have evidence suggesting efficacy, methodological flaws and possible conflicts of interests in their associated studies makes it difficult to make any useful recommendations regarding their use other than the need for further well-designed trials.[453,458,459]

Herbal Remedies for ARS

Aggregate Grade of Evidence: B (Level 1: 3 studies; level 3: 5 studies; level 5: 1 study).
Benefit: Symptom improvement.
Harm: Side effects depending on herbal remedy ingredients.
Cost: Low direct cost.
Benefits-Harm Assessment: Preponderance of benefit over harm has not been demonstrated.
Value Judgments: Lack of conclusive evidence to recommend herbal remedies.
Policy Level: No recommendation.
Intervention: None. Side effects should be considered if used.
*AGE combines data from various individual herbal therapies. There is insufficient evidence to recommend treatment with individual herbal therapies for ARS at this time.

Table VII-17. Evidence for herbal treatments in ARS.

Study	Year	LOE	Study Design	Study Groups	Clinical End-point	Conclusion

Gabrielian [452]	2002	3	DB parallel-group clinical study	Patients with acute upper respiratory tract infections with subgroup analysis of ARS were treated for 5 days with: Andrographis paniculate SHA-10/Eleutherococcus senticosus fixed combination extract Placebo	Symptoms scores	Statistically significant improvement in favor of herbal treatment
Bachert[453]	2009	3	DBRCT	Patients ARS treated with: 1. Pelargonium sidoides drops 2. Placebo	Sinus severity score. Radiologic changes Ability to work	Every result was statistically significant in favor of Pelargonium sidoides
Tesche[454]	2008	3	DBRCT; no placebo control	Patients with ARS and viral RS randomized to: 1. Cineole 2. combination of five different herbal components	Clinical and endoscopic assessment	Cineole was more effective than the combination herbal components, but no placebo group.
Ponikau[458]	2012	3	DBPCT	Patients with ARS treated for 7 days with: 1. intranasal lyophilized, reconstituted *Cyclamen europeaum* extract (Cyclamen) 2. placebo spray	Symptom severity Radiologic changes	*Cyclamen* was more effective at radiologic improvement but not superior to placebo for symptom severity
Pfaar[459]	2012	3	DBPCT	Patients with ARS treated with 8 days of amoxicillin and concomitantly with 15 days of: 1. Intranasal Cyclamen europaeum extract 2. placebo spray	Symptom scores Endoscopic assessment	Cylamen significantly reduced facial pain and endoscopic scores but failed to reach significance with total symptom scores
Zalmanovici [457]	2018	1	Systematic Review			No data to support use of *Cyclamen europaeum* extract for ARS
Fokkens[26]	2020	5	Guidelines			Some herbal supplements may have significant impact on symptoms
Koch[455]	2016	1	Systematic Review			Herbal medicine may be effective in ARS but more research is necessary

Guo[456]	2006	1	Systematic review of RCTs			Some evidence for benefit with bromelain and Sinupret® in ARS

VII.E. Complications of ARS

While a variety of complications can arise from ARS,[460,461] overall these are rare. Only about 1 in 95,000 hospital admissions in the United States is due to complications from ARS.[32] These are broadly subdivided as orbital, intracranial, and osseous complications.

Complications involving the orbit have traditionally been classified as described by Chandler, *et al.* This system includes group I – preseptal cellulitis, group II – orbital cellulitis, group III – subperiosteal abscess, and group IV – orbital abscess.[462] A fifth group, cavernous sinus thrombosis, will be described as an intracranial complication. The most frequent orbital pathogens include common respiratory pathogens. Concomitant infection with *Streptococcus anginosus* group and oral anerobes are also frequently seen, possibly indicating pathogenic synergy.[463] The vast majority of orbital complications from ARS present in the pediatric population. In the adult population, orbital complications are much rarer. In adults it is frequently seen in patients with a history of CRS who have previously undergone surgical intervention and have structural abnormalities of the lamina papyracea, for example dehiscence due to mucocele.[464]

Intracranial complications may present at any age, with greatest prevalence in the second and third decades of life.[465] Patients typically present with fever, headache, and mental status changes. Intracranial involvement may develop as a discrete collection of purulence (epidural abscess, subdural empyema, or brain abscess) or without suppuration (cerebritis or meningitis). These complications are most often secondary to frontal sinusitis, though ethmoid sinusitis has also been implicated.[465,466] Cavernous sinus thrombosis, however, is typically secondary to sphenoid sinusitis and presents with ophthalmoplegia, vision change, papilledema, and/or other cranial neuropathies.[466]

The Pott's puffy tumor, osteomyelitis and subperiosteal abscess of the frontal bone, makes up the osseous complication of ARS. With the advent of antibiotic therapy this has become much less common though head trauma remains a risk factor.[466] These patients, typically adolescents, are at risk for concurrent orbital as well as intracranial complications.[466-468]

The hallmarks of management are swift diagnosis, rapid initiation of broad-spectrum intravenous antibiotics, and in many cases surgical intervention.[464-466,468] CT is typically the first-line imaging modality in diagnosing complicated ARS. Magnetic resonance imaging (MRI) provides soft tissue visualization and is useful when there is concern for intracranial involvement. Magnetic resonance venography may be useful for evaluation of the cavernous sinus and other vasculature. Endoscopic sinus surgery is typically recommended in patients with these complications. While ESS is usually a sufficient approach for addressing orbital complications, open neurosurgical intervention is often required for even sub-centimeter intracranial abscess.[469]

VIII. Recurrent Acute Rhinosinusitis (RARS)

VIII.A. Incidence and Prevalence of RARS

It is difficult to accurately determine the true incidence of recurrent acute rhinosinusitis (RARS) as these patients often do not present to an otolaryngologist. The EPOS2020 document requires at least one diagnosis of post-viral ARS to be confirmed by objective evidence of paranasal sinus involvement through either nasal endoscopy and/or CT scan before considering the diagnosis of RARS.[26] However, RARS patients present mainly to their general practitioner or emergency room, most not undergoing nasal endoscopy or CT. An attempt had been made to identify RARS prevalence by studying medical claims data from 2003-2008 in the United States, and sub-analyzing the number of claims made for 4 or more episodes of documented ARS where the patient was prescribed antibiotics during all occasions.[232] An incidence of 0.035% was identified using this methodology with approximately 1 in 3000 adults affected per year. However, this number is likely an underestimate, as patients treated with watchful waiting, surgery or those who never filled their prescriptions remained unaccounted for.[206] Recent evidence suggests that RARS patients have an impairment in their QoL during exacerbations but this does not always correlate well with positive findings on nasal endoscopy.[204]

VIII.B. Diagnosis of RARS

There is significant heterogeneity and ambiguity in the diagnostic criteria for RARS, with the recent EPOS2020 and ICAR-RS-2016 documents having differing criteria. While ICAR-RS-2016 required at least 4 episodes of ARS in a 12-month period, EPOS2020 also requires the patient to present with at least 4 episodes of documented acute bacterial or post-viral rhinosinusitis in a 12-month period, with relative normalcy in the intervening periods. The EPOS2020 steering group recommended at least one diagnosis of post-viral ARS to be confirmed by objective evidence of paranasal sinus involvement through nasal endoscopy and/or CT scan before considering the diagnosis of RARS.[26] Post Viral RS is defined as an increase in symptoms after 5 days or persistence of symptoms after 10 days of onset of ARS with a total duration of less than 12 weeks.[31] Assigning 4 attacks of ABRS as a required criterion was arbitrarily chosen and primarily based on the fact that on average an individual would have 1.4 to 2.3 bouts of viral rhinosinusitis per year.[201] The diagnosis may be easily missed, due to the possibility of the patient presenting to different healthcare providers such as the family practitioner, emergency room, allergy specialist etc.[470]

Endoscopy. According to a meta-analysis of 17 studies, the single most important clinical finding in an acute patient is the presence of colored discharge in the middle meatus, along with clinical features of ARS.[297] However, according to Bhattacharya *et al.* only 2.4% of patients with RARS receive a nasal endoscopy at the end of 1 year.[232] RARS patients have significant impairment in their QoL scores during exacerbations, although this does not correlate well with positive findings on nasal endoscopy.[204,208] Endoscopy is recommended in this cohort of patients to visualize contributing factors, confirm the presence of mucopus in the middle meatus and for getting access to a culture specimen.[88]

Culture. The presence of mucopurulent discharge is mandatory for the diagnosis of RARS but doesn't always correlate with the presence of a bacterial infection.[297,471] Some studies have shown that the mucopurulence could be secondary to neutrophil influx into the sinuses which supports a bacterial as opposed to a viral etiology.[317,472-476] It is important to note that the growth of a pathogen or presence of neutrophils is not necessary for the diagnosis of RARS.

*Imaging***.** With the exception of EPOS2020, imaging is not primarily recommended by any of the guidelines for RARS in uncomplicated cases.[151,205,232,296,319,477-486] Imaging may be useful to study the anatomy of the sinuses prior to surgery, but there is mixed data on the presence of anatomical variances in patients with RARS when compared to CRS or normal patients. Of the 3 retrospective studies correlating anatomical variations with RARS incidence, 2 of them suggest a positive correlation whereas one did not find any correlation.[88,451,487] Most researchers however agree, that if need be, the scan should be done in-between acute episodes.[26,232,488]

Additional Testing. Testing for immunoglobulin deficiencies as well as for environmental allergens has been recommended by 2 separate guidelines for RARS.[232,475] A study of 94 children with RARS showed that 78.7% of these patients had IgG deficiency and 35.1% of these patients had AR.[489]

Table VIII-1. Summary of evidence for diagnosis of RARS

Items	Explanation
Aggregate Grade of Evidence	B **Endoscopy**: Level 1: 1 study; level 2: 2 studies; level 4: 1 study **Culture**: Level 1: 1 study; level 2: 1 study; level 4: 1 study **Imaging**: Level 2: 4 studies; level 3: 2 studies; level 4: 4 studies; level 5: 1 study **Additional testing**: Level 2: 3 studies

VIII.B.1. Establishing the Diagnosis of RARS

Establishing the diagnosis of RARS can be difficult, as often a provider will not see the patient exactly when they are at the height of their symptoms, and thus the exam and current symptomatology may be completely normal at the time of visit. An expert consensus has established appropriateness criteria for intervention for RARS based on properly establishing the diagnosis.[206] These criteria suggest that to confirm RARS, at least one episode should be confirmed by either CT or presence of mucopurulence on nasal endoscopy. The primary reason for this objective validation is that a majority of patients self-reporting ABRS do not actually show signs of this on a CT, and in one particular study, instead were given final diagnoses including rhinitis, migraine and facial pain disorder.[205]

This approach indicates the importance of instructing patients to come in to clinic to be evaluated using nasal endoscopy when they feel they are at the height of their symptoms before utilizing any treatment, and the need to fit them in during this time for evaluation. This also indicates that if nasal endoscopy does not show purulent drainage in spite of active symptomatology, then CT to fully evaluate the paranasal sinuses would be indicated. This can be helpful not only in proving sinonasal inflammation or infection, but also can disprove a sinus source of symptoms and allow the patient to pivot to another diagnostic pathway, such as primary headache workup and management.

In line with the above mentioned panel on appropriateness criteria for intervention in RARS, both otolaryngologists and radiologists have established expert panels to suggest appropriateness criteria for CT imaging in different forms of RS, and both groups agree that CT is indicated to completely evaluate RARS, although these expert opinions and consensus are not based on studies of very high level of evidence.[311,483]

Using Endoscopy and Imaging to Establish the Diagnosis of RARS

Aggregate Grade of Evidence: D (Level 4: 4 studies)
Benefit: Distinguish RARS from non-RS conditions
Harm: Although most point of care CT scanners are low-dose radiation, there is still a dose delivered to the patient; there may be delay in treatment as the patient waits for visit and endoscopy or CT scan; there may be discomfort associated with nasal endoscopy
Cost: Cost of either nasal endoscopy or CT scan or both
Benefits-Harm Assessment: Benefit very likely to outweigh harm.
Value Judgments: Importance of avoiding inappropriate treatment, importance of decreasing delay to appropriate treatment.
Policy Level: Option.
Intervention: Nasal endoscopy and/or CT imaging are an option during at least one episode of suspected RARS to appropriately confirm and diagnose RARS, and distinguish it from other diagnoses such as allergy exacerbation or primary headache syndromes. While there are considerable advantages in this approach, a policy level of "recommendation" cannot be made due to the level of the evidence.

Table VIII-2. Evidence for establishing the diagnosis of RARS

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Rudmik[206]	2019	4	Expert panel establishing appropriateness criteria	RARS	Establishing correct diagnosis of RARS	To establish the diagnosis of RARS, need four or more episodes of ABRS per year, with at least one of those episodes confirmed by CT or nasal endoscopy.
Barham[205]	2017	4	Prospective case series	Patients self-identified as having RARS	Abnormalities on sinus CT confirming sinonasal disease	Patients self-identifying as having RARS, with normal CT scans between episodes, rarely have positive CT scans during an exacerbation of symptoms.
Kirsch[483]	2017	4	Expert panel establishing appropriateness criteria	RARS	Establishing correct diagnosis of RARS	CT imaging can be used to help establish the diagnosis of RARS.
Setzen[311]	2012	4	Expert panel establishing appropriateness criteria	RARS	Establishing correct diagnosis of RARS	CT imaging can be used to help establish the diagnosis of RARS.

VIII.B.2. Differential Diagnosis of RARS

The differentiation of RARS from CRS remains difficult. Persistent RS lasting more than 12 weeks, with or without acute exacerbations, meets criteria for CRS. On a histopathological level, chronic changes including remodeling of the mucosa (basement membrane thickening, fibrosis, squamous metaplasia) are seen in CRS, as opposed to normal sinus anatomy seen in RARS in-between

episodes.[490] Recent research, however, suggests the symptom burden and health care costs of RARS and CRS are similar.[232,247,248]

The distinction of ABRS from AVRS is made based on the constellation and duration of symptoms indicative of a bacterial etiology.[31,88] ABRS lasts 10 or more days or is often associated with a double worsening of symptoms, compared to AVRS. Misdiagnosis has been reported based on the perceived association of discolored or purulent secretions alone with ABRS.[205]

Recent research by Beswick *et al.* calls into question alternative or concomitant diagnoses during diagnosis of RARS.[204] In patients meeting diagnostic criteria for RARS, one-half had a negative endoscopy during an acute exacerbation, indicating they may have been suffering from a different condition. Additionally, over one-third of patients had nasal inflammation seen in-between episodes, suggesting alternative or concomitant disease such as asthma or allergy. In patients with RARS, consideration should be given to potential predisposing factors, including asthma, cystic fibrosis, immunocompromised state, or ciliary dyskinesia.[88] Optional allergy and immune function testing may be helpful.[88]

Other conditions may produce episodic sinus symptom mimics leading to misdiagnosis. The differential diagnoses include headache (migraine, tension headache, cluster headache), AR, non-AR, TMJ disorder, dental pain, trigeminal neuralgia, or nonspecific facial pain. Among 27 patients presenting to an otolaryngologist for "sinus" symptoms, Barham *et al.* showed that only 1 patient demonstrated acute CT changes consistent with RARS; the final diagnoses for the remaining patients were rhinitis (47%), headache/migraine (37%), and nonspecific facial pain (12.5%).[205] Schreiber *et al.* (n=2991) showed that 88% of patients with a history of "sinus" headaches actually met International Headache Society criteria for migraine-type headache, originally misdiagnosed due to the false belief that nasal and ocular symptoms are not associated with migraine due to a tendency to associate nasal and ocular symptoms as being uncharacteristic of migraine.[491] Bhattacharyya *et al.* discovered that the unfamiliarity with RARS as a diagnosis, particularly among non-otolaryngologists, and the underuse of nasal endoscopy and CT imaging for RARS suggested an underdiagnosis of disease, resulting in significant health care costs.[232] Accurate diagnosis remains difficult but essential for optimal treatment outcome.

VIII.C. Pathophysiology of RARS

VIII.C.1. Contributing Factors for RARS: Allergy, Immunologic Defects, and Resistant Bacteria

Pathophysiologically, inflammatory edema of the sinonasal mucosa is thought to lead to obstruction of the sinus ostia, decreased MCC, and retained secretions. Several factors can predispose an individual to RARS. These include immunologic deficiencies, colonization with resistant bacteria, and allergies. Although RARS is well characterized as its own entity, few studies specifically delineate RARS from CRS or ABRS and some of what follows is informed from conglomerated data of these various conditions.

Patients with immunodeficiency are predisposed to developing RARS. The most common immunologic deficiency in patients with RARS is humoral in nature including selective IgA deficiency, IgG deficiency (both total and selective subtypes), and combined variable immunodeficiency (CVID).[492,493] Although the exact prevalence of immune deficiency in patients with RARS is unknown, a study by Chee *et al.* found that 40% of patients with RARS had some form of anergy.[493] Many patients with mild immunodeficiencies, especially selective IgA deficiency can be otherwise asymptomatic, increasing the difficulty in diagnosis. Patients with RARS have been found to have

abnormalities in the antimicrobial factors of their nasal glandular secretion; specifically decrease in levels of IgA, lactoferrin, and lysozyme proteins.[494] In patients with CVID, approximately 66% will develop RARS.[495] Other causes of immune deficits can also predispose patients to RARS such as human immunodeficiency virus-acquired immunodeficiency syndrome (HIV-AIDS) or patients with hematopoietic stem cell transplantation.[496,497] In patients with HIV-AIDS, there appears to be a correlation between decreasing CD4 count and increasing rates of ABRS.[496]

The microbiology of ABRS is well established with the most common pathogens being *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*.[498] Studies have shown similar bacterial pathogens implicated in RARS.[10] However, in patients with RARS, about 62.5% of bacterial isolates develop antimicrobial resistance.[499] In addition, the bacterial isolate during repeat culture changes in 59% of patients.[499] These changes can prove challenging in treatment of patients with RARS encouraging the use of culture driven antibiotic therapy and avoidance of incorrect antibiotic overuse.

The relationship between allergies and RARS is controversial. The inflammation associated with allergic disorders can lead to increased susceptibility to recurrent sinus infections. Some reports demonstrated an increase in positive allergy testing in patients with RARS while others suggested lower rates of allergies in patients with RARS compared to CRS.[500,501] This difference may be explained by difficulty in differentiating RARS from an acute on chronic rhinosinusitis exacerbation. In an attempt to differentiate AR from RARS, one study found an increase in the expression of toll-like receptor 9 in the sinonasal epithelium in patients with AR and RARS compared with patients with AR alone.[502] This finding may be the result of the upregulation of innate markers after repeated microbial insults.

In conclusion, there is a paucity of information on the pathophysiology of RARS in the literature and what is available is controversial. The available data suggests that patients with immunologic deficits, allergies, and colonization with resistant bacteria are predisposed to RARS (Table VIII-4).

Allergy, Immunologic Defects, and Resistant Bacteria as a Contributing Factor for RARS

Aggregate Grade of Evidence: C (Level 3: 4 studies, Level 4: 6 studies)
Benefit: Ability to identify patients who are predisposed to developing RARS
Harm: False identification of conditions that may not be associated with RARS
Cost: Cost associated with immune testing, allergy testing, or sinus culture
Benefits-Harm Assessment: Preponderance of benefit over harm
Value Judgement: Identification of patients at risk for RARS will allow for more targeted and effective therapeutic approach
Policy Level: Recommendation
Intervention: Consider immunologic testing, allergic testing, and bacterial culture in patients with concern for RARS

Table VIII-3. Evidence for non-anatomic pathophysiology contributing to RARS

Study	Year	LOE	Study Design	Study Groups	Clinical End-point	Conclusion
Bento [497]	2014	3	Retrospective cohort	Patients with hematopoietic stem cell transplantation	Frequency of RS	36% of patients developed RS.
Melvin [502]	2010	3	Retrospective cohort	13 patients with RARS and AR 8 patients with AR only	Flow cytometry for TLR9 in sinonasal epithelial cells	66% of patients with RARS and AR have increased TLR9 expression compared to 32% of patients with AR.
Chee [493]	2001	3	Retrospective cohort	79 patients with RS	Immunologic evaluation	40% of patients with anergy, 18% with IgG deficiency, 17% with IgA deficiency, 5% with IgM deficiency, 10% with CVID
Jeney [494]	1990	3	Retrospective cohort study	14 patients with RARS 24 patients without RS	Nasal secretion analysis after challenge with methacholine or histamine	Decrease in total protein, secretory IgA, lactoferrin, and lysozyme proteins in patients with RARS.
Poetker[501]	2008	4	Case Control	22 patients with RARS 22 patients with CRSsNP	Patient presentation and outcomes after sinus surgery	32% of patients with RARS were diagnosed with AR while 50% of patients with CRS were diagnosed with AR
Aghamohammadi[495]	2005	4	Case series	Patients with CVID	Frequency and spectrum of infections	66% of patients develop RARS.
Brook[499]	2004	4	Case Control	8 patients with RARS	Bacteria cultures	62.5 % of patients had bacteria with antimicrobial resistance and 59% had a change of organisms in repeat

						cultures.
Gutman[500]	2004	4	Case Control	48 patients with sinus surgery and allergy testing	Allergy testing results	63% responded to at least one allergen, 54% with perennial allergen.
Sethi [492]	1995	4	Case series	20 patients with immunologic deficiency and RARS	Immunologic findings	8 patients with selective IgA deficiency, 5 patients with CVID, 4 patients with hypogammaglobulinemia, 3 patients with low IgG1.
Zurlo [496]	1992	4	Case series	75 patients with HIV and radiographic RS	Clinical and laboratory findings	67% of patients were symptomatic, 43% had CD4 counts less than 100 cells/mm^3.

VIII.C.2. Contributing Factors for RARS: Anatomic Factors

The literature that evaluates the impact of anatomic variants in RS patients is comprised of radiographic studies that evaluate CT scans in these patients. There are three studies published examining the presence of anatomic variants in RARS patients suggesting that anatomy may play a role. One was a case-controlled study comparing sinonasal anatomic variants between RARS and control patients who had undergone imaging unrelated to sinonasal pathology (*i.e.*, pituitary and ear imaging) (Table VII-5). This study examined 36 adult RARS patients compared to 42 control patients without RS.[341] There was statistically higher number of infraorbital (Haller) cells and a smaller infundibular diameter in the RARS group compared to the control group. There was a trend toward association with NSD and concha bullosa in the RARS group, however the study numbers were small and may have been insufficient powered. This data suggests that anatomic changes of the osteomeatal complex may predispose one to RARS with important implications to surgical targets.

Another study investigating the role of anatomy in RARS was a single-institution case series investigating sites of inflammation within a given scan and correlation of this anatomy with clinical course.[207] This study examined the incidence and importance of anatomic variants, such as a frontal cells, infraorbital ethmoid cells, concha bullosa cells, or septal deviations in patients with RARS. They examined 26 patients and found that type 2 frontal cells correlated with a greater number of years with RARS (P=0.0363). The study did not find a higher incidence of anatomic variants in the RARS group compared to prior published literature reporting anatomic variants and did not find an association between Lund Mackay score and anatomic variants. Further study investigating anatomic associations with RARS along with the clinical associations will help better clarify the etiology and further intervention of this disease.

The final study investigating anatomy was a single-institutional case series of 160 patients with a history of RARS with categorization of anatomic variants that might impact the ostiomeatal complex.[503] More specifically, this study was examining patterns of concha bullosa, paradoxical middle turbinates and septal deviation as potential factors impacting the ostiomeatal complex. The study is unfortunately undermined by ambiguous objective inclusion criteria (patients with evidence of ARS on scan were excluded) and a lack of a control group limiting the ability to draw conclusions beyond that the concha bullosa size and degree of septal deviation correlate.

Table VIII-4. Evidence for Anatomic Contributing Factors for RARS.

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Alkire[341]	2010	3	Retrospective case-control	36 patients meeting strict criteria for RARS; 42 control patients	Anatomical variants seen on CT	Higher presence of infraorbital ethmoid cells and smaller infundibular widths in RARS patients
Loftus[207]	2016	4	Retrospective case series	26 patients meeting criteria for RARS were evaluated for anatomic variants	Anatomical variants seen on CT	Anatomic variants in RARS patients was not higher than the general population, but underpowered without control cohort
Mohapatra[503]	2017	4	Retrospective case series	160 patients with history of RARS, but negative scans	Anatomical variants seen on CT	Most common anatomic variants included septal deviation > concha bullosa > paradoxical middle turbinate, but no comparison group

VIII.D. Management of RARS

VIII.D.1. RARS Management: Intranasal Corticosteroids (INCS)

A total of 3 double-blinded RCTs (DBRCTs) were identified assessing the effect of INCS on symptom outcomes of RARS patients (Table VIII-6). All studies reported improvement in symptoms in the treatment groups and no serious adverse effects of INCS. A systematic review by van Loon *et al.* summarized the impact of INCS on symptom relief in RARS patients based on these 3 DBRCTs, citing overall limited evidence.[431] Dolor *et al.* (n=95) demonstrated significant difference in median days to clinical success (6 in treatment group versus 9 in placebo group; p=0.01) with fluticasone.[421] Meltzer *et al.* (n=407) demonstrated improvement of total symptom scores and specific symptoms of headache, congestion, and facial pain with mometasone.[435] Qvarnberg *et al.* (n=40) demonstrated improvement in facial pain and sensitivity with budesonide.[504]

One major limitation is that none of the studies defined RARS according to the AAO-HNS definition of 4 or more episodes yearly with absence of intervening symptoms, thereby limiting applicability to RARS patients. Another limitation was inclusion of additional therapeutic agents in addition to INCS. All studies included antibiotic co-treatment, and one also included nasal decongestant therapy. Therefore, the benefits of INCS as monotherapy and its potential in reducing antibiotic prescription are unclear. Another limitation is the variability of types and doses of INCS and duration of therapy. Finally, INCS were used in these studies during periods of acute exacerbation, and thus efficacy as a preventative therapeutic measure is unknown. Dolor *et al.* showed fewer patients experienced ARS recurrences during follow-up (7 in treatment group versus 13 in placebo group; p=0.06), but this difference was not significant.[421]

Intranasal Corticosteroids for RARS

Aggregate Grade of Evidence: B (Level 2: 3 studies).
Benefit: Generally well tolerated. May decrease time to symptom relief. May decrease overall symptom severity, as well as specific symptoms of headache, congestion, facial pain, and sensitivity.
Harm: Mild irritation (see Table II-1).
Cost: Moderate depending on preparation.
Benefits-Harm Assessment: Balance of benefit and harm.
Value Judgments: Patient populations studied did not adhere to the AAO-HNS clinical practice guidelines definition of RARS, and therefore conclusions may not be directly applicable to this population. No studies examined the efficacy of INCS in preventing ARS recurrences, so no conclusions can be made in this regard either.
Policy Level: Option.
Intervention: Option for use of INCS spray for sinonasal symptoms during acute exacerbations of RARS.

Table VIII-5. Evidence for INCS in the management of RARS.

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Dolor[421]	2001	2	DBRCT	10-day cefuroxime, 3-day xylometazoline, and 1. 21-day INCS 2. 21-day placebo	Symptoms; QoL scores (SNOT-20 and SF-12); number of ARS recurrences	INCS with xylometazoline and cefuroxime improves clinical success rates and accelerates time to recovery. No significant different in number of ARS recurrences.
Meltzer[435]	2000	2	DBRCT	21-day amoxicillin-clavulanate and 1. 21-day INCS 2. 21-day placebo	Symptoms	INCS produced greater relief of total and specific (obstructive) symptoms. No

						difference in secretory symptoms.
Qvarnberg[504]	1992	2	DBRCT	7-day erythromycin and 1. 3-month INCS 2. 3-month placebo	Symptoms	INCS resulted in greater reduction in facial pain and sensitivity. No difference in clinical outcomes.

VIII.D.2. RARS Management: Antibiotics

RARS patients average 4 courses of antibiotics yearly.[232,486] Current AAO-HNS guidelines do not provide recommendations regarding antibiotic use in RARS.[88] A recent, exhaustive systematic review investigated the effectiveness of short-course antibiotics on the severity and duration of symptoms and recurrences in RARS patients, and failed to identify any placebo-controlled studies.[486] Based on this lack of evidence, the authors of the systematic review concluded that uncomplicated ARS in patients with RARS should be prescribed antibiotics based on the same criteria used to manage primary or sporadic episodes of ARS. More recently, a randomized, double-blinded, placebo-controlled trial among children with RARS (n=40) showed azithromycin prophylaxis three times a week for 12 months significantly reduced RS episodes from 5 to 0.5 per year,[505] although it is difficult to extrapolate findings among a pediatric population (of which, 83% demonstrated IgG subclass deficiencies) to an adult population with RARS. Other limitations included the possible anti-inflammatory effects of macrolides contributing to the results, along with the difficulty in assessing the risk of long-term macrolides on bacterial resistance. After careful examination of the available literature, it is not possible to provide additional recommendations for the use of antibiotics in RARS different from recommendations for treating ABRS.

VIII.D.2. RARS Management: Endoscopic Sinus Surgery

A total of 7 studies were identified examining patient outcomes after ESS in RARS patients (Table VIII-7). Six studies looked at quality-of-life (QoL) scores and objective measures, while two studies reported antibiotic utilization. All studies used standardized inclusion criteria and disease definitions for RARS as defined by AAO-HNS guidelines.[88]

Bhattacharyya *et al.* reported significant improvement in Rhinosinusitis Symptom Inventory (RSI) domains, antihistamine use, workdays missed, and acute episodes among 19 RARS patients undergoing ESS with a mean follow-up of 19 months, although reductions in antibiotic use after ESS were not significant.[506] Poetker *et al.* showed significant improvement in the RSDI and CSS total and symptom domains, along with significantly fewer sinus medications used postoperatively, among 14 RARS patients with a mean follow-up of 30 weeks.[501] Bhandarkar *et al.* reported a 61.2% reduction in the average time on antibiotics postoperatively among RARS patients (n=21), similar to patients with CRS, with a mean

follow-up of 17 months.[507] Costa *et al.* showed that among 142 RARS patients undergoing ESS versus medical management, the ESS cohort experienced greater reduction of SNOT-22 scores at 3, 6, and 12 months follow-up.[208] A crossover cohort (n=45) who initially underwent medical management converted to ESS at an average period of 4.8 months, and these patients also showed significant symptom reduction after ESS. Steele *et al.* showed that RARS patients (n=20) experienced significant improvement in health utility values to near normative values postoperatively, similar to patients with CRSsNP, with a mean follow-up of 14 months.[508] Steele *et al.* also demonstrated significant improvements in SNOT-22 and RSDI scores, as well as decreased antibiotic use and decongestant use following ESS for RARS patients (n=20).[248] RARS patients reported fewer lost productivity days postoperatively, similar to CRSsNP patients, though the difference in pre- and post-operative scores was not statistically significant. Sohn *et al.* reported a RARS cohort (n=43) experienced significant improvement in SNOT-20 scores after ESS at 6 months follow-up.[509] Limitations with these studies include a lack of randomized control trial data and the inherent difficulties in studying RARS related to accurate diagnosis.

While all above studies met AAO-HNS criteria for RARS, additional inclusion criteria differed. Rudmik *et al.* developed an expert panel to develop appropriateness criteria for ESS candidacy.[206] Minimum criteria included 4 or more annual episodes of ABRS, confirmation of at least one episode using endoscopy or CT imaging, shared decision making between patient and physician, and either a failed trial of INCS or significant reduction in RARS-related productivity. Leung *et al.* performed a cost-benefit analysis suggesting that ESS becomes economically beneficial when patients experience a total of 5 or more episodes over a 12-month period.[202] This study considered lost work time and productivity, along with medication side effects and costs with recurrent infections, compared to the time, costs, and surgical risks of ESS and recovery.

Two studies involving balloon sinus dilation (BSD) in RARS patients were identified. Current guidelines delineate a role for BSD in RARS, although CT imaging is required showing evidence of ostial occlusion and mucosal thickening.[510] The first randomized, placebo-controlled, unblinded trial showed that patients who received in-office BSD and medical management for RARS (n=29), compared to patients receiving in-office sham procedure and medical management (n=30), reported significant improvements in CSS and RSDI scores at 8 and 24 weeks follow-up.[511] BSD also significantly reduced mean number of sinus infections at 24 weeks follow-up. Limitations of the trial included a lack of double blinding and variability in the surgeons' discretion regarding which sinuses to dilate, noting a high number of frontal sinuses performed. Levine *et al.* reported significant improvement in the SNOT-20 and RSI scores at 1 year among 17 RARS patients with in-office BSD of the maxillary sinus ostia and ethmoid infundibula.[512] Mean number of antibiotic courses, sinus-related physician visits, and acute infections were significantly decreased. However, use of INCS or antihistamines and workdays missed were not changed significantly.

There were no studies identified comparing ESS to BSD among RARS patients. Therefore, it is not possible to provide a recommendation for one option over the other, and both options should be discussed with the patient as part of the shared decision making process.

Endoscopic Sinus Surgery for RARS

Aggregate Grade of Evidence: B (Level 2: 1 study; level 3: 7 studies; level 4: 1 study).
Benefit: Postoperative improvement in patient symptoms. Reduction in postoperative antibiotic utilization, acute episodes, and missed workdays. Results appear comparable to CRS cohorts.
Harm: Surgery is associated with potential complications (see Table II-1).
Cost: Significant costs are associated with ESS.
Benefits-Harm Assessment: Preponderance of benefit over harm.
Value Judgments: Patients with RARS may benefit both symptomatically and medically from ESS or BSD. For BSD, pre-operative CT imaging of sinus/ostiomeatal complex involvement during an acute exacerbation is required.
Policy Level: Recommendation.
Intervention: ESS or BSD is recommended for patients with RARS.

Table VIII-6. Evidence for ESS in the management of RARS.

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Sikand[511]	2018	2	Unblinded RCT	In-office BSD and MedMgt In-office sham procedure and MedMgt	CSS, RSDI, recurrent infections	Significant improvement in CSS and RSDI scores. Reduced mean number of sinus infections.
Sohn[509]	2018	3	Case-control	ESS in RARS, CRSsNP, and CRSwNP	SNOT-20	Significant improvement in SNOT-20 scores.
Steele[508]	2016	3	Case-control	ESS in RARS and CRS	SF-6D	Significant improvement in health utility values.
Steele[248]	2016	3	Case-control	ESS in RARS and CRS	SNOT-22, RSDI, antibiotic utilization, decongestant use	Significant improvement in SNOT-22 and RSDI scores. Decreased antibiotic and decongestant use.
Costa[208]	2015	3	Case-control	ESS versus MedMgt in RARS	SNOT-22	Greater symptomatic improvement (SNOT-22 scores) compared to MedMgt.
Levine[512]	2013	3	Case-control	BSD in RARS and CRS	SNOT-20, RSI	Mean improvement in SNOT-20 and RSI scores in RARS group comparable to the

						CRS group.
Bhandarkar[507]	2011	3	Case-control	ESS in RARS and CRS	Antibiotic utilization	61.2% reduction in antibiotic utilization in RARS patients.
Poetker[501]	2008	3	Case-control	ESS in RARS and CRS	CSS, RSDI; Endoscopic exam, CT scores	Significant reduction in CCS and RSDI domain scores. Reduction in sinus medications use based on CSS scores.
Bhattacharyya[506]	2006	4	Case series	ESS in RARS	RSI	Significant decrease in RSI scores. Decreased antihistamine use, workdays missed, and acute episodes.

IX. Chronic Rhinosinusitis without Nasal Polyps (CRSsNP)

IX.A. Incidence and Prevalence of CRSsNP

CRSsNP is a common disease but the true prevalence is difficult to measure as the diagnosis involves a combination of both subjective symptoms and objective confirmation. Most epidemiological studies of CRS do not distinguish between CRSsNP and CRSwNP but rather CRS combined. Historically, studies which investigated the prevalence of CRS via questionnaires varied widely in reported estimates. National surveys in the U.S. assessing CRS symptoms have estimated the prevalence ranging from 2.1%-13.8%.[9,11-13] In Europe, the prevalence for CRS symptoms has been reported to range from 6.9%-27.1% depending on the country.[14] In China, a survey of 10,636 participants in 7 cities reported a prevalence ranging from 4.8%-9.7% depending on the city.[15] Recently, two CRS epidemiologic studies included objective confirmation of CRS with radiologic imaging. In those studies, the prevalence of CRS ranged from 1.7-8.8%.[18,19]

Billing codes for CRS have been analyzed to estimate the incidence of CRS. In a Canadian population-based analysis of ICD-9 codes, the incidence of CRS was found to be 2.3-2.7 per 1000 people over 1 year.[16] A similar analysis of ICD-9 codes in Pennsylvania found the average incidence of CRSsNP to be 1048±48 per 100,000 person-years.[17]

IX.B. Diagnosis of CRSsNP

CRS is defined by greater than or equal to 12 weeks of a combination of subjective and objective metrics. Diagnostically, CRSsNP and CRSwNP differ only in the objective finding of nasal polyposis. The cardinal symptoms of CRS are mucopurulent drainage (rhinorrhea or post-nasal drip), nasal obstruction, hyposmia and facial pressure/pain.[146] Additional regional and systemic symptoms associated with CRS include oropharyngeal discomfort, otalgia, halitosis, dental pain, cough, malaise, headache and fatigue.[146] These symptoms are highly sensitive individually but not specific.[513,514] Objective confirmation of inflammation by endoscopy or imaging is required.

The most common symptom of CRS is nasal obstruction/congestion.[31,149] Different study populations have shown variability in the relative prevalence of the other symptoms.[31,201] Evidence has shown combining two or more symptoms together with objective findings of disease (imaging, endoscopy) substantially increases diagnostic specificity and positive predictive value.[146,201,480] The 1997 American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) guideline used major and minor criteria for the diagnosis of CRS.[147] More recent guidelines from EPOS 2012 and AAO-HNS 2015 evolved to focus on the four most sensitive symptoms of CRS listed in Section V.B. The other regional and systemic symptoms may be present and related to CRS but are not included in the definition. Both

the EPOS 2012 and AAO-HNS 2015 guidelines require at least two of these four symptoms to be present to make the diagnosis of CRS.

Although these criteria are widely adopted for research purposes and clinical care, there remain opportunities to refine the diagnostic criteria. In order to improve specificity, EPOS 2012 stipulates that either nasal obstruction or discharge must be present to make the diagnosis of CRS. This strategy was validated in a European cohort by the Global Allergy and Asthma European Network of Excellence (GA^2LEN).[515] In an American cohort, Bhattacharyya found that more complex heuristics are required to improve upon equally weighting the four symptoms.[516] Recent studies conclude that facial pain is the least specific symptom of CRS and suggest it could be removed from the diagnostic criteria without adversely reducing sensitivity.[517,518] In addition, as understanding of CRS evolves, it is becoming increasingly clear that CRS is a broad definition encompassing multiple endotypes. Expanded diagnostic criteria may be possible as clarification of these subtypes emerges. At the time of this writing, however, there remains no consensus regarding altering the diagnostic criteria. Therefore, the ICAR-RS diagnostic criteria mirror the AAO-HNS 2015 criteria.

Differences in treatment responses and recurrence rates also supports separating the CRS into categories as CRSsNP shows improved outcomes and decreases in recurrence rates.[519] Endotype-driven diagnostic techniques are an emerging modality that may inform treatment strategies including candidacy for novel therapeutics.[55,520,521]

IX.B.1. Establishing the Diagnosis of CRS

Because of limited data, CRSsNP and CRSwNP are combined in this analysis.

The definition of CRS in adults is based on guidelines that have remained consistent over the last 3 decades. The diagnosis of CRS entails sinonasal inflammation for at least 12 consecutive weeks with the presence of at least 2 major symptoms and at least one documented objective finding.[143,522,523] The major symptoms include: 1) nasal obstruction or congestion, 2) nasal discharge (anterior or posterior), 3) facial pain or pressure, or 4) loss of smell.[479,524] While hyposmia is a positive predictor of CRS,[516,525] it is important to note many studies prior to 2008 did not distinguish between CRSsNP and CRSwNP.

The diagnosis must be confirmed by one of the following objective measures: 1) sinus inflammation and/or purulence on nasal endoscopy or (2) sinus inflammation on CT.[88,480,526] Reliance on symptoms alone for the diagnosis of CRS has a high false positive rate.[516] Self-reported CRS symptoms have a sensitivity of 84-87% and a lower, more variable specificity of 12.3-82%.[480,527] The addition of an objective measure improves the diagnostic accuracy.[88,480,522] While interrater variability on endoscopy for CRS exists,[528] the diagnostic accuracy of nasal endoscopy increases for patients with Lund-Kennedy scores $\geq$2.[253,529] The addition of nasal endoscopy does not improve the diagnosis of CRS in patients who fail to meet the symptom guidelines.[516]

Establishing the Diagnosis of CRS

Aggregate grade of evidence: B (Level 1: 5 studies; level 2: 4 studies; level 3: 5 studies; level 4: 1 study)
Benefit: Prompt identification of patients with CRS allows for treatment and reduced costs/loss of productivity.
Harm: Increased cost associated with diagnostic testing. Nasal endoscopy may cause discomfort and irritation while computed tomography yields low dose radiation.
Cost: Associated costs of in-office procedures and imaging.
Benefits-Harm Assessment: There is a significant benefit over harm in combining subjective symptoms and objective parameters in diagnosing CRS as well as ruling out other diagnoses which may otherwise be treated as CRS.
Value Judgement: Patients with possible CRS are often referred to otolaryngologists for further evaluation. Patients with symptoms similar to those of CRS that are referred to otolaryngologists whose objective examination does not show CRS, will be saved from the harm of incorrect and often repetitive antibiotic administration and be directed more rapidly along the correct pathway to alternate diagnosis.
Policy Level: Recommendation
Intervention: An algorithm can be used to diagnose CRS. Aside from the presence of two cardinal symptoms for ≥12 weeks, the addition of one objective finding on CT or nasal endoscopy greatly increases diagnostic accuracy.

Table IX-1. Evidence for establishing the diagnosis of CRS

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoints	Conclusions
Kim[529]	2019	1	Meta-analysis (16 retrospective studies)	Studies involving diagnostic evaluation of CRS, comparing endoscopy and CT with sensitivity and specificity analysis and correlation	Evaluate accuracy of nasal endoscopy vs CT in diagnosing CRS	Endoscopic and CT findings were significantly associated (r=0.8543). The diagnostic accuracy of endoscopy correlated with Lund-Kennedy score ≥ 2.

Orlandi[1]	2016	1	Systematic Review	Adult RS		Diagnosis based on 12 or more weeks of cardinal symptoms; objective evidence required for diagnosis.
Rosenfeld[88]	2015	1	Systematic Review (5 guidelines, 42 systematic reviews, 70 RCTs)	Adults with RS		The diagnosis of CRS should include the presence of sinonasal inflammation as seen on anterior rhinoscopy, nasal endoscopy or CT.
Kaplan[142]	2014	1	Clinical Practice Guidelines (Canada)	CRS		CRS diagnosed based on type and duration of symptoms plus objective findings of nasal inflammation.
Meltzer[479]	2011	1	Review of Consensus Statements	RS and subtypes		Require presence of 2/4 symptoms (nasal congestion, anterior/posterior mucopurulent drainage, facial pain/pressure, decreased smell). Diagnostic testing is key difference between CRS and ARS.
Cottrell[522]	2018	2	Literature review (3 guidelines, 1 consensus statement)	Adult CRS pts	Develop CRS-specific quality indicators to evaluate diagnosis and management	Strong recommendation for the diagnostic criteria. Diagnosis of CRS entails at least 2 CPODS present for 8-12 weeks plus documented objective finding (CT or endoscopy) of inflammation.
Thomas[530]	2008	2	Clinical Practice Guidelines	CRSwNP	Evidence-based methodology to identify and grade recommendations for management of RS	CRS is defined as presence of at least 2 symptoms for > 12 weeks, one of which must be nasal discharge or nasal obstruction in addition to presence of facial pain/pressure or hyposmia.
Lanza[523]	2004	2	Review	CRS patients	Diagnostic criteria for CRS	CRS defined as presence of 2+ major or 1 major & 2+minor for 12 consecutive weeks with objective evidence that disease is present. Single most important finding is presence of purulence in

						nasal cavity or posterior oropharynx.
Benninger[143]	2003	2	Review	CRS patients	Multidisciplinary task force formed to develop definitions for CRS	Duration of disease > 12 consecutive weeks or >12 weeks of physical findings Presence of 1+ signs of inflammation: • Discolored nasal drainage • Edema/erythema middle meatus • Generalized or localized edema (if not involving bulla or middle meatus, imaging required) Imaging modality confirming diagnosis
Workman[527]	2019	3	Prospective cohort study	Adults with RS	Evaluate the value of self-reporting questionnaires on diagnostic assessment of CRS	Sensitivity of self-reporting for CRS was 84% and specificity 82%
Hsueh[525]	2013	3	Retrospective cohort study	Adults with CRS Adults without CRS	Symptoms from Task Force on Rhinosinusitis and International Headache Society criteria	Symptoms from IHS for primary headache can differentiate CRS patients from non-CRS patients with CRS-symptoms. Hyposmia is positively predictive for CRS while facial pain/headache are negatively predictive
Raithatha[528]	2012	3	Prospective multi-institutional study	Adult patients with CRS complaints	Evaluate the interrater agreement of nasal endoscopy findings in CRS	Significant variability in interrater agreement for nasal endoscopy findings. Recommendation for standardization of nasal endoscopy interpretation
Bhattacharyya[480]	2010	3	Prospective Diagnostic Cohort	202 adult patients who presented for evaluation of CRS.	Improvement in diagnostic accuracy of CRS with use of nasal endoscopy	For patients meeting symptom criteria for CRS, a nasal endoscopy can improve diagnostic accuracy (improves the specificity, PPV, and NPV to 84.1, 66, 70.3 from 12.3, 39.9, 62.5, respectively) Patients with a positive endoscopy can be treated with empiric therapy for presumed diagnosis of CRS Addition of nasal endoscopy was not shown to statistically

						improve diagnosis of CRS in patients who failed to meet guidelines
Marple[526]	2009	4	Literature Review	Adult CRS	Evaluate algorithms for the diagnosis and management of CRS	Diagnosis of CRS requires presence of symptoms > 12 months. Patients with CRS symptoms but normal physical exam should undergo nasal endoscopy. Patients with negative physical findings of CRS should be evaluated for allergy or nasal surgery.
Bhattacharyya[516]	2006	3	Prospective double-blind diagnostic study	703 patients referred with CRS	Evaluate correlation between CRS symptoms and radiographic findings.	Presence of polyps and dysosmia can distinguish between normal and diseased patients. Failure of nasal steroids after 5-week trial suggest possible CRS and should prompt imaging confirmation Presence of polyps, absence of dental pain, low congestion scores in presence of dental pain predict true CRS

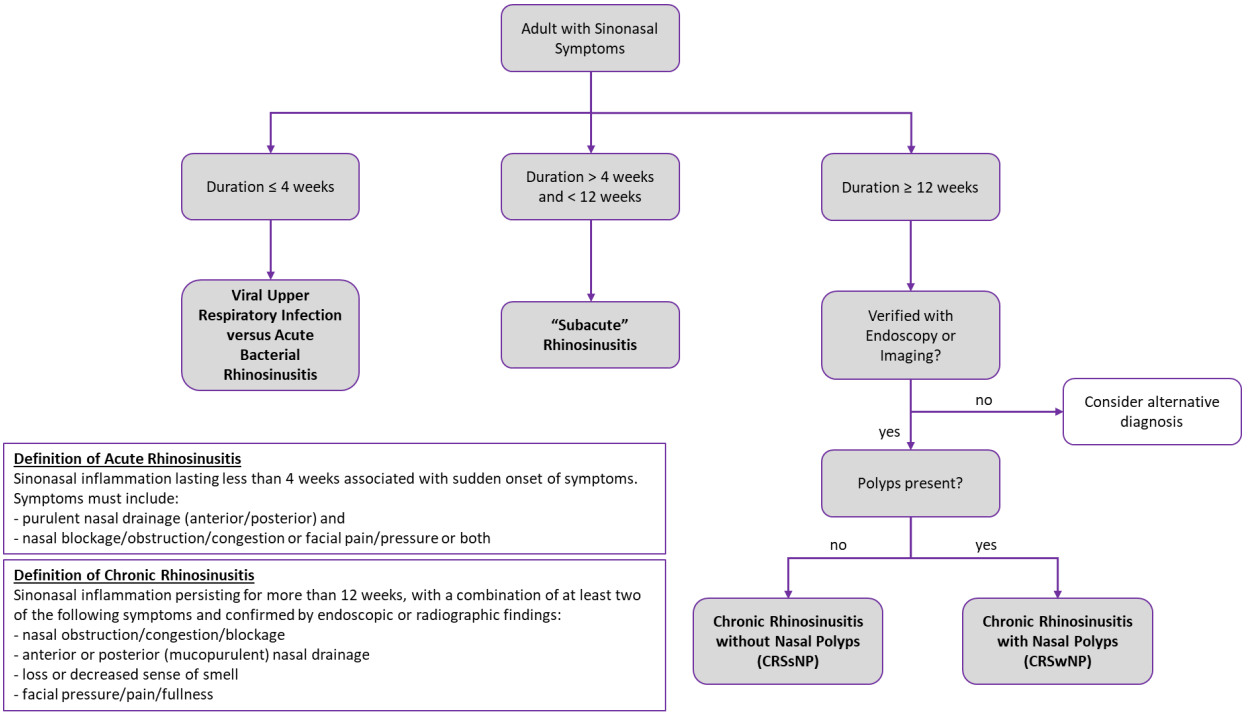


Figure IX-1. Diagnostic algorithm for diagnosing CRS

IX.B.2. Differential Diagnosis of CRSsNP

Because of the broad differential for CRSsNP, it is frequently difficult to differentiate it from other diseases without diagnostic modalities including nasal endoscopy and radiologic examination.[516,531] AR is a hypersensitivity of the nasal mucosa to foreign substances mediated through IgE antibodies.[532] In most cases, sneezing and itching are clues to distinguish AR from CRS, though not in all cases.[533] Another symptomatic mimic of CRSsNP is non-AR, which includes non-AR with eosinophilia syndrome (NARES), hormonal rhinitis, drug-induced rhinitis, irritant rhinitis, atrophic rhinitis and idiopathic rhinitis.[534,535] Although only a small proportion of patients with purulent CRS without coexisting chest disease complain of cough, CRS should be differentiated from gastroesophageal reflux and asthma by physical examination.

In the case of CRS with recurrent acute facial pain and pressure episodes, it is not easy to differentiate it from primary headache disorders, such as migraine and tension-type headache, because they are commonly accompanied by sinus-related symptoms like rhinorrhea and nasal congestion.[536-538] To rule out the primary headache and similar disorders, such as myofascial pain and temporomandibular joint pain, an accurate history and physical exam are needed. Chronic dental infection, foreign body, and both benign and malignant sinonasal neoplasia must be included in the differential diagnosis of unilateral

CRS.[539S1] Most of these conditions can be eliminated by a thorough physical exam including nasal endoscopy along with appropriate imaging (CT or MRI).

If nasal discharge is unilateral and clear, clinicians should rule out cerebrospinal fluid (CSF) rhinorrhea.[540] History of trauma and surgery, and salty taste of discharge may be important clues for diagnosis.[541] Detection of β2-transferrin in nasal secretions confirms CSF.[542]

Patients with obstructive sleep apnea often have similar symptoms as CRS patients, especially as facial pressure and nasal obstruction are common symptoms in both types of patients, so differential diagnosis is necessary.[543]

IX.B.3. Cost Effective Work Up of CRS

Because of limited data, CRSsNP and CRSwNP are combined in this analysis and recommendations.

There are few evidence-based reviews which directly address recommendations for the cost-effective diagnosis of adult CRS. Since any discussion of the cost effectiveness of CRS is dependent on disease definitions in use, the transition from a symptom-combination definition to more recent consensus statements requiring appropriate symptoms *combined* with objective signs of inflammation in the form of CT imaging or endoscopy has had significant implications on the costs of CRS diagnosis.[1,31,88,146,147,151]

Although relative consensus exists for the inclusion of objective findings within the diagnostic criteria of CRS there are scarce studies that address the optimal timing and sequence of such testing for use in validation of a CRS diagnosis. Published algorithms recommend establishing a symptom-based definition of CRS through the patient history, followed by nasal endoscopy.[544-546] Diagnostic imaging, especially CT imaging, is strongly recommended for evaluation for pre-operative planning for sinus surgery, and complications for CRS,[547] but also is critical for evaluating patients with unilateral CRS given the high prevalence of alternate pathology (*e.g.*, odontogenic, fungal or neoplastic). It is also helpful with the symptomatic patient with equivocal or normal findings on endoscopy where treatment with oral antibiotics or corticosteroids is being considered.[1,548,549] Furthermore, discussion of the cost efficiency of CRS diagnosis is highly dependent on healthcare system-specific direct costs and availability of professionals, diagnostic modalities, and therapeutic regimens for CRS. Indirect costs, including radiation exposure, time lost from work, societal costs from engendering antibiotic resistance, cost of incidental findings workup and any potential complications related to further diagnostic or therapeutic interventions, are more difficult to measure and will generally be excluded from this analysis. The following recommendations focus on diagnostic algorithms within the context of the cost and availability of modalities in the US, based on existing evidence.

IX.B.3.a. CRS Diagnosis Using "Symptoms Alone"

The symptom-based component for CRS diagnosis currently emphasizes the four cardinal symptoms of nasal obstruction, nasal discharge, facial pain or pressure, and reduction or loss of smell. Of note, component symptoms no longer utilize the "minor" symptoms (headache, fever, halitosis, fatigue, dental pain, cough, and ear symptoms) advanced by prior guidelines due to their frequent absence in CRS and overlap with other medical conditions.[13,514,515,549] Nonetheless, the cardinal symptoms, even when used in the combinations recommended by consensus statements, are common in the general population with between 10-13% of US and European adults meeting current CRS symptom-combination and duration definitions.[13,515] Of the cardinal symptoms, prior studies consistently demonstrate discolored nasal discharge and smell loss—individually and especially in combination—enhance positive predictive value of symptom criteria for CRS diagnosis.[514,516,548,550] Nasal obstruction is almost universal and has the highest average severity among patients with CRS, but its absence in the presence of other cardinal symptoms may be indicative of a non-CRS etiology.[516,525,546,551] Other studies suggest that facial pain (but not pressure) is not universal and its presence may also decrease the likelihood of a CRS diagnosis.[548,550] It has been shown that CRS diagnosis particularly in primary care and emergency room settings is limited in accuracy due, in part, to poor adherence to guidelines regarding objective inflammation documentation.[552] Prior studies comparing symptoms against a CT gold standard have suggested the specificity of symptoms in the range of 2-12% and positive predictive values ranging between 35-54%.[31,480,513] Together, these studies indicate a low diagnostic efficacy for the symptom-only based approach. Given the cost of resource utilization related to a diagnosis of CRS; the use of a poor diagnostic approach, although much less expensive to use, would likely result in unneeded healthcare utilization especially in the form of unnecessary antibiotic prescriptions. It should be noted that RS currently is the single most common indication for ambulatory antibiotic prescription.[553]

Using Symptoms Alone to Diagnose CRS

Aggregate Grade of Evidence: C (Level 3: 8 studies; level 4: 2 studies)
Benefit: A "symptoms alone" strategy is a patient-centered and widely available means for establishing possible diagnosis of CRS.
Harm: High rate of false-positive diagnoses may prevent or delay the establishment of correct underlying diagnoses and potential for inappropriate interventions resulting in direct and indirect healthcare costs (*e.g.*, time lost from work and potential adverse effects from treatments).
Cost: Low—performed at all specialist and non-specialist visits.
Benefits-Harm Assessment: Harm over benefit, if used as the sole clinical method for CRS diagnosis, as there is a significant risk of misdiagnosis.
Value Judgments: Assessing patient reported symptoms is an important component of the patient encounter, but is too inaccurate to be the only means used to diagnose CRS.
Policy Level: Recommend against.

Intervention: Recommendation against using a "symptoms-alone" strategy to make the diagnosis of CRS.

IX.B.3.b. CRS Diagnosis with Nasal Endoscopy

The diagnostic utility of nasal airway examination to evaluate for CRS is well established in the literature.[548,554-556] While anterior rhinoscopy may reveal mucopurulent drainage or severe nasal polyposis in some patients, this examination technique does not consistently provide sufficient illumination and visualization of structures beyond the inferior turbinate. Nasal endoscopy provides a more thorough examination of sinus drainage pathways and allows for determination of the presence of mucosal edema, nasal polyposis, and purulent drainage. Given the growing implications the presence of nasal polyps has on therapeutic choices, definitive phenotyping of CRS patients is becoming particularly important to ensure patients are prescribed indicated therapy. Additionally, nasal endoscopy can assist with obtaining cultures or biopsies of targeted sinonasal locations and establishing alternative pathologies that may be symptomatically similar to CRS, such as intranasal tumors, adenoid hypertrophy, or posterior septal deviation. In post-surgical patients, the surgical alterations of the anatomy also facilitate a thorough examination of the sinuses using nasal endoscopy alone. Bhattacharyya and Lee determined that compared to using a symptom-based criteria alone to predict the presence of CRS (specificity and positive predictive value of 12% and 39%, respectively, using a CT-based gold standard), the addition of nasal endoscopy to a symptom-based assessment substantially increases the diagnostic accuracy of CRS, with specificity and positive predictive values estimated at 84% and 66%, respectively, in one study; and 82% and 84% in another.[513,547]

Despite the high specificity and positive predictive value of nasal endoscopy in confirming a CRS diagnosis, endoscopy has been shown to be notably less sensitive, having false negative rates between 35-70%, when compared to CT.[480,529,546,554-556] The lower sensitivity is related to the inability of rigid and/or flexible endoscopy to assess the interior of all sinus cavities in un-operated patients.

From a cost-efficiency standpoint, the only prior decision analysis compared an algorithm where patients were seen in the otolaryngologist's office underwent nasal endoscopy followed by initiation of medical treatment with one where a patient underwent a CT scan after nasal endoscopy. In this analysis, it became less costly to treat a patient prior to obtaining the CT scan if the pre-CT CRS probability was over 50% using average medication, visit and diagnostic costs. Since the presence of objective findings on endoscopy have concordance with CT findings of over 80%, obtaining further CT confirmation at that visit will result in increased costs of USD$150 per patient (range: USD$25 to USD$250 more depending on costs of visits and prescriptions). However, if the endoscopy was negative, the pre-CT CRS probability of the symptomatic patient falls to below 50% and obtaining a CT to confirm the diagnosis is less costly due to savings from unnecessary future medical

treatment and otolaryngologist visits. There has not been a cost decision analysis comparing empiric medical therapy to nasal endoscopy as the sole diagnostic test.

Using Endoscopy to Diagnose CRS

Aggregate Grade of Evidence: B (Level 2: 2 studies; level 3: 3 studies).
Benefit: Higher positive predictive value and specificity for a CRS diagnosis compared to using symptoms alone, allowing for the avoidance of CT utilization costs and potential radiation exposure of imaging.
Harm: If the clinician still suspects CRS, a negative nasal endoscopy exam will still require a CT scan of the sinuses due to the potential for a false-negative endoscopy. Mild discomfort associated with the procedure.
Cost: For 2019, the Centers for Medicare & Medicaid Services in the United States set a national payment average for a diagnostic nasal endoscopy (Current Procedural Terminology 31231) at USD$197.77, which accounts for both service and facility reimbursements. This cost reflects the specialists' time to perform and review findings of endoscopy, capital needed to purchase the essential equipment, and expenses related to sterilizing and maintaining the endoscopes.[557]
Benefits-Harm Assessment: Preponderance of benefit as the initial technique to objectively establish CRS diagnosis by trained endoscopists, but the technique is limited by a reduced sensitivity relative to CT imaging.
Value Judgments: Endoscopy is an important diagnostic intervention that should be used in conjunction with a thorough history and physical exam for patients suspected of having CRS. It should be complemented with other diagnostic testing in the event of a negative endoscopy where CRS is still suspected.
Policy Level: Recommendation.
Intervention: Nasal endoscopy is recommended in conjunction with a history and physical examination for a patient being evaluated for CRS. CT is an option for confirming CRS along with or instead of nasal endoscopy.

IX.B.3.c. CRS Workup with Diagnostic Imaging

Clinical practice guidelines uniformly state that CT imaging, as opposed to the plain radiography or MRI, is the radiologic modality of choice for confirming CRS or as an alternative to nasal endoscopy.[88,547] In the settings where nasal endoscopy is unavailable (*e.g.*, in the primary care setting), imaging is the preferred modality to confirm CRS and, depending on the relative costs within a health system, may be preferred prior to a trial of medical therapy. Using expected pre-test probabilities in the patient with appropriate symptoms, a cost based decision analysis in the US context has demonstrated a strategy utilizing CT prior to initiating extended systemic antibiotic treatment or specialty referral results in USD$503 *lower* costs per patient (range USD$296-USD$761) due to reduction in unnecessary antibiotics and inappropriate referrals.[558] A similar study in the Canadian context however suggested this strategy would result in *increased* costs of CAD$1500 per

patient diagnosed with CRS but would improve the accuracy of referrals.[559] The differences between the two studies reflects the effect of medical visit, diagnostic procedural and pharmaceutical costs in influencing the most cost efficient diagnostic algorithm.

In specialty care, patients with appropriate CRS symptoms who have a negative endoscopy in whom an extended course of symptom-based empiric antibiotic therapy is being considered, an upfront CT would result cost savings of $320 per patient (range USD$138-USD$671) compared to treating the symptoms without confirming the CRS diagnosis.[558] Based on CMS costs and published drug cost information in the United States, the cost of an extended course of antibiotic therapy is almost similar to that of obtaining a CT, and adopting an upfront CT results in substantially reduced antibiotic utilization in symptomatic patients with alternate diagnoses like rhinitis or atypical facial pain.[560,561] It should be noted that these prior cost studies were carried out using 2010 CT and nasal endoscopy costs and the average reimbursement for both has fallen relative pharmaceutical and medical visit costs, likely further favoring confirmation via nasal endoscopy and CT prior to treatment.

Other benefits that are not measured in these cost-based studies are the societal benefits of reducing antibiotic overuse that results in antibiotic resistance. These benefits are traditionally weighed against additional imaging-related concerns like radiation exposure and access. The availability of alternative CT imaging modalities like cone beam technologies mitigates some of these concerns by facilitating CT availability at the point of care and lowering radiation exposure while maintaining the quality of diagnostic information necessary for CRS. In a recent study, patients demonstrated a poor understanding of radiation exposure involved in imaging, but the majority of patients expressed a preference for accurate treatment for CRS symptoms even if this care entailed additional costs associated with imaging.[562] Therefore, with cost-effectiveness of CT imaging in mind, practitioners should strongly consider CT imaging to confirm CRS diagnosis in the appropriately symptomatic patient prior to initiation of antibiotic or procedural management of RS. The utility of MRI for diagnosis of CRS is furthermore limited; MRI is generally useful only in specific instances such as delineation of mucoceles, AFRS, concern over skullbase integrity, or tumor-associated sinonasal inflammation.

Using Imaging to Diagnose CRS

Aggregate Grade of Evidence: B (Level 2: 1 study; level 4: 2 studies).
Benefit: CT imaging is more sensitive than nasal endoscopy and obtaining imaging earlier in the diagnostic algorithm reduces antibiotic utilization.
Harm: Concerns regarding radiation exposure.
Cost: For 2019, the CMS-based national average payment for CT imaging without contrast material of the maxillofacial area (Current Procedural Terminology 70486) was USD$141.47. This reimbursement fee for CT imaging accounts for costs for capital equipment, technical execution of the scan and the professional fee associated with interpretation of the CT scan.[557]

Benefits-Harm Assessment: Variable, dependent on the pre-test likelihood of disease, access to CT scan, and findings of physical exam and endoscopy.
Value Judgments: A patient's history of radiation exposure and preferences should be taken into account when deciding to confirm CRS with CT. Nasal endoscopy is another method of confirming CRS but is less sensitive and cannot delineate anatomy vital for surgical planning.
Policy Level: Recommendation.
Intervention: CT scanning is recommended for all patients meeting symptom-based criteria for CRS with a lack of objective clinical findings on anterior rhinoscopy or nasal endoscopy, or for pre-operative planning. It is an option for confirming CRS instead of nasal endoscopy.

Table IX-2. Evidence for the cost-effective diagnosis of CRS

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Symptom-Based Criteria						
Amine[546]	2013	3	Cohort study	Patients with 2 or more CRS-associated symptoms Patients with 1 CRS-associated symptom	Diagnosis of CRS based on CT imaging or endoscopy	Patients with more CRS symptoms had a higher liklihood of CRS diagnoses confirmed by CT. Nasal obstruction was the most sensitive, while hyposmia was the least sensitive
Ferguson[550]	2012	3	Cohort study	CRS-associated symptoms and radiographic evidence of CRS CRS-associated symptoms without radiographic evidence of CRS	Presenting patient symptomatology and comorbid illnesses	Hyposmia was more common symptom indicative of CT-confirmed CRS. Headaches, facial pain, and sleep disturbances were more significant in patients without radiographic confirmation.
Abrass[551]	2011	3	Cohort study	Patients with active CRS symptoms but negative endoscopy	Lund-Mackay grading of CT scans	Nasal obstruction was the only presenting symptom positively associated with positive scan results.
Pynnonen[514]	2007	3	Cohort study	Patient presenting for evaluation of CRS-associated		The prevalence of CRS was 60% in patients complaining

				symptoms		of CRS-associated symptoms, with chronic purulent rhinorrhea and hyposmia individually and in combination as significant predictors of CRS diagnosis.
Tahamiler [563]	2007	3	Cohort study	CRS-associated symptoms and atopy CRS-associated symptoms without atopy	CRS diagnosis confirmation as determined by nasal endoscopy and CT imaging	A majority of patients with symptom-based CRS had no CT and endoscopic pathology. Two major symptoms were insufficient for diagnosis.
Bhattacharyya [516]	2006	3	Cohort study	CRS-associated symptoms and radiographic evidence of CRS CRS-associated symptoms without radiographic evidence of CRS	Symptomatology scores prior to the use of CT imaging to determine diagnostic evidence of CRS	The diagnosis of CRS based on symptom criteria is insufficient overall
Hwang[513]	2003	3	Cohort study	Patients undergoing CT scanning of the sinuses (n=115)	Presenting symptoms and CT scoring for diagnosis of CRS	Sensitivity of the symptom criteria from the Task Force on Rhinosinusitis for detecting a positive scan was 89%, but the specificity was 2%
Stankiewicz[531]	200	3	Cohort	Patients	History,	47%

	2		study	meeting subjective criteria for definition of CRS	physical examination including anterior rhinoscopy and endoscopy, and upfront CT imaging	concordance between subjective symptomatology and CT imaging for a CRS diagnosis. There was no significant difference between symptom severity and CT positivity
Dietz de Loos[564]	2013	4	Case-control study	CRSwNP CRSsNP	Scoring of each patient-reported symptoms (RSOM-31)	Total symptomatology scores were similar, though specific symptom prevalences differed between groups.
Tan[548]	2013	4	Case-control study	CT-confirmed CRS CRS-associated symptoms but negative CT	Prospectively patient-reported symptom scores and endoscopy findings	Positive nasal endoscopy, hyposmia, and discolored nasal discharge predicted CRS diagnosis.
Nasal Endoscopy						
Kim[529]	2019	2	Systematic review of retrospective or observational studies	16 studies of CT and nasal endoscopy scores	Accurate CRS diagnosis by nasal endoscopy as confirmed by CT scans	High correlation between positive nasal endoscopy and positive CT scan findings
Wuister[555]	2014	2	Systematic review of exploratory cohort studies	Three studies (n=3899) of nasal endoscopy and CRS diagnosis	Accurate CRS diagnosis by nasal endoscopy as confirmed by CT scans	CT confirmation unnecessary with positive endoscopy
Agius[556]	2010	3	Cohort study	Patients presenting for evaluation	Diagnosis of CRS based on nasal	Good correlation between nasal

				with facial pain	endoscopy findings and CT imaging	endoscopy findings and CT imaging results
Bhattacharyya[480]	2010	3	Cohort study	Patients presenting for evaluation of CRS-associated symptoms	Diagnosis of CRS based on nasal endoscopy findings and CT imaging	Diagnostic nasal endoscopy may help reduce CT utilization, reducing cost and radiation exposure
Stankiewicz[554]	2002	3	Cohort study	Patient presenting for evaluation of CRS-associated symptoms	Diagnosis of CRS based on nasal endoscopy findings and CT imaging	Positive endoscopy correlated well with CT results, while negative endoscopy correlated to a lesser degree with CT imaging
Diagnostic Imaging						
Tan[561]	2011	2	Randomized control trial	Symptoms suggestive of CRS but negative nasal endoscopy who received point-of-care CT scan at the initial visit Symptoms suggestive of CRS but negative nasal endoscopy who received empiric medical therapy	Compliance with follow-up as well as number and costs of antibiotic prescriptions	Utilizing CT imaging during the initial encounter reduced unnecessary antibiotic prescriptions by 60% and improved patient follow-up compliance
Leung[558]	2014	4	Economics-based decision analysis model	Patients with presumed CRS diagnosis based on symptomatology but negative endoscopy in	Standardized costs incurred for diagnostic, treatment, and potential adverse event costs were calculated for	Use of CT in the primary care setting can save USD$297-USD$321 in costs per patient when

				the primary care setting Patients who received upfront CT scans in the primary care setting	each study group	compared to diagnosing based on symptoms alone.
Leung[560]	2011	4	Economics-based decision analysis model	Two algorithms were evaluated: 1. upfront CT for patients with CRS-associated symptoms but negative endoscopy 2. empiric medical therapy for patients with CRS-associated symptoms but negative endoscopy	Treatment cost values	In patients meeting symptom criteria for CRS but without endoscopic evidence of inflammation, upfront CT scanning is more cost-beneficial than empiric medical therapy

IX.C. Pathophysiology of CRSsNP

IX C.1. Contributing Factors for CRSsNP: Allergy

Chronic rhinosinusitis is characterized by persistent inflammation of the paranasal sinuses. The pathophysiology of CRS involves both the innate and adaptive immune responses. The immune polarization is based on cytokines produced by different types of T cells and innate lymphoid cells (ILCs). Type 1 immune response is associated with IFN-γ production from Th1 and ILC1s, type 2 response is mediated by ILC2s and Th2 cells (associated with production of IL-4, IL-5, and IL-13 cytokines), and type 3 is characterized by ILC3s and Th17 cells with production of IL-17 and IL-22. Type 2 inflammation is characteristic of CRSwNP, especially in western countries, while accumulating evidence suggests that the inflammatory pathogenesis of CRSsNP is heterogeneous and type 1, 2 and 3 pathways are implicated.[61,565] Recent evidence indicates that the heterogeneous pattern in CRSsNP may be geographically dependent.[54] US-based studies show a higher frequency of type 2 inflammation than type 1 in CRSsNP [61,565,566] consistent with findings in Europe.[54] In contrast CRSsNP patient from China were found to be type 1 predominant[54] while in Korea a mixed type 1/type 3 pattern was found with the type 3 response appearing to be the dominant inflammatory pattern.[567] Overall this suggests that CRSsNP may be a spectrum of disease mechanisms with genetic, immunologic and environmental factors likely playing a role.

Although allergic inflammation is characteristic of type 2 inflammation, there are no controlled studies on the role of allergy in the pathophysiology of CRSsNP. A postulated mechanism by which allergy predisposes individuals to CRS is allergen-induced inflammation of the nasal mucosa leading to ostial obstruction and creating an environment of persistent inflammation. While many studies have investigated the relationship between allergy and RS, few have done so in a pure CRSsNP population. Furthermore, there is a paucity of controlled studies examining the role of allergy in the pathophysiology of CRSsNP and existing epidemiologic studies use varying definitions of atopy/allergy with some using evidence of sensitization only (via skin testing or specific IgE) and others using sensitization with concomitant clinical symptoms to define allergic patients. Associations based on these epidemiologic studies are conflicting and difficult to interpret.

In 2014, Wilson *et al.* reviewed the role of allergy in CRSwNP and CRSsNP.[568] They considered only studies that delineated CRS into CRSsNP or CRSwNP subtypes. In both CRSsNP and CRSwNP, they found the aggregate LOE linking allergy to these forms of CRS to be level D due to conflicting prevalence data, complemented by expert opinion and reasoning from first principles. In CRSsNP specifically, they found 9 epidemiologic studies that addressed the role of allergy. Four of these studies supported an association, while 5 did not. They concluded that allergy testing should be considered an option in CRSwNP and CRSsNP patients, inasmuch as there was a theoretical benefit of finding inflammatory triggers, there is little harm, and the low aggregate level of evidence did not support a strong recommendation either for or against this practice. Since then Benjamin *et al.* found the presence of AR in CRSsNP correlated to more severe sinus disease radiographically compared to nonatopic CRSsNP patients.[185] A cross sectional case control study in Europe found higher rates of allergy as assessed by medical history and confirmed by skin testing in patients with

CRSsNP compared with reference controls though no significant differences in rates of self reported AR or asthma was found.[195]

Despite the association of AR and CRS, the role of IT in CRS remains unclear. A review of CRS patients undergoing IT by DeYoung included 7 studies which suggested IT improved sinus related outcomes.[569] However. given the small quantity and quality of the studies it was concluded there was weak evidence to support the use of IT an adjunctive treatment in CRS and no studies to date have examined its role specifically in CRSsNP.

Allergy as a Contributing Factor for CRSsNP

Aggregate Grade of Evidence: D (Level 1: 2 studies; level 2: 6 studies; level 4: 1 study. Conflicting evidence.)
Benefit: Management theoretically reduces triggers and could potentially modify symptoms of AR associated with CRS. Robust data on benefits are lacking.
Harm: Mild local irritation associated with testing and immunotherapy and mild sedation seen with some antihistamine drugs. Severe complications are rare (see Table II-1).
Cost: Moderate direct costs for testing and treatment; some tests and therapies require significant patient time (*e.g.*, office-administered skin testing and subcutaneous immunotherapy).
Benefits-Harm Assessment: Preponderance of benefit over harm has not been demonstrated for avoidance or immunotherapy. Benefits are largely theoretical and should be balanced against the significant cost of testing for allergies and instituting avoidance measures.
Value Judgments: None.
Policy Level: Option
Intervention: Allergy testing and treatment are an option in CRSsNP.

Table IX-3. Evidence for allergy as a contributing factor for CRSsNP

Study	Year	LOE	Study Design	Study Groups	Clinical End-point	Conclusion
DeYoung[569]	2014	1	Systematic Review	CRSsNP CRSwNP AFRS	Sinus-specific outcomes after IT in patients with CRS	Conclusions are limited by the paucity of available data. No RCTs.
Wilson[568]	2014	1	Systematic Review	CRSsNP CRSwNP CRSsNP and wNP	Relationship between allergy and CRSsNP and CRSwNP	Conflicting evidence on role of allergy in CRSsNP.
Khan[195]	2019	2	Multicenter cross-sectional case control study	CRSsNP CRSwNP Control	1) atopic comorbidities 2) sinus treatment	Higher prevalence of self-reported atopy in CRSsNP vs controls

Kim[567]	2019	2	Cross-sectional	CRSsNP CRSwNP Control	Immunologic profiling of uncinate process tissue	Korean CRSsNP shows a mixed types 2 and 17 phenotype.
Stevens[61]	2019	2	Cross-sectional	CRSsNP CRSwNP	mRNA and protein endoytypic markers	CRSsNP has a predominately type 2 inflammatory endotype.
Tan[565]	2017	2	Cross-sectional	CRSsNP CRSwNP Control	Immunologic profiling of nasal mucosal tissue	CRSsNP is heterogeneous with a higher frequency of a type 2 inflammatory pattern.
Wang[54]	2016	2	Cross-sectional	CRSsNP CRSwNP Controls	Immunologic profiling of nasal mucosa tissue	CRSsNP have heterogeneous inflammatory patterns which are geographically dependent.
Stevens[566]	2015	2	Cross-sectional	CRSsNP CRSwNP AERD	Immunologic profiling of uncinate process tissue	CRSsNP has a type 2 inflammatory pattern.
Benjamin[185]	2019	4	Retrospective case-control	CRSsNP CRSwNP	Prevalence of atopy Radiographic disease severity	Atopy was associated with more severe sinus disease in CRSsNP

IX.C.2. Contributing Factors for CRSsNP: Biofilms

Many organisms in the sinonasal tract have the ability to form a biofilm, which is a community of bacteria or fungi that surrounds itself with a protective extracellular matrix.[570] Using "quorum sensing" molecules, bacteria communicate density status and begin to form a biofilm once an appropriate microbe concentration has been reached.[571] The protection of the biofilm renders the bacteria or fungus more resistant to external insults, including host defenses. The organisms themselves also undergo a phenotypic change[572] to require less oxygen and nutrients, which confers additional resistance to conventional antibiotics.[573] Microbes that would normally be vulnerable to effective antibiotics in the planktonic state are up to 1000 times more resistant in the biofilm state.[574] Antibody action, phagocytosis and complement binding can be equally unsuccessful in this setting.[571]

Biofilms *in vivo* can often be difficult to detect and culture. Reliance on conventional growth techniques results in an "enrichment bias" in which the organisms with the fastest growth rates are overrepresented thereby not reflecting the true polymicrobial constituents of *in vivo* biofilms.[575] Identification of a biofilm-forming pathogen in diseased mucosa therefore requires special techniques to obtain an accurate result.[576] Biosensor molecular detection and fluorescent *in situ* hybridization (FISH) have both proven to be effective.[577,578] Interestingly, a study comparing FISH to culture technique showed very little overlap in the identities and relative quantities of bacteria detected.[578] At the current time there is no gold standard for identification nor quantification of biofilms *in vivo* nor *in vitro.*

The precise relationship between biofilm formation and CRS pathogenesis is poorly understood, *i.e.*, whether biofilms are an early event in some individuals driving recalcitrant disease, or whether they are a "late" entity resulting from multiple therapeutic interventions is controversial.[579,580] However, biofilm presence in the sinonasal tract is correlated with recalcitrant CRS,[581] and outcomes after ESS are worse in patients that have evidence of biofilms.[582,583] Specifically, postoperative symptoms, ongoing inflammation, and recurrent infections were all increased in biofilm-positive surgery patients.[570,584-587] Biofilm formation in CRS may also be associated with increased need for surgical intervention. While around 20% of patients with CRS show biofilm formation,[570] up to 50% of CRS surgical candidates are biofilm-positive.[584] Importantly, biofilms can also be found in control patients without CRS, showing that they are neither necessary nor sufficient to cause the pathology.[588]

Treatment of biofilm-positive CRS is difficult and therapeutic strategies are far from fully elucidated. Conventional treatment requires physical removal or disruption of the biofilm matrix which can be accomplished with surgical intervention and aggressive irrigations, however too aggressive of an antibiofilm intervention may leave the epithelium compromised.[578,589,590]

Antibiotics such as ceftazidime, piperacillin, ciprofloxacin, and vancomycin are ineffective when given systemically at typical concentrations and higher concentrations of these compounds are often not clinically safe, sometimes requiring a 60-1000 fold increase in dosing to achieve an effect.[591,592] Topical therapy may be a more effective approach. Mupirocin has been shown to reduce biofilm mass,[592] but it is unclear if there is a maintained effect after antibiotic application has ceased.[593] Macrolides inhibit quorum sensing in *P. aeruginosa*, and their prescription may become a useful therapeutic strategy for treating biofilm-associated CRS.[584] Combination therapies that have synergistic antimicrobial effects are a promising avenue of research. A ciprofloxacin and ivacaftor eluting stent reduces *P. aeruginosa* biofilm formation *in vitro*.[594] Furosemide, which acts as a cation channel blocker, also reduces biofilm size.[595] Corticosteroids have shown some inhibitory effect against *S. aureus* biofilm formation specifically,[596] while another study demonstrated that corticosteroids were effective against *S. aureus, P. aeruginosa* and *S. epidermidis* biofilm formation.[597]

Other less conventional treatments have been trialed, with varying degrees of success. Bacteriophages have been shown to reduce the biofilm burden of *Pseudomonas aeruginosa* clinical isolates from CRS patients.[598] Colloidal silver (CAg)[599] as well as a topical nitric oxide donor[600] reduce *S. aureus* biofilm burden. Detergent agents have appreciable biofilm-disrupting effects, but

currently are not in use due to several side effects, including ciliary toxicity and reversible hyposmia.[589,590,601-604] Photodynamic therapy has demonstrated promising efficacy in reducing preformed biofilms *in vitro* and preliminary toxicity studies have not shown deleterious side effects.[605,606] Lastly, low frequency ultrasound treatments also seem effective in reducing biofilms, also without observed side effects.[607]

A promising new approach to understanding biofilms involves bitter taste receptors in the upper respiratory tract. Acyl-homoserine lactones (AHLs) produced by gram-negative bacteria serve as biofilm "quorum-sensing molecules," and these molecules are ligands for airway bitter taste chemoreceptors.[608] Detection of these molecules allows the host to mount an innate defensive response before the bacteria reach the density required for biofilm formation.[609] One of these bitter taste receptors, T2R38, is activated by AHLs and has downstream effects of increased MCC and bactericidal nitric oxide (NO) production. Microbial swabs from CRS patients with a non-functional mutation in the T2R38 gene were more likely to grow robust biofilms *in vitro,*[610] while those patients were also at a higher risk for needing surgical intervention for their disease.[611] Bitter taste testing for the presence of T2R38 could potentially predict CRS severity or necessity of treatment,[612] and bitter compounds themselves could serve as therapeutic agents by directly activating the host immune response against biofilm formation in CRS.[613-615] Further clinical studies are needed in this realm.

Biofilms as a Contributing Factor for CRSsNP

Aggregate Grade of Evidence: C (Level 3: 2 studies, Level 4: 5 studies)

Table IX-4. Evidence for biofilms as a contributing factor for CRSsNP

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoints	Conclusion
Glowacki[587]	2014	3	Presence of biofilms during ESS and post-surgical outcomes	33 CRS with biofilms 33 CRS without biofilm (Control)	SNOT-20 score, Lund-Kennedy score, Lund-Mackay score	CRS subjects with biofilms had greater subjective and objective severity of disease preoperatively. CRS subjects with biofilms have more persistent and severe disease post-ESS.
Tan[581]	2012	3	Prospective study of biofilms in CRS	15 CRSsNP 5 control	Surface biofilm presence	67% of CRSsNP subjects had biofilm present, while 0% of control patients had biofilm present. All patients with presence of intracellular *S. aureus* had presence of biofilm.

Zhang[583]	2015	4	Retrospective cohort Study of biofilm presence and QoL	156 CRS	SNOT-22 score	15% of CRS patients had biofilm-forming bacteria present. Patients with biofilm-forming bacteria had significantly worse postoperative SNOT-22 scores than those without biofilm-forming bacteria. QoL improvements after ESS are significantly worse 6 months post-surgery in subjects with biofilm-forming bacteria.
Adappa[610]	2016	4	Presence of biofilms in CRSsNP subjects and versus T2R38 taste receptor phenotype	59 CRS Subjects	*In vitro* biofilm formation	Linear association between *in vitro* biofilm formation and T2R38 taste receptor phenotype. This association was exclusively driven by CRSsNP subjects.
Singhal[585]	2010	4	Prospective study of QoL post-ESS in patients with and without biofilms	51 CRS	SNOT-20 score, Lund-Kennedy score,Lund-Mackay score	71% of patients had biofilms present at the time of surgery. Patients with biofilms had significantly worse preoperative objective severity scores. Patients with biofilms had significantly worse postoperative SNOT-20 and Lund-Kennedy Scores.
Zhang[582]	2009	4	Prospective Study of Intraoperative biofilm formation	27 CRS	Surface biofilm presence	Biofilms identified in 9/15 postoperative samples 6 months later. Presence of biofilms correlated with objective Lund-Kennedy and Lund-Mackay scores.
Bendouah[586]	2006	4	Biofilm capacity of cultured bacteria from ESS patients and post-surgical outcomes	19 CRS	Favorable vs. unfavorable post-ESS evolution (objective and subjective)	Biofilm-forming capacity of cultured bacteria during ESS correlated with unfavorable clinical evolution following ESS.

IX.C.3. Contributing Factors for CRS: Fungus

Because of limited data, CRSsNP and CRSwNP are combined in this analysis.

A broad range of opinions have been expressed on potential roles for fungus in the pathogenesis of CRS, ranging from "all forms of CRS are caused by fungus" to "fungus has no role in CRS."[616,617]

Although a recent Cochrane review found no evidence for the efficacy of anti-fungal treatment in CRS,[618] there is some room for nuance and discussion.

Fungal spores are ubiquitous in the environment and not surprisingly detected from the nasal cavity of both CRS patients and normal controls.[619] *Aspergillus, Cladosporium, Candida, Aureobasidium, and Alternaria* are the most frequently recovered fungal species from nasal lavages and swabs from the middle meati.[620,621] When maxillary sinus secretions were sampled specifically, fungi were detected in only 20% of controls versus in over 80% of CRSwNP patients.[622] However, the presence of fungi seen in the sinuses of CRS patients may be explained by delayed MCC, and may therefore be a downstream effect of inflammation rather than a cause. In the same study that specifically sampled the sinus cavity rather than the nasal cavity for the presence of fungi, T helper 2 cell memory for the specific fungal species found in the sinus cavity was noted in 100% of AFRS and 65% of other CRSwNP patients, but in 0% of control subjects.[622] These findings support a possible role of fungi in the Type 2 immune response characteristic of CRSwNP.

Sinonasal epithelial cells have a robust innate immune response against fungi. Immunologic responses to fungi have been observed in CRS patients. Sinonasal epithelial cells (SNECs) produce antifungal peptides and proinflammatory cytokines that recruit other immune cells *i.e.,* tissue-resident macrophages and neutrophils and, at the later stage eosinophils, that directly contribute to fungal clearance. Production of cathelicidins and defensins, two key antimicrobial peptides associated with mucosal innate immunity were upregulated in CRS patients but notably not in CRS patients with eosinophilic mucin such as AFRS.[623] In addition, CRS with eosinophilic mucin was also noted for deficient pulmonary surfactant protein (SP-D).[624] A microarray analysis comparing sinonasal mucosal tissue from CRSwNP versus AFRS patients noted that the most differentially downregulated gene in AFRS was histatin 1, an antimicrobial peptide with antifungal activity.[625] Defects in the innate immune response to fungi would hinder clearance of inhaled spores allowing the spores to germinate and contribute to the pathogenesis of some CRSwNP such as AFRS.

Since the ICAR-RS-2016 review, several studies have been published describing molecular mechanisms by which fungi can lead to the Type 2 immune response. As noted above, fungal spores can germinate into a hyphal form within the sinuses generating several components capable of inciting an immune response including proteases and parts of the cell wall such as b-glucans. IL-33 is a key epithelial cell derived cytokine and driver of the Type 2 immune response. Sinonasal epithelial cells increase IL-33 expression and production when challenged with fungi.[626,627] This increase in IL-33 is in part associated with a fungal serine protease activated receptor 2 (PAR2).[628] In AFRS, PAR2 expression is increased on SNECs.[628,629] In addition, fungi can also drive an increased intracellular uptake of calcium via $P2X_7$ receptor activation that also leads to increase in IL-33 secretion.[627] These two pathways describe how fungi can initiate the Type 2 immune response of CRSwNP via IL-33.

Activation of PAR2 by fungal protease can also suppress the antiviral Type 1 immune response by SNECs, skewing towards a Type 2 immune response.[630] Homma *et al.* describe *in vitro* studies in which SNECs pre-incubated with *A. fumigatus* extract suppressed the Type 1 response typically incited by human rhinovirus serotype 16 exposure. This pathway was PAR2 dependent. Exposed to

fungi, SNECs may become more vulnerable to viral infections and skew these cells to a Type 2 immune response through activation of PAR2.[630]

In addition, fungi have been linked to the pathogenesis of allergic asthma.[630] Similar to CRSwNP, asthma is characterized by a Type 2 immune response associated with elevated eosinophils and cytokines such as IL-4, IL-5 and IL-13. Millien *et al.* describe fungal protease cleaving locally present fibrinogen into fibrinogen cleavage products (FCPs) that can activate Toll-like receptor 4 (TLR4). Activation of TLR4 in SNECs leads to increased IL-13 receptor expression, increased MUC5AC (a protein found in mucus) and increased production of antimicrobial peptides. This pathway also leads to elevated T helper 2 response to fungi with increased IgE production and ultimately pulmonary hyperreactivity (asthma). Given the high comorbidity of allergic asthma with CRSwNP and the FCP activated-TLR4 pathway in SNECs leading to increased mucus production and Type 2 immune response, it seems likely that this fungi activated pathway contributes to the pathophysiology of some subtypes of CRSwNP. These new studies highlight pathways by which fungi can incite the Type 2 immune response characteristic of CRSwNP.

However, direct causal studies linking fungi to the etiopathology of CRS are lacking. An animal model of CRS would be needed to perform these causal studies. Although mouse models for CRS have yet to be widely used, several models have been proposed initiated by either challenge with a fungal allergen or a Staphylococcal enterotoxin suggesting an etiologic role of these agents in CRS. To date though, these models utilized non-physiologic routes of challenge such as intraperitoneal injections or required an adjuvant in addition to the allergen. As such, fungi as the etiologic agent of CRS still remains inconclusive. Future studies differentiating AFRS from CRS therefore remain a priority for rhinologic research.

Fungus as a Contributing Factor for CRS

Aggregate Grade of Evidence: C (Level 4: 14 studies)

Table IX-5. Evidence for fungus as a contributing factor for CRS

Study	Year	LOE	Study	Study Groups	Clinical Endpoint	Conclusions
Dietz[628]	2019	4	Case-control study	CRSwNP (n=49); Controls (n=13)	SNECs challenged with fungal components and monitored IL-33 expression	Fungal protease activates IL-33 expression from SNECs in PAR2 dependent pathway.
Ebert[629]	2014	4	Case-control study	AFRS (n=15); Controls (n=5; CRSwNP (n=5)	Microarray analysis and PCR	PAR3 expression 2-fold elevated expression in AFRS vs control.

Porter[622]	2014	4	Case-control study	CRSsNP (n = 21); CRSwNP (n = 37); AFRS (n = 26); Controls (n = 15)	Positive fungal culture of sinus lavage Th2 memory based on ELIspot	Fungal cultures were more frequently positive in CRSwNP and AFRS patients compared to CRSsNP and controls. T helper 2 memory to fungi found in sinus cavities only noted in CRSwNP or AFRS.
Shaw[626]	2013	4	Case-control study	CRSsNP (n=30); CRSwNP (n=73); Controls (n=8)	IL-33 and ST2 expression from sinonasal mucosa Flow cytometry analysis of ILC2 from sinoaasal mucosa	SNECs challenged with fungi lead to increased IL-33 expression and release.
Orlandi[631]	2009	4	Case-control study	CRS (n = 10) Controls (n = 7)	Cytokine production following fungal exposure; Fungal-specific serum IgG and IgE levels	Cytokine levels did not correlate with presence of CRS. Fungal-specific IgE, not IgG, levels strongly correlated with IL-5 production.
Tosun[632]	2007	4	Case series	CRS patients with and without intranasal fungi determined by PCR	Laboratory and clinical parameters	Multiple laboratory and clinical parameters did not differ between the 2 groups.
Murr[621]	2006	4	Case-control study	CRS (n = 37); Controls (n = 37)	Fungal recovery on qPCR; Correlation of qPCR and QoL measures	Fungal recovery rate was the same between the 2 groups. Fungal results did not correlate with SNOT-20 or SF-36.
Kim[620]	2005	4	Case-control study	CRS (n = 82); Controls (n = 40)	Fungal culture and PCR results	93% of CRS patients and 98% of controls were positive for fungus on PCR. Fungal culture rates were similar.

Pant[633]	2005	4	Case-control study	Eosinophilic mucin CRS; AFRS; AFRS-like; Nonallergic fungal eosinophilic RS; Nonallergic, nonfungal eosinophilic RS; AR with fungal allergy; Control	*Alternaria* and *Aspergillus* fungal-specific IgG and IgA levels	Fungal-specific IgG and IgA levels were higher in eosinophilic mucin CRS patient groups compared to healthy controls. Fungal-specific IgG and IgA levels were not different from AR and non-eosinophilic mucin CRS patients.
Scheuller[634]	2004	4	Case-control study	CRS (n = 19); controls (n = 19)	Fungal recovery on PCR and qPCR	Fungal PCR recovery rates did not differ. For those with positive fungal results, quantitative PCR was identical for the 2 groups.
Shin[635]	2004	4	Case-control study	CRS (n = 18); controls (n = 15)	Cytokine production following exposure to fungi; Fungal-specific serum IgG levels	Blood cells from 90% of CRS patients but 0% from control patients produced more IL-5, IL-13, IFN-γ. Fungal-specific IgG was elevated in CRS patients but not controls.
Taylor[636]	2002	4	Case series	CRS patients	Presence of chitin	All specimens were positive for chitin.
Ponikau[616]	1999	4	Case-control study	CRS (n = 210); controls (n = 14)	Fungal culture results	96% of CRS patients had positive fungal cultures; 100% of controls had positive fungal cultures.
Srisomboon[627]	2020	N/A	*In vitro* studies	N/A	Fungal induced IL-33 secretion from bronchial epithelial cells	Human bronchial epithelial cells challenged with *A. alternata* increase IL-33 secretion via voltage-dependent anion channel.

IX.C.4. Contributing Factors for CRS: Neo-osteogenesis

Because of limited data, CRSsNP and CRSwNP are combined in this analysis.

Bone involvement in CRS is identified in 36-66% of patients and may play a role in CRS pathogenesis and the recalcitrant disease process.[265,637-646] The first experimentally-induced RS in animal studies initially reported presence of bone involvement and inflammation in the 1990s.[647,648] Kennedy *et al.*[638] followed this with descriptions of ethmoid bone remodeling in human subjects. Another study by Giacchi *et al.*[649] identified higher rates of periosteal reaction, increased bone turnover, and the formation of immature woven bone in CRS patients when compared to controls. Similarly, histological samples analyzed by Lee *et al.*[640] demonstrated evidence of bone remodeling in CRS patients, which was more prevalent in those undergoing revision surgery as opposed to primary surgery patients. Snidvongs *et al.*[650] ultimately proposed that these bony changes be referred to as neo-osteogenesis, as opposed to osteitis, after human studies failed to demonstrate inflammatory infiltration within the bone itself. However, osteitis and neo-osteogenesis continue to be used interchangeably in the literature.[638,640,649-652]

Histological evaluation most accurately confirms the presence of neo-osteogenesis, although CT continues to be the diagnostic test of choice due to ease of access and superior bony detail.[265,640,642-646,651,653-655] Single-photon emission CT (SPECT) was found to be extremely sensitive in predicting neo-osteogenesis on histopathology, but its use in clinical practice remains limited.[655,656] A number of osteitis grading systems have been proposed. The Kennedy Osteitis Score (KOS)[640] and the Global Osteitis Scoring Scale (GOSS)[657] are routinely referenced in the literature, but no system has been standardized.

Evidence continues to correlate neo-osteogenesis with greater disease severity. A study by Lee *et al.*.[640] observed average Lund-Mackay scores to be 22 for neo-osteogenesis patients versus 6.5 for patients without neo-osteogenesis. Several follow up prospective studies have further corroborated the connection between neo-osteogenesis and disease severity and suggested that the presence of neo-osteogenesis is a poor prognostic indicator for post-surgical outcomes.[656,657] Kim *et al.*[658] retrospectively reviewed their series of 81 patients, identifying that 48.1% of neo-osteogenesis patients had poor outcomes compared to 24.1% of non-neo-osteogenesis patients. In a study by Telmesani *et al.*,[641] 53% of neo-osteogenesis patients had recurrence of disease following surgery compared to 10% in patients without neo-osteogenesis. Sacks *et al.*[659]demonstrated no difference in endoscopy scores at 12 months post surgery, but noted that patients with neo-osteogenesis were more likely to need post-operative systemic steroids. Likewise, several case series have reported increased neo-osteogenesis in revision surgery cases.[640,660,661] However, data from Gunel *et al.*[637] conflicts with these findings as they found no difference in the incidence of neo-osteogenesis histopathologically between primary and revision surgery cases.[637] Despite the link between neo-osteogenesis and objective markers of clinical severity, multiple studies have failed to show a correlation between the presence of neo-osteogenesis and worse patient reported symptoms.[659,661,662]

Although there is a clear association between neo-osteogenesis and CRS, it is uncertain whether the bone propagates recurrent inflammation, or is the result of chronic inflammation. As such, the role of neo-osteogenesis in the pathogenesis of CRS has been a strong focus of recent investigations,

including the interplay with bacterial infection.[662-665] Dong *et al.*[664] reported the presence of neo-osteogenesis in 85% of patients with bacterial biofilms. A follow up study by Huang *et al.*[662] correlated the presence of *Pseudomonas aeruginosa* to neo-osteogenesis, although a recent study failed to corroborate these findings.[666] Cellular roles associated with bone remodeling have also been investigated, particularly the role of eosinophils and osteoblasts. Eosinophils are known to contribute to the pathogenesis of certain subsets of CRS, and may also influence bone remodeling as increased expression of transforming growth factor β1 (TGF-β1) was identified in bone from CRSwNP patients.[667] This is further supported by Snidvongs *et al.*[254],who correlated serum and tissue eosinophilia to the presence of neo-osteogenesis. Serum eosinophilia has also been linked with P-glycoprotein levels and radiographic osteitis scores.[668] Early studies investigating the role of osteoblasts in sinus neo-osteogenesis demonstrated decreased osteoblast adhesion and proliferation, and increased bone mineralization in CRS osteoblasts compared to controls.[669] More recently, Khalmuratova *et al.*.[670] reported an association between RUNX2 expression, a key osteoblast differentiation transcription factor, and neo-osteogenesis, that was further activated by the proinflammatory cytokines IL-13 and IL-17A.

Finally, current techniques in gene expression profiling and proteomics have permitted investigations into the molecular basis behind neo-osteogenesis. The bone morphogenic protein (BMP) family is one signaling pathway that has been investigated. Growth differentiation factor 5 (GDF5), a member of the BMP family, was found to be upregulated in osteitic bone.[671] Additionally, Wu *et al.*[672] identified that downregulation of pro-osteoblastic BMP signaling correlates to increased neo-osteogenesis in CRSwNP patients. Lastly, Kong *et al.*[673] correlated upregulation of receptor activator nuclear factor κB ligand (RANKL) to degree of neo-osteogenesis, and noted that blocking RANKL in a mouse model of CRS resulted in protection from mucosal inflammation and osteitis. The upshot of these data is that there appear to be several mechanisms related to the formation of neo-osteogenesis, although further investigation is required to uncover a deeper understanding of how they relate to the pathophysiology of CRS and identify targets for therapy.

Several treatment strategies for neo-osteogenesis related to CRS have been suggested, including radical surgery to remove all affected bone[638,640,646,657]. However, strong evidence for this surgical approach is lacking. Long-term intravenous (IV) antibiotics have also been proposed to treat the bacterial biofilms associated with neo-osteogenesis, although this treatment does not appear to target neo-osteogenesis itself because no histologic studies have identified bacteria in the bone specimens.[644-646] Topical antibiotic irrigations were also trialed in animal models, but demonstrated no impact on bone histopathology.[674]

In conclusion, the role of neo-osteogenesis in the pathophysiology, propagation, and recalcitrance of CRS has yet to be definitively determined. Additional research is required to investigate causality and not just association with the severity of CRS.

Neo-osteogenesis as a Contributing Factor for CRS

Aggregate Grade of Evidence: C (Level 2: 7 studies; level 3: 12 studies; level 4: 5 studies)

Table IX-6. Evidence for neo-osteogenesis as a contributing factor for CRS

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoints	Conclusions
Snidvongs[646]	2019	2	Systematic review	CRS patients		Pathogenesis of neo-osteogenesis in CRS remains unknown.
Leung[645]	2016	2	Systematic review	CRS patients		HU correlate with Histopathological grade of osteitis.
Sethi[644]	2015	2	Systematic review	CRS patients		Previous surgery correlates with higher overall GOSS.
Bhandarkar[265]	2013	2	Systematic review	CRS patients		Neo-osteogenesis may impact improvement following treatment.
Georgalas[653]	2013	2	Systematic review	CRS patients		No evidence for long-term antibiotics or radical surgery.
Videler[643]	2011	2	Systematic review	CRS patients		No evidence of active bacterial infection in the bone.
Chiu[642]	2005	2	Systematic review	CRS patients		Neo-osteogenesis may impact disease management.
Khalmuratova[670]	2019	3	Prospective case control	CRS patients (n=67), Control (n=11)	Protein expression	IL-13 and IL-17A induce RUNX2, transcription factor in osteoblast proliferation and differentiation.
Kong[673]	2019	3	Prospective case control	CRSwNP (n=63), CRSsNP (n=8), Control (n-12) undergoing ESS	Histopathology, GOSS, Protein expression	Levels of RANKL correlate with osteitis scores and disease severity.
Wu[672]	2019	3	Prospective case control	CRS patients with neo-osteo (n=10), control (n=10)	Protein expression, GOSS, KOS	BMP signaling dysregulation correlates with degree of osteitis.
Gunel[671]	2017	3	Prospective case control	CRSsNP and neo-	Gene expression	GDF5 upregulated in osteitic bone.

				osteogenesis (n=8), Control patients (n=8)	profiling	
Emre[654]	2015	3	Prospective case control	CRSwNP (n=20), CRSsNP (n=20), control (n=20)	CT bone density (HU)	HU different between controls and CRS patients.
Wang[667]	2015	3	Prospective case control	CRSwNP (n=23), CRSsNP (n=16), control (n=10)	GOSS, histopathology, protein expression	Increased TGF-β1 expression in ethmoid bone of CRSwNP compared to controls and CRSsNP.
Dong[664]	2014	3	Prospective case control	CRS patients undergoing surgery (n=84), control (n=22)	Histopathology, biofilm volume and score, GOSS, CT (HU)	Osteitis histopath grade higher with increasing biofilm volume and score.
Stevens[669]	2014	3	Prospective case control	CRS patients undergoing surgery (n=9), controls (n=5)	GOSS, osteoblast phenotype and proliferation, bone mineralization	Decreased osteoblast adhesion and increase calcium content in CRS.
Wood[652]	2012	3	Prospective case control	CRSwNP (n=8), CRSsNP (n=8), control (n=6)	Presence of bacterial colonies in bone samples	No difference in bacterial colonization of bone between CRS patients and controls.
Georgalas[657]	2010	3	Prospective case control	CRS (n=102) and controls (n=68) undergoing sinus CT	Global Osteitis Scoring Scale, Lund-Mackay grading scale	Neo-osteogenesis more common in CRS. Correlation between previous surgery and neo-osteogenesis.
Telmesani[641]	2010	3	Prospective case control	CRSwNP patients undergoing primary (n=50) and revision (n=32) ESS	Histopathology. Disease recurrence	Neo-osteogenesis associated with worse mucosal disease and revision surgery. Neo-osteogenesis predicted higher recurrence.
Saylam[656]	2009	3	Prospective cohort	CRS patients with and without neo-osteogenesis	SPECT scores, subjective response to treatment	Poor response to treatment in SPECT positive patients.
Giacchi[649]	2001	3	Prospective	CRS patients	Histopathology	Neo-osteogenesis

			case control	undergoing ESS (n=20), control (n=5)		and bone resorption identified in CRS.
Kennedy[638]	1998	3	Prospective case control	CRS patients (n=24) & controls (n=9) undergoing ESS	Histology of bone and mucosa	Bone remodeling increased in CRS group compared to controls.
Gunel[637]	2015	4	Prospective case series	CRS patients undergoing primary (n=74) and revision (n=37) ESS	Histopathology	No difference in neo-osteogenesis between primary and revision surgery.
Huang[662]	2015	4	Retrospective case series	CRS patients undergoing ESS with (n=30) and without (n=60) neo-osteogenesis	SNOT22, LM score, GOSS, Bacterial profile	Pseudomonas isolated more frequently in CRS with neo-osteogenesis.
Gunel[668]	2014	4	Prospective case series	CRS patients (n=38)	Histopathology, GOSS, KOS, P-glycoprotein expression	GOSS and KOS correlated with P-gp expression.
Snidvongs[650]	2014	4	Prospective case series	CRS patients undergoing primary ESS (n=22)	Histopathology	Neo-osteogenesis present, no bone inflammation.
Sacks[659]	2013	4	Prospective case series	CRS patients undergoing primary ESS (n=53)	Radiographic osteitis scores, SNOT22, endoscopic scores, steroid use	Neo-osteogenesis associated with need for oral steroid post-op.
Snidvongs[661]	2013	4	Retrospective cohort	CRS patients undergoing surgery (n=88)	KOS, GOSS histopathology, endoscopy, Lund-Mackay, QoL	KOS higher with revision surgery and CRSwNP. No correlation between QoL and neo-osteogenesis.
Snidvongs[254]	2012	4	Retrospective case series	CRS patients undergoing ESS (n=88)	Radiographic osteitis, Lund-Mackay scores, endoscopy, histopathology, SNOT22	Eosinophilia is associated with neo-osteogenesis, symptoms do not correlate.
Bhandarkar[639]	2011	4	Prospective case series	CRS patients undergoing ESS	Lund-Mackay score, Endoscopy, CT neo-osteogenesis,	Neo-osteogenesis may predict less post-op QoL improvement.

					Symptom scores	
Cho[660]	2008	4	Retrospective case control	CRS patients undergoing primary (n=25) and revision (n=15) surgery, controls (n=25)	CT scores, New bone formation, Bone density (HU)	LM scores, new bone formation, and ethmoid bone density were significantly higher in the revision surgery group.
Catalano[655]	2007	4	Prospective case series	CRS patients undergoing ESS	SPECT, Histopathology	SPECT sensitive for detecting osteitis on histopathology.
Cho[651]	2006	4	Retrospective case series	CRS patients undergoing primary ESS	Lund-Mackay score, CT (HU), histopathology	HU were increased with high grade histopathology.
Kim[658]	2006	4	Retrospective case series	CRS patients having undergone primary ESS (n=81)	CT scans for hyperostosis, postoperative endoscopic outcomes	Patients with hyperostosis (64%) more likely to have poor outcomes.
Lee[640]	2006	4	Prospective case series	CRS patients undergoing ESS	CT scan for neo-osteogenesis, histopathology	Neo-osteogenesis based on CT in 36% v. pathology 53%. Higher prevalence in revision surgery.

IX.C.5. Contributing Factors for CRS: Gastroesophageal Reflux

Because of limited data, CRSsNP and CRSwNP are combined in this analysis.

Laryngopharyngeal reflux (LPR) is the retrograde dispersal of gastric contents into the upper airway. In the United States, the estimated prevalence of gastroesophageal reflux symptoms ranges from 6% to 30%.[675] The pathophysiology linking LPR to CRS is unclear, although there appear to be several putative mechanisms suggesting that reflux disease may be a causal factor and an aggravating factor of CRS.

The exposure of nasopharyngeal and sinonasal mucosa to injurious gastric contents has been studied in adults[676-686] with gastroesophageal reflux disease (GERD) identified as a significant risk factor for poor outcomes following ESS.[687] Ulualp and Toohill identified a high rate of pharyngeal acid reflux and overall reflux events in adult CRS patients versus controls.[688] Ulualp *et al.* confirmed a significantly higher prevalence of reflux in refractory CRS patients versus controls (7/11, 64% versus 2/11, 18%).[684] Pincus *et al.* corroborated this, finding 25/30 (83%) patients with refractory CRS had positive pH studies, with improvement in most evaluable patients treated with proton pump inhibitors (PPIs) over one month (14/15, 93%).[677] Conversely, the prevalence of CRS in patients with reflux/GERD was 20.7% (95% CI, 12.0%-29.5%) (Bohnhorst *et al.* 2015).[689]

Loerhl and Smith[677] postulate that reflux causes an autonomic reflex leading to an inflammatory response and impaired MCC.[690] This is supported by Delehaye, who illustrated higher SNOT-20 scores in CRS patients with GERD compared to those with only extra-esophageal symptoms of reflux (Mean 19.3 versus 7.4, $p < 0.005$) and a prolonged saccharin test demonstrating delayed nasal mucociliary transport time in the study group.[691] Not all data implicates direct acid or non-acid exposure in CRS pathophysiology. Jecker *et al.* found that in 20 surgically refractory CRS patients there were significantly more reflux events in the *distal* pH probe when compared to the 20 healthy controls.[683] CRS patients additionally had a higher DeMeester index (32.9 +/- 8.7 versus 6.6 +/- controls), and the patients' esophageal mucosa was exposed to gastric acid for a mean of 95 minutes during the recording period relative to 16.6 +/- 4.6 minutes in controls. However, the *location* of the reflux events was somewhat paradoxical; with greater than ten times more events in the esophagus (95.5 +/- 31.0) relative to the hypopharynx (8.5 +/- 2.5) ($p<0.01$). This data gives credence to an alternative mechanism to explain sinus inflammation in the absence of direct acid injury, such as a vagally mediated reflex - the so-called *esophagonasal reflex*.[692] This was further explored by Wong *et al.*, who analyzed the nasal symptoms of 10 healthy volunteers after esophageal infusion of hydrochloric acid (HCl).[693] The infusion of HCl led to a non-significant rise in mean symptom score, as well as a reduction of nasal patency as measured by nasal inspiratory peak flow. Of the 267 recorded reflux episodes, none reached the nasopharynx.

Ozmen *et al.* found a higher rate of pharyngeal acid reflux events (PARE) using dual probe pH monitoring in the pharynx and LES in 29/33 CRS patients (88%) compared to 11/20 controls (55%).[682] Specific pepsin activity was identified in 82% of the study group compared to 50% of controls ($p =0.014$). Loehrl *et al.* demonstrated reflux events at all tested sites, including the nasopharynx, in 20 medically refractory CRS patients.[694] The authors performed nasopharyngeal biopsies of all subjects, with none testing positive for pepsin (0/20). However, in five subjects who underwent nasopharyngeal lavage, 100% were positive for pepsin, compared to zero of five healthy controls. DelGaudio examined medically and surgically refractory CRS patients compared to controls.[676] He demonstrated that nasopharyngeal reflux events occurred in 39% of surgically refractory patients compared with 10% of controls below a pH of 4, and 76% compared with 24% below a pH of 5. Reflux scores, CRS symptoms and SNOT-20 scores, and endoscopic examination scores were significantly higher in the study group.

Gastric acid and protease exposure has been well established as leading to dilation of the intercellular spaces in esophageal mucosa, with impaired mucosal integrity, and could be equally deleterious to upper airway mucosa.[695] DelGaudio postulates that nasal mucosa is susceptible to injury even at higher pH events, and cites a higher incidence of nasopharyngeal reflux events with pH <5 in refractory CRS patients.[676] Pepsin, which is found in higher levels in the middle turbinates of CRS patients relative to controls, is believed to mediate high pH injury, damaging the epithelial barrier by digesting intercellular junction proteins, promoting a pro-inflammatory milieu, damaging mitochondria, and upregulating MAP Kinase and downstream heat shock protein 70 in human nasal epithelial cells, indicating a response to cellular damage.[696-698]

H. pylori has also been implicated in CRS pathogenesis.[699,700] Vceva *et al.* identified *H. pylori* DNA in

the nasal polyp tissue of 28.6% (10/35) of their study group but did not find any in the middle turbinates of their control cohort, in spite of the ubiquitous *H. pylori* DNA found in the gastric mucosa of all study and control patients.[699] Ozdek *et al.* found that 33% of patients with classic CRS were positive for *H. pylori* DNA, while none of their control group was positive.[701] In their meta-analyses, Leason *et al.* found the *H. pylori* prevalence in CRS was 31.7%, and that 87.5% of subjects with intranasal *H. pylori* had GERD.[681]

Proton pump inhibitors play a key role in management of suspected reflux-associated CRS. Vaezi *et al.*, in a DBRCT demonstrated a reduction in PND, SNOT-20, and Quality of Life in Reflux and Dyspepsia scores in PND patients treated with lansoprazole 30mg twice daily for 16 weeks versus placebo.[679] Median symptoms score improvement for patients treated with a PPI at eight and 16 weeks was 55 and 50 respectively, relative to 3.5 and 5.0 for controls. DiBaise *et al.* found that 67% of 19 adult patients with GER and CRS had improvements in measures of sinonasal health after reflux treatment.[702] DiBaise *et al.* in an open label study of 11 refractory CRS patients with GERD treated with omeprazole for 12 weeks, found that sinus and global satisfaction scores improved in most patients, peaking by week eight and maintaining thereafter. Anzic *et al.* performed a DBRCT where patients with diagnosed LPR and comorbid CRS received eight weeks of omeprazole 20mg twice daily. They found objective reductions in reflux symptom index and scores, improved symptoms of comorbid CRSsNP, and improved endoscopy scores.[679]

CRS remains a multifactorial disease, with existing data suggesting that reflux can be an important contributor in some cases, especially in refractory disease. When reflux is present, treatment should include addressing the nasal inflammatory condition as well as the reflux. The long term use of PPIs must be weighed with inherent risks of long term PPI use, including pneumonia, susceptibility to enteric infections such as *Clostridium difficile*, micronutrient deficiencies, osteoporosis, rebound reflux disease after treatment cessation, and PPI-resistance.[703,704] For this reason, various other treatments have been tested for a safer management of GERD or LPR. Alginate compounds have demonstrated, in various studies, an efficacy comparable to PPIs in the management of this disease with a comforting safety profile.[705-707] In particular, magnesium alginates showed interesting results in children with LPR and uncontrolled asthma, with a significant improvement of both reflux and airway related inflammation.[708] With this data in mind, we conclude that with the evidence available, we cannot recommend the use of PPIs for the treatment of CRS, although it may be a useful adjunct in cases where post-nasal drip is a leading symptom.

Reflux as a Contributing Factor for CRSsNP

Aggregate Grade of Evidence: B (Level 1: 1 study; level 2: 2 studies; level 3: 3 studies; level 4: 9 studies)

Table IX-7. Evidence for reflux as a contributing factor for CRS

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Leason [681]	2017	1	Meta-analysis	32 studies relating GERD and CRS, n =255,323	Review of different pathogenic factors contributing to CRS	*H. pylori* prevalence in CRS 31.7%; 87.5% of subjects with intranasal *H. pylori* had GORD. 52.4% of CRS patients have reflux. Nasopharyngeal reflux more common in persistent CRS.
Anzic [679]	2017	2	RCT (n=60)	60 patients with diagnosed LPR and comorbid CRS, randomized groups n = 33, treatment with omeprazole 20mg OD 8 weeks n = 27 placebo	Reflux symptom index (ReSI), reflux finding score (RFS), CRS score, nasal endoscopy score, and eosinophil cationic protein	ReSI and RFS decreased significantly in treatment group after 8 weeks of therapy ($p<0.001$). CRS and endoscopy scores decreased significantly in treatment group compared to placebo.
Vaezi[680]	2010	2	RCT (n = 75)	Patients with chronic PND without RS or allergy; randomized to lansoprazole 30mg BID or to placebo	PND symptoms at 8 and 16 weeks	PND symptoms mitigated by reflux therapy, implicating reflux as causal factor in PND.
Pincus[677]	2006	3	Cohort	30 refractory CRS patients tested for reflux; 60% of patients with reflux treated with PPI	Reflux events in the nasopharynx, above the cricopharyngeus, and 5cm above the LES. Sinus and GERD symptoms	Sinus and GERD symptoms improve after reflux management, suggest role for reflux in pathophysiology of CRS.
Wong[692]	2004	3	Cohort	40 patients with CRS	Incidence of PARE with 24h 4-sensor probe pH monitoring at NPx, hypopharynx, proximal and distal esophagus	Rare NPx reflux events in CRS. Suggests that acidic reflux may not have role in CRS pathogenesis.
DiBaise[678]	2002	3	Cohort	CRS patients tested for	Dual pH-probe	82% of CRS

				GERD, subsequently treated with PPI (n = 11). GERD control patients without CRS (n =19)	testing, laryngoscopy, nasal endoscopy. Individual sinus symptoms (ISS) and global satisfaction (GS) after 12 weeks of treatment	patients had abnormal pH test at proximal and/or distal pH sensor locations. After GERD medical therapy, CRS symptom improvement in 25-89%.
Katle[685]	2017	4	Case Control	46 adult patients with CRS 45 healthy controls	Reflux questionnaires for both groups, 24 hour multichannel intraluminal impedance pH monitoring	Higher median reflux episodes compared to controls. Higher abnormal impedance readings compared to 11.1% of controls.
Bhawana[709]	2014	4	Case Control	50 adult patients with CRS (100 meati) 50 adult controls (100 meati)	Intra-nasal middle meatal pH testing	Mean middle meatal pH in the CRS group was higher.
Loehrl[694]	2012	4	Case-control	Refractory CRS, post-ESS, (n=22)	NPx tissue biopsy (analyzed for pepsin), dual pH probe testing, probe in NPx and UES	Positive pharyngeal pH probes in 19/20 surgically refractory CRS patients and positive nasal pepsin assays in 5/5 patients tested.
Vceva[699]	2012	4	Case control	Adults with intranasal polyposis 30 controls with concha bullosa	Presence of intranasal *H. pylori* detected in nasal tissue with rtPCR, anti- *H. pylori* Ig or with ELISA	*H. pylori* DNA is found in 28.57% of nasal polyp tissue on PCR in study group, not detected in controls ($p<0.001$ *H. pylori* specific IgA and IgG antibodies more commonly found in CRS patients.
Ozmen[682]	2008	4	Case-control	CRS (n = 33) Controls (n = 20)	PARE with 24h dual-probe pH monitoring	Higher prevalence of PARE and nasal pepsin in CRS patients.

Jecker[683]	2006	4	Case-control	Chronic polypoid RS, prior ESS (n = 20) Healthy volunteers (n = 20)	24h pH probe monitoring (double-pH probe): event number, fraction of time pH <4	CRS group with more esophageal, but not hypopharyngeal reflux events.
DelGaudio[676]	2005	4	Case-control	Post-ESS with inflammation (n = 38) Post-ESS sans inflammation (n = 10) Controls (no CRS, no ESS; n = 20)	PARE with 24h triple-probe pH monitoring at NPx, UES, (pH events <4 and 5), and distal esophagus (pH<4)	Patients with refractory CRS post-ESS have more reflux events at all studied anatomic sites; largest difference is NPx reflux.
Ozdek[701]	2003	4	Case-control	Mucosa from CRS patients (n = 12) Mucosa from controls with concha bullosa (n = 13)	*H. pylori* DNA/RNA	*H. pylori* present in 4/12 CRS patients and 0/13 controls.
Ulualp[684]	1999	4	Case-control	Refractory CRS (n = 11) Healthy controls (n = 11)	PARE documented around UES, LES	Higher prevalence of PARE in CRS.

IX.C.6. Contributing Factors for CRSsNP: Vitamin D Deficiency

Vitamin D (VD3) circulates in its inactive form (25VD3) and is converted to its active form (1,25VD3) by 1α hydroxylase. This active form has anti-inflammatory and anti-bacterial actions,[710-712] thus prompting studies on its potential role in CRS. Our understanding of CRSsNP is limited, but it is thought to represent a heterogeneous disease process, characterized by the absence of nasal polyps.[154] The literature on the effects of vitamin D on CRSsNP consists primarily of studies comparing CRSsNP and controls, and is limited to case series and case-control studies looking at systemic and local sinonasal vitamin D levels and metabolism.

Clinical studies investigating systemic vitamin D levels in adult CRSsNP patients predominantly demonstrate a lack of association between CRSsNP and systemic vitamin D deficiencies.[713-720] This lack of association is further supported in a pediatric study.[717] While systemic $25VD_3$ levels appear to be normal in CRSsNP patients, active or passive smoke exposure is associated with decreased systemic $25VD_3$.[719] Active smoking was also shown to decrease serum 25VD3 and 1,25VD3 in perimenopausal women without CRS.[721] A study looking at ethnic background and its effect on CRS found that African Americans with severe CRS had significantly lower serum $25VD_3$ levels than both Caucasian patients and race/sex matched controls, but a limitation of this study is that polyp status was not defined.[722] Of the reviewed studies, one study from Iran found an association between CRSsNP and vitamin D deficiency. The authors discuss how cultural differences, specifically dressing style (which in turn affects the amount of sun-exposed skin and vitamin D synthesis), can affect systemic vitamin D levels. Given the limited population studied, results of this investigation may not be generalizable to other geographic regions.

Investigations looking at local sinonasal vitamin D levels further support the lack of association between CRSsNP and vitamin D deficiency. Two studies from the same group found no association between CRSsNP and decreased sinonasal VD3 levels[719] or sinonasal 1,25VD3 levels.[715] Cigarette smoke exposure also decreased local 25VD3 levels in sinonasal tissues.[719] A separate study looked at sinonasal tissue dendritic cell infiltrate levels and its relationship with systemic vitamin D levels given the role of vitamin D as a potent steroid hormone that acts on immune cells. CD209+ dendritic cells were found to inversely correlate with vitamin D3 levels. Unlike CRSwNP patients, there was no increase in CD209+ dendritic cell infiltrate in sinonasal tissue of CRSsNP patients.[717]

Studies have also looked at vitamin D metabolism as it pertains to CRS. It has been shown that CRSsNP sinonasal epithelial cells have the ability to convert $25VD_3$ to $1,25VD_3$.[719,723] In contrast to CRSwNP patients, CRSsNP patients do not demonstrate reduced sinonasal 1α hydroxylase levels.[715] When looking at gene expression, a separate study similarly found that sinonasal vitamin D receptor (VDR) gene expression was not reduced in CRSsNP patients. However, in this same study, cytochrome P450 family 27 subfamily B member 1 gene expression (CYP27B1, the gene encoding 1α hydroxylase) was lower in the sinonasal mucosa of CRSsNP compared to controls, despite having normal systemic 1,25VD3 levels suggesting that the local regulation of vitamin D may be independent of serum 1,25VD3.[724] A separate study similarly found a 2-fold down-regulation of CYP27B1 expression in CRSsNP patient compared to controls. When examining the effect of cigarette smoke exposure, CYP27B1 expression was further down-regulated in all study groups including CRSsNP patients.[719]

Vitamin D Deficiency as a Contributing Factor for CRSsNP

In summary, two statements can be made about Vitamin D in CRSsNP:

(1) CRSsNP is not associated with systemic 25VD3 deficiencies

Aggregate Grade of Evidence: C (Level 4: 11 studies; level 5: 2 studies)

(2) Smoke exposure in CRSsNP patients can lower systemic and local 25VD3 levels

Aggregate Grade of Evidence: N/A (Level 4: 1 study)

Table IX-8. Evidence for vitamin D deficiency as a contributing factor for CRSsNP

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Wang[713]	2019	4	Retrospective case-control	42 Control 25 CRSwNP 21 CRSsNP	Serum 25VD3 SNOT22 LM score	No difference in serum 25VD3 between CRSsNP and controls.
Habibi[725]	2019	4	Case-control	50 Control 35 CRSsNP 32 CRSwNP	Serum 25VD3	Serum 25VD3 is lower in CRSsNP compared to controls.
Christensen[724]	2017	4	Case-control	13 Control 8 CRSsNP 10 CRSwNP	Sinonasal Vitamin D Receptor (VDR) gene expression level Sinonasal CYP2R1,	No difference in VDR expression between CRSsNP and controls. CYP27B1 gene

					CYP27B1, CYP24A1 gene expression levels Nasal symptom score (NSS)	expression lower in CRSsNP compared to controls. CYP24A1 upregulated in CRSsNP compared to controls.
Konstantinidis[71] 4	2017	4	Case-control	32 Control 30 CRSsNP 32 CRSwNP 31 CFsNP 27 CFwNP	Serum 25VD3 Lund Kennedy score Lund Mackay score	No difference in serum 25VD3 levels between CRSsNP and Controls. 25VD3 inversely correlated with Lund-Kennedy and Lund-Mackay scores in CRS and CF.
Schlosser[715]	2016	4	Case-control	18 Control 13 CRSwNP 13 CRSsNP 6 AFRS	Sinonasal 1α hydroxylase level Sinonasal 1,25 VD3 SNOT22 Serum 1,25VD3	No difference in sinonasal 1α hydroxylase and 1,25VD3 between CRSsNP and Controls. No difference in serum 1,25 VD3 between CRSsNP and controls.
Mostafa[716]	2016	4	Case-control	19 Control 25 AFRS 15 CRSwNP 15 CRSsNP	Serum 25VD3 Serum Calcium Serum Phosphate	No difference in 25VD3 between CRSsNP and controls. No difference in serum calcium between groups. Phosphate is higher in Controls and CRSsNP when compared to AFRS and CRSwNP patients.
Sansoni [726]	2015	4	Case-control	12 Control 31 CRSsNP	Serum 25VD3 Sinonasal MCP-1, RANTES, and bFGF levels	Serum 25VD3 did not correlate with MCP-1, RANTES, and bFGF in CRSsNP. Serum 25VD3 higher in CRSsNP than controls.
Mulligan [719]	2014	4	Case-Control	21 Control (CSF leak/pituitary tumor patients) 40 CRSsNP 45 CRSwNP	Serum and sinonasal 25VD3 Sinonasal CYP27B1 gene expression Sinonasal 25VD3 to 1,25VD3 conversion	No difference in serum or sinonasal 25VD3 between CRSsNP and controls. Cigarette Smoke associated with lower 25VD3 levels.

Wang[720]	2013	4	Case-Control	25 CRSwNP 20 CRSsNP	Serum 25VD3 Polyp grade Lund Mackay Score Total IgE	No difference in serum 25VD3 level between CRSsNP and controls.
Mulligan[717]	2012	4	Retrospective Case-Control	14 Control 17 CRSsNP 5 CRSwNP 14 AFRS	Serum 25VD3 Number of CD209+ Dendritic cells in nasal biopsy/high powered field	No difference in serum 25VD3 between CRSsNP and controls.
Mulligan[718]	2011	4	Retrospective Case-Control	14 Control (CSF Leak) 20 CRSsNP 9 CRSwNP 14 AFRS	Serum 25VD3 Dendritic cells as percentage of total peripheral blood mononuclear cells	No difference in serum 25VD3 between CRSsNP and controls.
Pinto[722]	2008	4	Case-Control	68 Control 86 CRS	Serum 25VD3	Serum 25VD3 is lower in urban African Americans with CRS than controls or Caucasians with CRS.
Sultan[723]	2013	5	*In vitro*	8 patients including healthy, CRSwNP and CRSsNP subjects	Sinonasal 1α hydroxylase mRNA/protein staining Sinonasal 1,25VD3 level Cathelicidin mRNA expression	Human sinonasal epithelial cells express 1α hydroxylase, can generate the active 1,25VD3 and cathelicidin.
Sugimoto[727]	2007	5	*In vitro*	6 patients with CRS	Osteocalcin concentration TGFβ concentration Mineralization area	Vitamin D3/Vitamin K combination creates greatest neo-osteogenesis by ethmoid bone osteoblasts.

IX.C.7. Contributing Factors for CRSsNP: Superantigens

Studies on *Staphylococcus aureus* (SA) and its superantigens have mainly focused on CRSwNP. It has been shown that CRS patients with and without polyps have significantly increased SA nasal carriage rates and biofilm formation compared to healthy subjects. The presence of SA biofilm has been associated with the presence of superantigen specific IgE.[728,729] However, within the sinus tissue, no SE-IgE antibodies could be detected in 20% CRSsNP subjects, whereas they could be demonstrated in about 50% of the CRSwNP patients. In line with these findings, serum specific IgE to Staphylococcal enterotoxin B (SEB) was significantly increased in CRSwNP patients compared with the controls, but not in CRSsNP patients.[730]

A recent study differentiating type 2 from non-type 2 CRSsNP showed that IgE formation to *S. aureus* enterotoxins (SE-IgE) was exclusively present in type 2 CRSsNP and associated with increased tissue

IgE and markers of eosinophilic inflammation, but less pronounced compared to CRSwNP.[731] In summary, unlike for type 2 disease including CRSwNP, there is no evidence supporting a prominent role of superantigens in the etiology or pathogenesis of on non-type 2 CRSsNP.

With these studies, there is limited data available that supports any role for superantigens in the pathophysiology of CRSsNP.

Superantigens as a Contributing Factor for CRSsNP

Aggregate Grade of Evidence: C (Level 3: 2 studies)

Table IX-9. Evidence for superantigens as contributing factors for CRSsNP

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoints	Conclusions
Delemarre[731]	2020	3	Cross-sectional endotyping study of CRSsNP subjects	240 CRSsNP	SE-specific IgE Th2 cytokines	Slightly less than half of CRSsNP subjects have a type 2 immune response endotype based on marker cytokines, and this is partially characterized by the presence of SE-specific IgE.
Cui[730]	2015	3	Cross-sectional study of serum samples from control, CRSsNP, and CRSwNP subjects for SE-specific IgE	30 CRSwNP 30 CRSsNP 30 Control	Serum SE-specific IgE	No significant differences in serum SE-specific IgE were found in CRSsNP. CRSwNP had significantly elevated SE-specific IgE in serum

IX.C.8. Contributing Factors for CRS: Microbiome Disturbance

Because of limited data, CRSsNP and CRSwNP are combined in this analysis.

In health, the anterior nasal cavity, middle meatus, and sphenoethmoidal recess are populated by a stable microbiome that appears to be highly individualized.[732-735] Characteristic findings in health include increased bacterial diversity, low abundance of pathogens, and limited anaerobes.[736] Particular organisms (namely *Propionibacteria*, *Corynebacteria*) may be more abundant in the healthy state, although precise speciation is subject to technical limitations and absent reproducibility at this time[736-738] Of interest, 20% of healthy individuals exhibit persistent

Staphylococcus aureus nasal carriage, 60% are transiently colonized, and 20% almost never carry *S.aureus*, with broad implications for other health outcomes.[739]

In contrast to the rich assemblages of bacteria that populate the sinuses in the healthy state, CRS patients harbor qualitatively different microbial communities[740-743] that may be less stable over time.[744] Importantly, there is a large inter-individualpersonal variability, and there does not appear to be a single causative organism for CRS that is reproducibly observed across all studies. However, loss of diversity, preponderance of opportunistic pathogens over commensals, and expansion of anaerobes are routinely observed. The absence of causative organisms and differences in bacteria observed across studies may hint at the importance of community function, or may be in part due to intricacies of the disease process and its subtypes.

In a cohort of 82 subjects, Ramakrishnan and colleagues examined microbiome alterations by phenotype and noted that the presence of polyps was not associated with microbiota alterations in CRS, but CRS patients with asthma or purulence had markedly different microbiota.[741] In this study, the authors did not find differences in alpha diversity indices (richness, evenness, complexity) of CRS patients when compared to controls but demonstrated that increased diversity was associated with improved surgical outcome, suggesting that a diverse microbiome may be beneficial to restoration of sinus health. Although others have reported differences in CRSwNP compared to controls,[745] most publications do not observe differences in CRS populations driven by polyp status. Studying CRS phenotypes, Hoggard and colleagues did not observe differences unique to CRSwNP, but reported that asthmatics and CRS patients with CF were more likely to exhibit dysbiosis with wide variability in community structure.[746] Similarly, Mahdavinia *et al.* performed a cross-sectional study of 111 CRS subjects, and did not observe nasal polyps to associate with a unique surface microbiome.[747] They were able to link comorbid AR with the lipopolysaccharide protein biosysnthesis pathway using predictive metagenomics, suggesting a functional relevance for the microbiome in atopic CRS. Chalermwatanachai and colleagues profiled the microbiota in 41 CRSwNP subjects compared to 18 controls, finding differences in microbes between the asthmatics and nonasthmatics, and demonstrating that pathogenic organisms found in CRS subjects outcompeted *Propionibacterium acnes* in co-cultivation experiments.[748] Cope *et al.* utilized sinus brushings in 59 CRS subjects and 10 controls to cluster 4 subgroups of CRS subjects according to pathogenic microbiota and their predicted functions, as well as host mucosal inflammatory response.[749] The authors observed that one of these four groups had a higher incidence of nasal polyposis, and was defined by a predominance of *Corynebacteria* and increased IL-5. Hoggard *et al.* reported a cross-sectional analysis on 93 CRS subjects and 17 controls, evaluating microbiota alongside ten tissue cytokines and 6 cell types.[50] The authors identified 8 clusters of patients, strongly segregated by the presence of polyposis, asthma, cytokine profiles, and the loss of health-associated groups of bacteria. In aggregate, these studies indicate microbiome differences in CRS asthmatics, and occasionally in CRSwNP although the effect appears more strongly associated with the presence of asthma in these patients.

Given the common themes observed in these studies, and lack of clarity within detailed results published by various authors, Wagner Mackenzie *et al.* combined available 16S rRNA sequence data in a meta-analysis in 2017.[738] Their results demonstrated the common classes of bacteria observed

across studies at a high level, but most strikingly concluded that bacterial communities in CRS are dysbiotic and ecological networks fostering colonization by healthy communities were fragmented in the diseased state. In their study, CRS was defined by loss of bacterial diversity, increased dispersion of bacterial communities, and loss of Actinobacteria and *Propionibacteria* that characterize the healthy state.

To understand if, and how, bacteria influence host immune processes, several groups have associated microbiota surveys with host cytokine profiling or tissue function assays. Biswas and colleagues evaluated 23 CRS subjects (8 CRSwNP, 8 CRSsNP, and 7 cystic fibrosis) and 8 controls, and found two subgroups of CRS patients.[750] One group was characterized by low bacterial diversity and dominance of pathogens such as *Pseudomonas*, *Haemophilus*, and *Achromobacter*. The other group was characterized by preponderance of B cells and CRSwNP more so than its microbial signature, suggesting that integration of microbes with other clinicopathologic features may be required. In a separate report, the authors utilized proteomics and 16S rRNA sequencing of middle meatus swabs in addition to tissue immune cell profiling, to correlate several bacterial taxa in CRS subjects with dyregulation of various host proteins.[751]

Although CRS appears to be associated with shifts in microbiota and loss of diversity, it is unclear whether there is a causal relationship of the microbiome in disease or if alterations are a by-product of disease pathophysiology and/or frequently applied therapies. Given the inherent confounders of CRS disease processes and prior therapies, causality and mechanistic understanding for the microbiome in CRS has been challenging to ascertain. Whether there is a direct effect of the microbes, a dysfunctional host reaction to microbes, both, or neither (*i.e.*, bystander effect) has been the subject of ongoing debate. In addition to the bacterial dysbiosis that may be present in CRS, a dysfunctional host reaction to microbiota may also be present. For example, Aurora *et al.* found minimal differences between the bacterial and fungal microbiomes of CRS versus healthy subjects, but when peripheral leukocytes were exposed to different microbiota, CRS patients produced significantly more IL-5.[752] Such data suggest that a dysfunctional and hyperresponsive host immunologic reaction is at least as important as any underlying microbial difference between CRS and healthy states.

In addition to bacterial alterations seen in the microbiome in CRS, viral and fungal changes may also be seen.[753-759] Further *in vivo* studies of the relationship of viruses and fungi to the sinus microbiome in health, CRS, or AECRS are an area of ongoing interest and will likely evolve with the application of new technologies.

Cross-sectional and case-control study designs have been used to associate microbiota with CRS disease severity or histopathology.[736,760] Intervention study design and associations with outcomes have also been attempted as another way to support the microbiome's role in human disease.

Nasal irrigations and intranasal corticosteroids. It is plausible that some degree of observed alterations in local microbiota in CRS studies could result from repeated and prolonged medical therapies.[738,761] Topical INCS formulations may have some inherent antimicrobial activity,[596,762] or their resultant local immune modulation may shift nasal microbiota, with effects that persist even

beyond the duration of treatment.[763] Similarly, nasal saline irrigation may confer some antimicrobial effect,[764] although literature results associating topical saline use with local microbiome alterations are limited by study design.

*Antibiotics***.** Antibiotic administration results in variable and potentially dramatic alterations in mucosal bacterial communities, although existing supporting evidence in the paranasal sinuses is limited.[765,766] In a cross-sectional study by Feazel *et al.*, recent antibiotic use correlated with significant reductions in bacterial diversity and increased *S. aureus* abundance.[740] However, other reports have not reproduced these findings.[741] In two prospective studies of antibiotics administered for AECRS, Merkley *et al.* and Liu *et al.* observed conflicting effects on bacterial diversity, where one study found increased diversity and the other study found decreased diversity after therapy.[767,768] Further work using novel study designs will be required to understand short-term, long-term, and individualized effects of antibiotics on the sinonasal microbiome.

Surgery. Kim *et al.* performed a prospective, randomized, single-blinded trial to evaluate the effects of balloon sinus dilation versus large antrostomy on maxillary sinus microbiota and inflammation.[769] The authors found no difference between bacterial burden, cytokine profiles, or endoscopy score between the two treatments. However, significant differences in relative postoperative abundance of *Staphylococcus*, *Lactococcus*, and *Cyanobacteria*, were noted between sides suggesting that the local anatomic environment may influence surface microbial colonization.

Jain *et al.* studied 23 patients undergoing ESS and observed unpredictable shifts in community composition with high inter-subject variability, but a general association with increased richness.[770] These findings were echoed in a study of 12 patients undergoing ESS and postoperative antibiotic therapy by Hauser and colleagues, who additionally reported a high degree of resilience suggesting that some patients' microbiota may not change much in the long-term despite a rather drastic intervention.[771] In contrast, Cleland and colleagues observed decreased richness after sinus surgery in a cohort of 23 CRS patients.[772] Preliminary work suggests that specific microbiota and ecological changes after surgical intervention may be associated with improved outcomes[741] The importance of these associations is unclear at this time, and will certainly be the focus of continued study.

Probiotics. Prebiotic or probiotic administration has received interest in various fields as an alternative method to antibiotics for direction of the microbiome away from pathogen colonization and toward restoration of healthy commensals. Preclinical study suggests potential value of probiotic manipulation for CRS through direct immune modulation of PBMCs,[773] and by antagonism of colonization by the sinus pathogen, *S.aureus.*[774] Clinical studies at this time are nascent, and are addressed in Section IX.D.8.

In conclusion, although CRS microbiome studies are in their early stages, overall composition and diversity disturbances have been observed in several studies. It is worth noting that some of the initial study findings have not been replicated, due to small cohorts and different experimental methods. The results in the literature are varied and challenging to interpret in aggregate. While implicated taxa may be present in health and CRS, no consistent enrichment of a particular organism has been uniformly identified. There is considerable interest in the functional relevance of the

microbial community that may contribute to sinus health or disease. Further investigations of the sinonasal microbiome may promote better understanding of CRS, leading to novel therapeutic interventions with potential opportunity for personalized medicine.

Microbiome Disturbance as a Contributing Factor for CRS

Aggregate Grade of Evidence: C (Level 3: 4 studies, Level 4: 4 studies)

Table IX-10. Evidence for microbiome disturbance as a contributing factor for CRS

Study	Year	LOE	Study Design	Study Groups	Clinical End-point(s)	Conclusion
Jain[775]	2018	3	Longitudinal study	20 CRS patients receiving doxycycline or prednisone compared to 6 untreated CRS patients	SNOT-22	Bacterial profiles dominated by *Corynebacterium* and *Staphylococcus* in all 26 patients. Treatment with doxycycline or prednisone had variable and unpredictable changes. No bacterial taxa significantly correlated with changes in SNOT-22 scores after treatment.
Jain[770]	2017	3	Longitudinal study examining postoperative changes	23 CRS no control	CRS 5-symptom score survey	Richness increased after surgery for most patients, without significant changes in other diversity measures. Samples dominated by Firmicutes, Proteobacteria, Actinobacteria.
Cleland[772]	2016	3	Longitudinal study	23 CRS 11 control	SNOT-22 VAS	*Acinetobacter johnsonii* and *Corynebacterium confusum* more prevalent in control population. No prevalent species identified in CRS. *S.aureus* with increased relative abundance in CRS vs control. *A. johnsonii* associated with improved in SNOT-22 and VAS. *Pseudomonas aeruginosa* associated with significant negative effect on SNOT-22.
Ramakrishnan[741]	2015	3	Longitudinal study	56 CRS 26 control	Requirement for further medical or surgical	Patients with optimal outcomes showed increased diversity measures and enrichment of Actinobacteria, including

					intervention	*Corynebacteria*.
Copeland[776]	2018	4	Cross-sectional study	21 CRS 12 control	SNOT-22	Diversity similar among sinuses, with large interpersonal variation. Proteobacteria significantly more abundant in CRS. At genus level only *Escherichia* was significantly different with higher abundance in CRS. 18 OTUs positively correlated with SNOT-22 scores, 9 of which were *Escherichia*. One OTU negatively correlated with SNOT-22 – *Corynebacterium.*
Karunasagar[777]	2018	4	Cross-sectional study using molecular methods comparing culture-negative CRS	20 CRS no control	SNOT-22	Bacteria detected in all culture-negative cases. *Staphylococcus, Enterobacter*, *Pseudomonas* were dominant groups.
Lal[778]	2017	4	Cross-sectional study	46 CRS 11 AR 8 control	SNOT-22	Bacterial diversity significantly reduced in middle compared to inferior meatus in CRSsNP patients. MM diversity lower in CRSsNP. Linear regression analysis based on SNOT-22 scores did not reveal any statistically significant differences for diversity measures.
Joss[779]	2016	4	Cross-sectional study comparing molecular and culture methods	19 CRS no control	SNOT-22	*Corynebacterium* and *Staphylococcus* high in most patients. *Staphylococcus* likely to culture even when low abundance.
Abreu[737]	2012	4	Cross-sectional with secondary mouse model	10 CRS 10 control	SNOT-20	CRS patients with decreased diversity compared to controls. 228 groups correlated with lower SNOT-20 scores. *Corynebacteria* positively correlated with increased symptom severity.

IX.C.9. Contributing Factors for CRSsNP: Anatomic Variation

There are a multitude of sinonasal anatomic variations that are described and may theoretically contribute to the pathology of CRS. These variations are generally thought to narrow anatomic drainage pathways, such as the frontal sinus or the osteomeatal complex.[332,338,340,342,348,780-786] Examples of sinonasal variants include infraorbital (Haller) cells, concha bullosae, paradoxical curvature of the middle turbinates, nasal septal deviation (NSD), suprasphenoid ethmoidal cells (Onodi), and frontal sinus variations including frontal sinus cells, supraorbital cells, suprabullar cells, frontal bullar cells, and intersinus septal cells. These variants are often present in the general population as well, suggesting that variations alone may not cause pathology without other factors. Additionally, underlying disease processes may also contribute to variation. For example, maxillary pathology may lead to medial displacement or thinning of the uncinate process, which could be interpreted as contributing to the disease process, when, in fact, the variation may result from the disease process.

Multiple studies have described an association between anatomic variation and development of CRSsNP. Caughey *et al.*[342] found patients with infraorbital ethmoid cells had overall increased Lund-Mackay CT scores for the frontal, ethmoid, and maxillary sinuses, but only the ethmoid and maxillary sinuses had increased scores when comparing individual sinuses. In the same study, patients with a concha bullosa had increased Lund-Mackay scores for maxillary sinuses only. The form of RS (CRS vs. ARS) was not delineated, but the study suggests that obstruction of the OMC can lead to ethmoid and maxillary mucosal disease. Similarly, Khojastepour *et al.*[333] found that infraorbital cells are associated with maxillary mucosal disease on cone beam CT scan in patients presenting for rhinoplasty evaluation. In addition, other studies have demonstrated that sphenoethmoidal cells (Onodi cells) may be associated with radiographic sphenoid mucosal thickening, again, ostensibly from narrowing of the natural sinus ostia.[787]

Jain *et al.*[338] performed a retrospective cohort study and compared groups with limited sinus disease, pansinusitis, and a control group without sinonasal disease. The authors examined CT sinuses and found a significantly higher average number of anatomical anomalies (accessory ostia, conchae bullosae, Infraorbital ethmoid cells, lateralized uncinate processes, and paradoxical middle turbinates) in patients with limited sinus involvement on CT compared to the other cohorts. Specifically, the authors found that the group with limited sinus disease had 96 anatomic variations in 22 patients, while the control group had 68 variants in 27 patients, and the pansinusitis group had 72 variants in 28 patients (p=0.003). They proposed that these anatomical variants cause limited disease when they impair function of the OMC while a primary mucosal abnormality is responsible for individuals with more global disease. In a similar study the same group demonstrated that in cohorts undergoing anterior ESS only or ESS for CRSsNP or CRSwNP that the patients undergoing surgery for CRSsNP and anterior ESS were more likely to have anatomic variants than the CRSwNP cohort, supporting again the idea that CRSwNP is a more global disease process and that anatomic factors may play a role in more limited disease.[788] In another surgical study, Qualliotine *et al.*[789] found that patients with concha bullosae had worsened QoL scores and improved more after surgery than patients without that specific anatomic abnormality.

Sedaghat *et al.*[785] found sinonasal anatomic variants (concha bullosae, intersinus frontal cells, frontal air cells and infraorbital ethmoid cells) predispose to progression to CRS over time in patients with underlying AR. In this study the authors performed a retrospective review of a cohort of patients initially diagnosed with AR, who had follow up of at least 4 years. They found that a significant proportion progressed to develop CRS, and examined the factors that contributed. Among other factors, such as asthma, anatomic variants were associated with faster progression to the development of CRS. This study is limited by the retrospective design, and the relatively small sample size as only 24 patients were identified that progressed from AR to CRS, but the authors concluded that anatomic narrowing may promote development of inflammation in the sinuses and development of CRS in AR patients.

Lien *et al.*[790] demonstrated an increased incidence of frontal sinusitis associated with cells that affect the posterior or posterolateral aspect of the frontal recess (suprabullar, supraorbital, and frontal bullar cells) with no association found with frontal cells. Langille *et al.*[791] showed a significant relationship between the presence of frontal cells and mucosal thickening on CT imaging.

In contrast to these studies showing an association between anatomic variants and sinonasal disease, there is also a significant body of literature that does not demonstrate a relationship. Nouraei *et al.*[784] and Bolger *et al.*[348] found no relationship between anatomical variations of the middle turbinate or other structures that could affect the OMC and impact on Lund-Mackay score. Cho *et al.*[340] noted no correlation between middle turbinate variations or NSD and presence of sinus inflammation on CT scan. Similarly, papers by Shpilberg *et al.*[334] and Balikci *et al.*[792] found that anatomic variants such as concha bullosa, NSD, and agger nasi cells are common, but not associated with CRS. Kalaiarasi *et al.*[793] also demonstrated that concha bullosa was not associated with ipsilateral CRS except in the case of extensive conchae. In two studies focusing on the frontal sinuses of patients with a history of CRS, the presence of frontal recess cells and agger nasi cells were not associated with a higher incidence of frontal sinusitis.[794,795] Additionally, no association was found by DelGaudio *et al.*[795] between frontal sinusitis and size of the frontal recess. When specifically studying frontal sinus anatomy, DeConde *et al.*[7966] showed that the frontal sinus outflow dimensions, presence of intersinus septal cell, and an anterior ethmoid artery on a boney mesentery did not impact QoL gains from endoscopic frontal sinus surgery.

In conclusion, there is literature both supporting and refuting an association between anatomic variations and CRSsNP. The papers demonstrating an association show a generally small effect with some contribution of anatomic variation in the disease process. Overall this suggests a small, if any, role of anatomic variations in the pathogenesis of CRSsNP.

Anatomic Variations as a Contributing Factor for CRSsNP

Aggregate Grade of Evidence: D (Level 3: 2 studies; level 4: 19 studies). Results of studies are conflicting.

Table IX-11. Evidence for anatomic variations as contributing factors for CRSsNP

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
DeConde[796]	2015	3	Prospective cohort	63 CRS patients undergoing frontal sinus surgery	Frontal recess anatomic variants, preoperative to postoperative SNOT-22 score change.	Anatomic measurements and variations did not correlate with changes in SNOT-22 scores.
Sedaghat[785]	2013	3	Cohort study	59 patients treated over 7 years for AR	Presence of anatomic variants and progression to CRS	Faster progression to CRS in AR patients with at least one anatomic variant.
Qualliotine[789]	2020	4	Retrospective case-control	87 patients with concha bullosa; 50 without, all undergoing ESS	Preopertive QoL scores and post operative improvement	Worse QoL in extra-nasal rhinologic scores in concha patients; more post operative improvement in concha patients.
Kalaiarasi[793]	2018	4	Retrospective case series	202 patients undergoing CT scans for sinonasal symptoms	Presence of concha bullosae and relationship with RS	Concha bullosae are not associated with CRS except in the case of extensive conchae.
Senturk[787]	2017	4	Retrospective case series	Sinus CTs of 618 patients, 326 with Onodi cells	Presence of Onodi cells and presence of sinus inflammation	Increased risk of radiographic sphenoid sinusitis with Onodi cell.
Khojastepour[333]	2017	4	Retrospective case series	Sinus cone beam CTs of 120 patients considering rhinoplasty	Presence and volume of Haller cells as well as uncinate variants	Haller cells associated with mucosal thickening in the maxillary sinuses.
Wu[788]	2017	4	Retrospective case-control	86 patients undergoing limited ESS or ESS for CRSsNP or CRSwNP	Reduction in symptoms and number of follow up visits needed	Anterior ESS and ESS for CRSsNP was associated with more anatomic variants than CRSwNP.
Balikci[792]	2016	4	Retrospective case series	296 patients undergoing sinus CT	Presence of concha bullosa, NSD, associated RS	Concha bullosa and NSD are common and not associated with CRS.
Shpilberg[334]	2015	4	Retrospective case series	Sinus CTs of 192 patients with CRS	Presence of anatomic variants and associated with radiographic	No association between radiographic disease and

					mucosal disease	anatomic variants.
Aramani[797]	2014	4	Retrospective Case series	Sinus CTs of 54 consecutive patients with suspect CRS	Presence of anatomic variants	More than 50% of patients had two variants or more, and most had at least one.
Eweiss[794]	2013	4	Retrospective case series	CT scans of 70 patients	Presence of frontal and ethmoid anatomic variants and the presence of frontal sinusitis	No significance found between presence or absence of frontal recess/ sinus cells or agger nasi cells and frontal sinusitis.
Jain[338]	2013	4	Retrospective case-control study	22 patients with limited RS, 28 patients with diffuse disease, 27 controls	Presence of anatomic variants	Frequency of total anatomical variants in the limited group was significantly higher than in the pansinusitis and control groups.
Langille[791]	2012	4	Retrospective case series	CT scans of 328 patients	Presence of frontal sinus cells and presence of mucosal thickening	Frontal cells had a significant association with the presence of mucosal thickening.
Cho[340]	2011	4	Case-control study	Sinus CTs of 73 healthy controls; 461 CTs of patients with rhinologic symptoms	Presence of anatomic variations of MT and NSD correlated to presence of rhinologic symptoms	MT abnormality or NSD were not associated with increased incidence of RS.
Lien[790]	2010	4	Retrospective case series	CT scans of 192 patients	Presence of anatomic variants within the frontal and ethmoid regions and the presence of frontal sinusitis	Frontoethmoid cells posterior and posterolateral to the frontal recess were associated with frontal sinusitis.
Nouraei[784]	2009	4	Retrospective case series	300 CT scans from patients with symptoms of CRS	Anatomic variants and Lund-Mackay scores	No relationship was found between anatomical variations and Lund-Mackay score.
Caughey[342]	2005	4	Case-control	250	Presence and size	Conca bullosa,

			series	consecutive sinus and orbital CT scans	of concha bullosa, infraorbital ethmoid cells, NSDs, and severity of mucosal thickening	infraorbital ethmoid cells, narrow nasal cavities associated with sinus disease. No associations of frontal sinus disease and anatomic variants.
DelGaudio[795]	2005	4	Retrospective case series	117 patients seen at a tertiary rhinology center	Presence of anatomic variants; anterior-posterior diameter and area of the frontal isthmus	Frontal sinusitis and diameter and area of frontal isthmus was not different for patients with and without frontal cells.
Sirikci[786]	2004	4	Retrospective case series	1450 paranasal sinus CTs examined over a 5 year period	Presence of ethmomaxillary sinus (EMS, an enlarged posterior ethmoid cell occupying the superior portion of the maxillary sinus)	EMS was present in 0.7% of patients. No relationship between EMS and RS.
Stallman[344]	2004	4	Retrospective case series	CT scans of 1095 consecutive patients with sinus complaints	Presence of concha bullosa, sinus mucosal thickening, and nasal NSD	Concha bullosa significantly correlated to contralateral nasal NSD but not paranasal sinus disease.
Jones[798]	1997	4	Case-control	100 CT scans from patients with CRS compared to 100 CT scans from patients with orbital disease	Presence of anatomic variants and mucosal thickening on CT	No significant bony anatomical differences between CRS group and controls.

IX.C.10. Contributing Factors for CRS: Septal Deviation

Because of limited data, CRSsNP and CRSwNP are combined in this analysis.

Since the publication of ICAR-RS-2016, nasal septal deviation (NSD) as a contributing factor to CRS has been considered in several studies. The largest, published in 2016, analyzed the data from the Korean National Health and Nutritional Examination Survey (years 2008–2012) which was aimed at determining the prevalence and risk factors of CRS, AR and NSD in Korea. Ahn, *et al.*[23] enrolled

35,511 subjects and performed an interview regarding nasal symptoms and a nasal endoscopic examination. Afterwards the subjects were divided into 3 age groups: children (aged 7-12 years), adolescents (aged 13-19 years), and adults (aged ≥ 20 years). CRS was classified as CRSwNP and CRSsNP, and its prevalence was estimated in adults according to the EPOS 2012 guidelines on the basis of symptoms and/or nasal endoscopic findings. NSD was evaluated via nasal endoscopy after nasal decongestion in the adolescent and adult groups. When obstructive symptoms were present for more than three months, NSD was defined as symptomatic. In this study, the prevalence of NSD combined with CRS was estimated at 4.3%, with a prevalence of 1.2% and 3.1% for CRSwNP and CRSsNP respectively. After adjusting the results for risk factors of adult CRSsNP, NSD still increased the risk for CRSsNP, while it did not increase the risk for CRSwNP.

In 2018 Sohn published a prospective case series of 304 patients aged ≥ 18 years, affected by either RARS, CRSsNP, or CRSwNP.[509] All of them were evaluated for clinical presentation and anatomic variants using preoperative CT. Differences in the postoperative improvement of each category according to the results of the SNOT-20 survey were reported. A significantly greater prevalence of anatomic variants, such as agger nasi cells, Haller cells, and NSD were found in the RARS group with an NSD prevalence of 86.5 %. NSD was present in 41.5% of CRSsNP and 56.3% of CRSwNP.[509]

Fu *et al.*[799] published a case control retrospective study on patients undergoing revision ESS between January 2010 and December 2017 for CRS, as defined by the clinical practice guideline of the AAO-HNS. Patients were defined as eligible for revision ESS if appropriate medical therapy failed and radiographic evidence of persistent disease was found. In total, 489 patients underwent revision ESS. The authors reported that untreated NSD was significantly associated with radiographic markers of CRS severity and likely represents one of many local factors contributing to the multi-factorial pathogenesis of CRS. They therefore recommended correction of clinically significant NSD during primary ESS in order to reduce the risk of persistent or recurrent CRS.[799]

Septal Deviation as a Contributing Factor for CRS

Aggregate Grade of Evidence: C (Level 2: 1 study; level 3: 1 study, Level 4: 1 study)

Table IX-12. Evidence for septal deviation as a contributing factor for CRS

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Ahn[23]	2016	2	Case series	35511 participants, who underwent an interview regarding nasal symptoms and a nasal examination,	To determine the prevalence and risk factors for CRS, AR, and NSD in Korea	The prevalence of NSD combined with CRS was 4.3%, with 1.2% for CRSwNP and 3.1%for CRSsNP. After adjusting for risk factors of adult CRSsNP, NSD still increased the risk of CRSsNP (adjusted OR, 1.16; 95% CI, 1.02-1.32) but not CRSwNP.

Sohn[509]	2018	3	Case series	304 patients	Clinical presentations and anatomic variants among patients with RARS, CRSsNP, and CRSwNP. Differences in the postoperative improvement of each category were also evaluated.	The different anatomic variants found among patients with RARS, CRSsNP, and CRSwNP can facilitate surgical prognostic evaluation.
Fu[799]	2019	4	Case-control study	489 patients	To evaluate the impact of untreated NSD on recalcitrant CRS among patients undergoing revision ESS	Untreated NSD is associated with radiographic markers of CRS severity among patients undergoing revision ESS and may contribute to the multi-factorial pathogenesis of persistent CRS.

IX.C.11. Contributing Factors for CRSsNP: Innate immunity

Multiple innate immune mechanisms exist at the sinonasal mucosal surface to defend the host against environmental organisms and pathogens. Innate immunity includes nonspecific innate immune mucosal defense and pathogen-specific innate mechanisms that are directed against shared microbial patterns. Nonspecific innate immune mucosal defense includes, but is not limited to, sinonasal MCC, secreted antimicrobials, and complements. One example of a pathogen-specific innate immune mechanism is pattern recognition receptors (PRRs). The two best-characterized classes of PRRs are the TLR family and the nucleotide-binding oligomerization domain-like receptors (NLR) family.[800] It has been hypothesized that dysregulation of PRR pathways and innate immune effectors likely contribute to the inflammatory state in CRS.

This section will cover antimicrobial proteins, PRR, and bitter taste receptors in innate immunity. The contribution of innate immune cells and epithelial-derived innate cytokines are further described in Table IX-15.

Key Antimicrobial Proteins and Peptides. Seven studies revealed that the activities of select innate antimicrobial proteins and peptides are increased in patients with CRSsNP. Only 1 study showed that the activity of an innate immunity antimicrobial protein was decreased in patients with CRSsNP.

Lee *et al.*[801] showed that surfactant protein A (SP- A) mRNA and protein levels were significantly increased in the sinonasal tissue of CRSsNP compared to that of normal controls. Woods *et al.*[802] found that immunostaining of lysozyme was significantly increased in mucosal biopsy specimens of CRSsNP compared to control, but not at the mRNA level. Schlosser *et al.* and others[803 804]

demonstrated that factor B, complement components C3 and C5 mRNAs level were significantly higher in sinus mucosa biopsy specimens of CRSsNP compared to that of control patients. Trefoil factor family (TFF) proteins are also involved in epithelial protection and repair.[805,806]

On the contrary, one study showed decreased innate peptide activity in CRSsNP, although in a different family of proteins. Richer *et al.*[807] found that S100A7, A8 and A9 mRNA levels were significantly decreased in CRSsNP when compared with controls.

Pattern Recognition Receptors (PRRs) and Bitter Taste Receptors. The specific patterns of microbial components are recognized by PRRs, which are components of the innate immune system in mammals. The TLRs represent the primary PRRs, playing an important role in recognizing specific microbial components and triggering a signaling cascade that directly activates the immune cells.[808] The TLR family consists of at least 13 members. For example, TLR4 was identified as a receptor that responds to gram-negative bacteria lipopolysaccharide (LPS). The MyD88-dependent pathway and TRIF-dependent pathway were predominant TLR-mediated signaling pathways that have been identified. [809] These pathways subsequently induce profound inflammatory cytokine genes. More recently, the evidence demonstrates that activation of TLR4 by inhaled pathogens results in a doubling of basal exosome secretion and subsequent induce a 4-fold increase in NO production.[810]

A number of investigations have demonstrated altered activity of PRRs in CRSsNP. Van Crombruggen *et al.* examined the receptor for glycation end products (RAGE) in CRSsNP and controls. They found sinus mucosal protein levels of the soluble form of RAGE to be elevated in CRS while the membrane form was decreased.[811] Zhang *et al.*[812] showed that TLR4 and TLR7 mRNAs and proteins levels were significantly lower in the sinonasal tissue of CRSsNP compared to that of CRSwNP and controls. Similarly, Detwiller *et al.*[813] revealed that patients with CRSsNP showed lower mean expression of TLR2 mRNA in mucosal biopsy specimens compared to controls. Conversely, Hirschberg *et al.*[806] showed the tissue TLR2 mRNA level in patients with CRSsNP was significantly higher compared to healthy controls. However, two studies found that there were no significant differences between CRSsNP patients and controls in terms of the level of tissue TLR9 protein or mRNA.[813,814] These studies suggest that altered PRR responses, especially TLR2, 4 and 7, may play a role in CRSsNP.

Taste receptor family 2 (T2R) bitter taste receptors were originally identified and named based on their role in type 2 taste cells of the tongue. The function of T2R is to detect the presence of potentially harmful ingested chemicals.[815] One T2R isoform, taste receptor family 2 isoform 38 protein (T2R38) has recently been linked with sinonasal innate immunity, upper airway infection. The activation of T2R38 by bacteria increases NO production, ciliary beat frequency, and anti-bactericidal activity.[612] The evidence showed the T2R38 genotype PAV/PAV or PAV/PAV T2R38 are less susceptible to gram-negative bacterium sinonasal infection than PAV/AVI or AVI/ AVI patients.[612] TAS2R38 polymorphisms have been associated with an increased risk of CRS.[611] These findings indicate the potential role of T2R in the pathogenesis of CRSsNP.

Innate Immune Cell and Epithelial Derived Cytokines. The proportion of macrophage, mast cells, fibroblast and basophils in the sinonasal tissue in CRSsNP are similar to that in healthy subjects. Patients with CRSsNP demonstrate local neutrophilic inflammation. However, there are conflicting

data suggesting whether a local eosinophilia is present. The expression levels of epithelial-derived innate cytokines in most CRSsNP patients were similar to that in healthy subjects.

In summary, the evidence demonstrating key epithelial innate immune mediators are differentially expressed is relatively sparse with no cohesive picture yet formed. Additional work in this area will shed meaningful light on the pathophysiology of CRSsNP.

Table IX-13. Summary of studies on altered epithelial innate immunity in CRSsNP

Study	Year	Study Groups (size)	Tissue	Technique	Type of Innate Immunity	Findings	Innate Immunity Activity
Key Antimicrobial Proteins and Peptides							
Li[805]	2014	CRSsNP (12) CRSwNP (12) Control (7)	Sinonasal tissue (CRS) Sinonasal tissue (control)	RT-PCR IHC	TFF1, TFF3	TFF1 and TFF3 mRNAs and proteins levels were significant higher in ethmoid tissue of CRSsNP versus control.	Increased
Woods[802]	2012	CRSsNP (37) CRSwNP (39) Control (6)	Sinus mucosa (CRS) Sinus mucosa (control)	RT-PCR IHC	Lysozyme	Lysozyme protein, but not the mRNA, was increased in patients with CRSsNP versus control.	Increased
Schlosser[803]	2010	CRSsNP (7) AFRS (8) Control (6)	Polypoid/inflamed mucosa (CRSsNP, AFRS) Normal mucosa	RT-PCR IHC	Factor B , C3, C5 C7	Factor B, C3 and C5 mRNAs level were significantly higher in sinonasal tissue of CRSsNP versus control.	Increased

Cui[804]	2009	CRSsNP (72) CRSwNP (95) Control (110)	Blood (CRS) Healthy blood	ELISA	C3, C4	Serum C3 level was significantly increased in CRSsNP compared with control.	Increased
Richer[807]	2008	CRSsNP (23) CRSwNP (18) Control (21)	Epithelial cells from the inferior turbinate Nasal polyps Uncinate tissue (CRSsNP, control)	qRT-PCR IHC	S100A7, S100A8, S100A9	S100A7, A8 and A9 mRNA levels in the nasal tissue were significantly decreased in CRSsNP.	Decreased
Lee[801]	2006	CRSsNP (10) Control (10)	Maxillary sinus mucosa (CRSsNP, control)	RT-PCR IHC	SP-A	SP-A was increased in CRSsNP versus control.	Increased
Hirschberg[806]	2016	CRSsNP (19) CRSwNP (24) Control (12)	Ethmoid mucosa (CRSsNP) Polyps (CRSwNP) Sinus tissue (control)	RT-PCR	b-defensins 1 and 4, cathelicidin and lactoferrin	Lactoferrin mRNA level was higher in CRSsNP compared to controls.	Increased
Abigail [816]	2018	CRSsNP (28) CRSwNP (25) Control (17)	Anterior ethmoid tissue	ELISA and IHC	S100A12	S100A12 was significantly elevated in CRSsNP compared to normal controls.	Increased
Pattern Recognition Receptors							

Detwiller[813]	2014	CRSsNP (19) CRSwNP (17) Control (9)	Ethmoid bulla or anterior ethmoid mucosa (CRS, control)	qRT-PCR	TLR2, TLR9	TLR2 mRNA was decreased in CRSsNP. There were no differences in TLR9 between controls and CRSsNP patients.	Decreased or Normal
Zhang[812]	2013	CRSsNP (40) CRSwNP (38) Control (23)	Nasal polyps (CRS) Nasal tissue (control)	qRT-PCR IHC	TLR2, TLR4, TLR7	TLR2, 4 and 7 mRNAs and proteins levels were lower in CRSsNP compared to controls.	Decreased
Van Crombruggen [811]	2012	CRSsNP (22) CRSwNP (19) Control (17)	Inflamed sinonasal tissue	qRT-PCR IHC	sRAGE mRAGE esRAGE	sRAGE levels were increased and mRAGE levels were decreased in CRSsNP compared to CRSwNP and controls.	Decreased and Increased
Hirschberg [806]	2016	CRSsNP (19) CRSwNP (24) Control (12)	Ethmoid mucosa (CRSsNP) Polyps (CRSwNP) Sinus tissue (control)	RT-PCR	TLR2, TLR5, TLR6, TLR7, TLR8, TLR9	TLR2 mRNA level was significantly higher in CRSsNP compared to	Increased

						controls.	
Park[814]	2018	CRSsNP (12) CRSwNP (24) Control (12)	Nasal tissue Nasal polyps	IHC	TLR 9	There were no differences in TLR9 between controls and CRSsNP patients.	Normal

Table IX-14. Summary of studies on altered non-epithelial innate immunity in CRSsNP

Study	Year	Study Groups (size)	Tissue	Technique	Type of Innate Immunity	Findings	Innate Immunity Activity
Eosinophils							
Huang[817]	2017	CRSsNP (37) CRSwNP (66) Control (9)	Blood	FACS	Blood eosinophils	No significant difference was observed in blood eosinophils between CRSsNP and controls.	Normal
Takahashi[818]	2017	CRSsNP (33) CRSwNP (45) AERD (31) Control (24)	Nasal lavage fluids	FACS	Eosinophils of nasal secretion	The eosinophil microparticles were significantly increased in CRSsNP compared to controls.	Increased
Sejima[819]	2012	CRSsNP (9) CRSwNP (19) Control (14)	Nasal tissue Nasal poly	H&E staining ELISA	Tissue eosinophils	The number of eosinophils and the level of ECP was significantly	Increased

			ps			increased in CRSsNP compared to controls.	
Cao[820]	2009	CRSsNP (94) CRSwNP (151) Control (50)	Nasal tissue Nasal polyps	H&E staining IHC	Tissue eosinophils	No significant difference was observed in tissue eosinophil counts between CRSsNP and controls.	Normal
Van Zele[821]	2006	CRSsNP (8) CRSwNP (10) CF-CRSwNP (13) Control (9)	Nasal tissue Nasal polyps	H&E staining ELISA IHC	Tissue eosinophils	CRSsNP had a significantly higher level of eosinophil cationic protein (eosinophils) compared to controls.	Increased
Neutrophils							
Sejima[819]	2012	CRSsNP (9) CRSwNP (19) Control (14)	Nasal tissue Nasal polyps	H&E staining ELISA	Tissue neutrophils	CRSsNP had a significant higher protein level of MPO (neutrophils) compared to controls.	Increased
Van Zele[821]	2006	CRSsNP (8) CRSwNP (10) CF-CRSwNP (13) Control (9)	Nasal tissue Nasal polyps	H&E staining ELISA IHC	Tissue neutrophils	CRSsNP had a significant higher protein level of MPO (neutrophils) compared to controls.	Increased

Macrophages							
Cao[820]	2009	CRSsNP (94) CRSwNP (151) Control (50)	Nasal tissue Nasal polyps	H&E staining IHC	Tissue macrophages	There was no significant difference between CRSsNP and controls in terms of the number of CD68 + cells (macrophages).	Normal
Van Zele[821]	2006	CRSsNP (8) CRSwNP (10) CF-CRSwNP (13) Control (9)	Nasal tissue Nasal polyps	H&E staining ELISA IHC	Tissue macrophages	There was no significant difference between CRSsNP and controls in terms of the number of CD68 + cells (macrophages).	Normal
Mast cells							
Shaw[822]	2012	CRSsNP (6) CRSwNP (9) Control (2)	Nasal tissue Nasal polyps	H&E staining TR-PCR FACS	Tissue mast cells	There was no significant difference in mast cells between CRSsNP and controls.	Normal
Takabayashi[823]	2012	CRSsNP (70) CRSwNP (91) Control (42)	Nasal tissue Nasal polyps	RT-PCR ELISA IHC	Tissue mast cells	There was no significant difference in mast cells between CRSsNP and controls.	Normal
Basophils							

Takahashi[818]	2017	CRSsNP (33) CRSwNP (45) AERD (13) Control (24)	Nasal lavage fluids	FACS	Basophils of nasal secretion	No significant difference was observed in basophils between CRSsNP and controls.	Normal
Mahdavinia[824]	2014	CRSsNP (15) CRSwNP (16) NP with AERD (10) NP without AERD (17) Control (15)	Nasal tissue Nasal polyps	IHC H&E	Tissue basophils	No significant difference was observed in basophils between CRSsNP and controls.	Normal
Fibroblasts							
Park[825]	2017	CRSsNP (20) CRSwNP (20) Control (10)	Nasal tissue Nasal polyps	Immunofluorescence FACS RT-PCR	Tissue fibroblast (Vimentin + α-SMA+ cells)	No significant difference was observed in fibroblasts between CRSsNP and controls.	Normal
Carroll[826]	2016	CRSsNP (22) CRSwNP (13) Control (24)	Nasal tissue Nasal polyps	IHC	Tissue fibroblast	No significant difference was observed in fibroblasts between CRSsNP and controls.	Normal
Oyer[827]	2013	CRSsNP (15) CRSw	Nasal tissu	FACS Cell Culture	Tissue fibroblast (FSP+	No significant difference	Normal

		NP (6) Control (13)	e Nasal polyps		VCAM+ cells)	was observed in fibroblasts between CRSsNP and controls.	

Table IX-15. Epithelial-derived innate cytokines in CRS

Study	Year	Study Groups (size)	Tissue	Technique	Type of Innate Immunity	Findings	Innate Immunity Activity
Il-25							
Hong[162]	2018	CRSsNP (20) CRSwNP (90) Control (16)	Nasal tissue Nasal polyps	RT-PCR IHC	Tissue IL-25	There was no significant difference in IL-25 between CRSsNP and controls.	Normal
Ozturan[828]	2016	CRSsNP (20) CRSwNP (20) Control (20)	Sinoasal tissue Nasal polyps	ELISA	Tissue IL-25	IL-25 was not elevated in NPs.	Normal
Xu[829]	2016	CRSsNP (65) CRSwNP (50) Control (27)	Sinoasal tissue Nasal polyps	RT-PCR IHC	Tissue IL-25	IL-25 mRNA level was not increased the CRSwNP group compared to the control .	Normal
Shin[830]	2015	CRSsNP (65) CRSwNP (50) Control (27)	Sinoasal tissue Nasal polyps	IHC RT-PCR ELISA	Tissue IL-25	IL-25 mRNA level was significantly higher in the CRSsNP group compared to controls	Increased
Lam[831]	2012	CRSsNP (18) CRSwNP (12)	Nasal tissue Nasal polyps	RT-PCR	Tissue IL-25	There was no significant difference	Normal

		Control (7)				in IL-25 between CRSsNP and controls.	
IL-33							
Hong[162]	2018	CRSsNP (20) CRSwNP (90) Control (16)	Nasal tissue Nasal polyps	RT-PCR IHC	Tissue IL-33	There was no significant difference in IL-33 between CRSsNP and controls.	Normal
Kim[832]	2016	CRSsNP (61) CRSwNP (166) Control (19)	Sinoasal tissue Nasal polyps	RT-PCR IHC	Tissue IL-33	IL-33 protein level was significantly higher in the CRSsNP group compared to controls.	Increased
Lam[831]	2012	CRSsNP (18) CRSwNP (12) Control (7)	Nasal tissue Nasal polyps	RT-PCR	Tissue IL-33	The mRNA level of IL-33 was not increased in CRSsNP.	Normal
TSLP							
Hong[162]	2018	CRSsNP (20) CRSwNP (90) Control (16)	Nasal tissue Nasal polyps	RT-PCR IHC	Tissue TSLP	There was no significant difference in the level of TSLP mRNA between CRSsNP and controls.	Normal
Nagarkar[833]	2013	CRSsNP (60) CRSwNP (86) Control (47)	Nasal tissue Nasal polyps	RT-PCR ELISA	Tissue TSLP	There was no significant difference in the level of TSLP mRNA between CRSsNP and controls.	Normal

Lam[831]	2012	CRSsNP (18) CRSwNP (12) Control (7)	Nasal tissue Nasal polyps	RT-PCR	Tissue TLSP	There was no significant difference in the level of TSLP mRNA between CRSsNP and controls.	Normal
Boita[834]	2011	CRSsNP (5) CRSwNP (10) Control	Nasal tissue Nasal polyps Epithelia cells	IHC	Tissue TLSP	TSLP protein levels were significantly increased in CRSsNP compared with controls.	Increased

IX.C.12. Contributing Factors for CRS: Epithelial Barrier Disturbance

Because of limited data, CRSsNP and CRSwNP are combined in this analysis.

Sinonasal mucosa functions as a mechanical and immunological barrier to a range of exogenous agents that may initiate and contribute to mucosal inflammation. When the mechanical barrier fails, immunological activation of epithelial receptors can lead to the dysregulated secretion of pro-inflammatory cytokines and chemokines with resultant cellular injury, chronic inflammation and tissue remodeling. CRS has been described through the immune barrier hypothesis as a disease borne from dysfunctional sinonasal mucosa and altered cellular and immunological responses. [835] Different patterns of upstream epithelial defects have been characterized in the phenotypes of CRS and more recently with geographical variances in the immunological responses identified in the same phenotypic class of disease.[836]

There are two components of the mechanical barrier; respiratory mucus and, in health, a relatively impermeable epithelial barrier. The function of mucus is to trap foreign material and cilial motility propels it towards the nasopharynx. Nasal mucus consists of water, glycoproteins and intrinsic antimicrobial agents including antioxidants and antiproteases.[837] Mucin glycoproteins are key components and two forms exist; secreted gel-forming mucins that are responsible for its viscoelastic properties and membrane-bound mucins that bind pathogens. In conjunction with effective ciliary function, mechanical elimination of pathogens and nasal irritants occurs. Alteration in the expression of secreted and membrane-bound mucins has been reported in adult CRS patients when compared to control patients.[838,839] No differences have been identified between the pediatric CRS and control populations, suggesting that these alterations may possibly be related to the duration of the disease process.[837] Cilial function is critical in the mechanical clearance of nasal mucus. Genetic and acquired defects are associated with a high incidence of sinonasal inflammation and CRS [840-843] in disease conditions such as cystic fibrosis and primary ciliary dyskinesia.

Beneath the mucus reside the epithelial cells, which are linked by tight and adherenz junctions. Tight and adherent junctions comprise the apical junctional complex (AJC), creating a relatively impermeable barrier. Disruption of proteins in the AJC can result in a 'leaky' barrier, and thus allow the entry of pathogenic microbes, allergens or antigens into the underlying tissue.[844] Alterations in this epithelial barrier have been recognized in other Type 2 inflammatory diseases including atopic dermatitis, asthma and eosinophilic esophagitis,[845] and both cell-intrinsic and extrinsic mechanisms have been described. [846] It remains controversial in the setting of CRS as to whether the epithelium is inherently dysfunctional or disruption is a consequence of exogenous factors, however, studies have demonstrated increased barrier permeability in both nasal epithelial cell cultures and tissue samples within CRSwNP patients.[847-849]

In both CRSwNP and CRSsNP, the epithelium is known to be structurally and functionally abnormal, which may be crucial in the development and progression of CRS. For example, the epithelium in CRSwNP appears to respond inappropriately to physical insults or common pathogens and this can lead to aberrant epithelial damage including hyperplasia with an increase of poorly proliferated basal cells forming multiples layers or squamous metaplasia.[159,180,850] Furthermore, goblet cell hyperplasia with excessive mucus production, abnormalities in cilia architecture and function can be found in hyperplasia or squamous metaplasia of the nasal epithelium.[182,851,852] A recent study from single-cell transcriptomes of epithelial cells from the non-polyp and polyp demonstrated that in humans for the emerging paradigm of stem cell dysfunction altering the set point of barrier tissues, where basal cells form

'memories' of chronic exposure to the type 2 immunity environment, shifting the entire cellular ecosystem away from productive differentiation and propagating disease.[853] These pathological findings are similar to that seen in asthma where the epithelium damage and more mucus-producing cells than normal make the airway epithelial barrier more permeable and more sensitive to infectious pathogens.

The polypoid form of CRS and a Type 2 cytokine milieu have been associated with significantly decreased levels of AJC proteins including Zona Occludin-1 (ZO-1), claudin-1, E-cadherin and desmoglein-1 and -2[847,849,854,855] as well as diminished intrinsic protective anti-protease activity.[807,856]. A range of exoproteins from bacteria including *S. aureus*, and *P. aeruginosa*[857-860] can disrupt epithelial tight junctions, potentially allowing pathogenic bacterial invasion and underlying tissue damage.[846] Bacterial proteins are not the only exogenous compounds with the potential to disrupt epithelial TJs in ALI models; air pollution-related particulate matters,[861] cigarette smoke extract[862] and nasal mucus itself[863] have all been implicated.

The activity of proteases and their equilibrium with protease inhibitors have been implicated in both direct epithelial disruption and stimulation of cell surface protease-activated receptors, specifically in Type 2 skewed endotypes of CRSwNP. These enzymes may originate from aero-allergens such as house dust mite or pollen,[864], fungi[629,865] and bacteria including *S. aureus* and *P. aeruginosa*.[860,866,867] Protease disrupts ZO-1 and occludin in tight junctions[868] and decreased levels of the protease inhibitors Cystatin A and serine protease inhibitor Kazal-type 5 (SPINK5) at both a transcriptional and metagenomic level have been reported in CRS patients.[869] It has also been recognized that activated neutrophil-secreted proteases lead to epithelial degradation,[859] in addition to upregulating proteins involved in nasal mucus secretion.[869]

Taken together, these studies suggest that mucociliary dysfunction may play a role in the pathogenesis of CRS broadly, whereas intrinsic or acquired abnormalities in sinonasal mucosa leading to a porous epithelial barrier are more closely linked to CRSwNP.

Table IX-16. Evidence for epithelial barrier disturbance as a contributing factor for CRS

Study	Year	LoE	Study groups	Tissue	Techniques	Specific gene targets	Findings	Effect on epithelial barrier
Pothoven[848]	2015	5	CRSwNP, CRSsNP, Control	Mucosa, NP. Epithelial cell culture	Transepithelial resistance, RT-PCR	OSM	OSM expression increase in NP. OSM Stimulation resulted in reduced barrier function.	Decreased structural epithelial barrier function.
Den Beste[847]	2013	5	AFRS vs Control	Epithelial cell cultures	Transepithelial resistance, IHC, Western Blot	Junctional Adhesion molecule-A, Claudin-2	Decreased transepithelial resistance in AFRS. Decreased expression	Decreased structural epithelial barrier function.

							of Occludin and Junctional Adhesion molecule-A. Increased expression of claudin-2.	
Lee[612]	2012	5	Primary human nasal cells genotyped for TAS2R38	Epithelial cell culture	NO production, MCC, bactericidal activity	T2Rs	Increase NO production and mucociliary transport velocity.	Increased MCC and antibacterial properties.
Seshadri[870]	2012	5	CRS, Control	Mucosa and NP	Microarray, RT-PCR, ELISA, Immunoblot, IHC	SPLUNC1, LPLUNC2, Lactoferrin	Decreased SPLUNC1 , LPLUNC2 and Lactoferrin in CRSwNP.	Decreased antimicrobial barrier functions.
Soyka[849]	2012	5	CRSwNP vs CRSsNP	Mucosa, Polyp	Trans-tissue resistance, IHC, Western blotting, RT-PCR	Occludin, ZO1	Decreased TRR in CRSwNP specimens. Decreased expression of Occludin and ZO1.	Decreased structural epithelial barrier function.
Rogers[855]	2011	5	CRSwNP, CRSsNP	Mucosa, Epithelium cell culture	IHC, Western blot	Claudin-1, Occludin	Reduced Claudin-1 and Occludin in NP. Reduction in tight junction protein expression following cytokine exposure.	Decreased structural epithelial barrier function.
Tieu[871]	2010	5	CRS	Nasal lavage, mucosa and NP	IHC, ELISA	S100	Decreased S100 in CRS.	Decreased antimicrobial barrier functions.
Richer[807]	2008	5	CRSwNP , CRSwNP,	Epithelial cell	RT-PCR, IHC	S100A7, S100A8,	CRSw/sNP Decreased	Reduced expression of

			Control	culture		S100A9, SLC9A3R 1, SPINK5	S100A7, S100A8. CRSsNP decreased S100A9. CRSwNP decreased SPINK5.	genes involved in epithelial barrier maintenance and repair.

IX.C.13. Contributing Factors for CRSsNP: Ciliary Derangements

Proper MCC is of paramount importance in eradicating pathogens and debris from the sinonasal tract. Cilia beat in a directional fashion to move mucus to the sinus natural ostia and ultimately to the nasopharynx/oropharynx, where it can be cleared by expectoration or swallowing.[872] A variety of cholinergic, adrenergic, and peptidergic pathways are involved in the regulation of ciliary beating, and ciliary beat frequency (CBF) can be dynamically modulated for maximal efficiency of mucociliary transport. Substances that are introduced to the surface of the respiratory epithelium bind to receptors that have potent downstream effects on CBF.[873-875] During infection, CBF increases to stimulate mucus clearance[612,876,877] as well as to disseminate innate immune products.[878] Microbes directly impact ciliary function, and can often "hijack" normal ciliary regulation to prevent appropriate mucus movement.[873]

In CRS, patients may have dysfunctional ciliary beating from direct effects of the organisms or from an inappropriate inflammatory response.[879-881] Mucociliary stasis is a common finding of CRS, which propagates the disease as the stagnant mucus can harbor infection and sustain inflammatory mediators.[841] While there does not seem to be a detectable difference between baseline CBF in CRS patients and control patients, cilia from CRS patients show an attenuated response to substances that reliably increase CBF in controls.[877] This blunted response to ciliostimulatory substances may underlie the perpetuation of pathology in CRS. Pathogens such as *P. aeruginosa, H. influenzae, S. pneumoniae* and *S. aureus* secrete toxins that directly suppress ciliary motion.[882-885] Pyocyanin, a toxin produced by *P. aeruginosa*, not only causes progressive slowing, but also makes the cilia unable to respond to mechanical simulation by other factors.[886,887] *H. influenzae* toxins destroy cilia entirely at high concentrations, resulting in mucus stasis from ciliary loss.[888] These toxins, when present chronically, create an environment that is very favorable for CRS development.

An overactive inflammatory environment or defects in cellular transport may also be the cause of some CRS ciliary pathology. TNF-α, IL-1β, IL-5, and IL-8 are consistently elevated in CRS cases,[43,879,889,890] and chronic elevation of these factors often blunts ciliary response.[880] TNF-α has been shown to prevent CBF increases in response to mechanical stimulation,[874] while cycles of inflammation can cause ciliary loss or ciliary abnormalities in a chronic setting.[873] IL-13 or IFN-γ exposure can each result in decreased cilia differentiation and function.[891] Sodium and chloride transport play a large role in MCC as well. Sodium absorption is increased in nasal cell culture from CRS patients, resulting in greater mucus viscosity and more difficult clearance, as the cilia have to work harder to transport the same load.[892] Cigarette smokers have increased rates of CRS[893,894] in part because of the reduction in chloride transport caused by compounds in cigarette smoke precipitating a reduction in CBF.[895,896]

Acquired dysfunction of the cystic fibrosis transmembrane conductance regulator (CFTR) can also lead to inhibition of ciliary beat frequency and the mucociliary apparatus. Numerous studies *in vitro*, *ex vivo*,

and *in vivo* (rabbits and humans) have identified CFTR dysfunction and concomitant impact on ciliary function in the setting of infection (viral and bacterial), inflammation, hypoxia, and external perturbations such as tobacco smoke exposure.[896-907] Administration of cigarette smoke to the nares of healthy smokers causes an acute blockade of CFTR activity, as measured by nasal potential difference, suggesting exposure to cigarette smoke rapidly inhibits CFTR activity *in vivo*, as well as reduced ASL hydration *in vitro*.[908] Furthermore, cigarette smoke condensate inhibits transepithelial chloride secretion through CFTR and calcium activated chloride channel transmembrane member 16A (TMEM16A) and ciliary beat frequency in upper and lower respiratory airway epithelial cells *in vitro.*[896,906] Hypoxia has been suggested to play a significant role in acquired mucociliary dysfunction and the pathophysiology of CRS among non-cystic fibrosis individuals.[909] Obstruction of the sinus ostia can lead to reduced oxygen tension in the sinus mucosal tissue[910] and release of inflammatory mediators, thereby causing stasis of hyperviscous mucus. *In vitro* experiments of hypoxia on ion transport physiology in both murine nasal septal epithelial (MNSE) and human sinonasal epithelial (HSNE) cultures, revealed an impaired transepithelial ion transport related to reduced CFTR function.[904] HSNE cells incubated in a hypoxic environment show a globally decreased transepithelial Cl^- secretion and *increased* sodium absorption. These findings indicate that persistent hypoxia may lead to acquired defects in sinonasal Cl^- transport in a fashion likely to confer mucociliary dysfunction in CRS. Blount *et al.* established sinonasal epithelial CFTR and TMEM16A-mediated Cl^- transport and mRNA expression were robustly decreased in an oxygen-depleted environment.[907] This was subsequently identified to reduce the airway surface layer (ASL) and CBF in hypoxic epithelium as measured by micro optical coherence tomography.[898]

Treatment of ciliary dysfunction in CRS involves the respiratory epithelium returning to normal excitability and the establishment of an appropriately regulated inflammatory environment. It appears that the cilia are capable of recovering their excitability and normal activity in a healthy state. In one study, ciliated cells that were removed from the inflammatory milieu of CRS regained their ability to be stimulated and again functioned in a normal fashion.[842] Therefore, most effort clinically should be directed in treating the underlying CRS, as opposed to treating the dysfunctional cilia separately. Topical antimicrobial therapy results in an increase in CBF back to expected levels.[911]

In cases of irreversible ciliary dysfunction, structural components of the cilia may be abnormal. Increased expression of CP110, a negative regulator of ciliogenesis, has been observed in CRS patients and may contribute to the poor ciliary recovery.[852] Other studies have hypothesized that the ciliogenesis process may be dysregulated.[805] If the cilia that are generated are in any way functionally abnormal or absent, there is increased risk of biofilm formation and other CRS risk factors.[851,912-914] Furthermore, use of CFTR modulators (*i.e.*, ivacaftor and natural polyphenols) has been proposed as a method with which to treat acquired CFTR and mucociliary dysfunction.[915-923] Studies have shown that ivacaftor augments ASL depth, accelerates MCC, and pharmacologically reverses acquired CFTR dysfunction due to cigarette smoke exposure.[909] Treatment of infection in a rabbit model of *Pseudomonas aeruginosa* RS resulted in improvement in acquired mucociliary dysfunction (CFTR and ciliary function).[924,925]

Aggregate Grade of Evidence: C (Level 3: 2 studies, Level 4: 1 study)

Table IX-17. Evidence for ciliary derangements as a contributing factor for CRSsNP

Study	Year	LOE	Study Design	Study Groups	Clinical End-point(s)	Conclusion
Tipirneni[899]	2018	3	Quantification of mucus strand velocity in CRS vs. control explants	CRS and control sinonasal mucosal explants	Methacholine-stimulated mucociliary velocity	Methacholine-stimulated mucus strand velocity is significantly decreased in mucosal explants from CRS subjects compared to those from control subjects.
Chen[877]	2006	3	Quantification of stimulated CBF in CRS vs. control explants	CRS and control sinonasal mucosal explants	ATP-stimulated CBF	Exogenously applied ATP causes a 50-70% increase in CBF in control tissue, while CRS explants do not demonstrate similar increases in CBF in response to ATP.
Scadding[911]	1995	4	CBF in CRS patients at baseline and after 3 months of antibiotics	10 CRS subjects	CBF	CBF was significantly increased in all subjects following a 3 month antibiotic course.

IX.C.14. Contributing Factors for CRSsNP: Immunodeficiencies

In the subset of adult patients who have CRS that is refractory to usual therapy, primary immunodeficiency (PID) should be considered. The most common clinical manifestations of PID include RS, chronic otitis media, and chronic lung diseases (CLDs) such as pneumonia and bronchiectasis.[926-932] An association between hypoimmunoglobulinemia and CRS has been described in the literature and multiple studies have demonstrated PID as a risk factor for the development of CRS.[492,493,929,930,933-940] The association is further strengthened in that other studies show an increased incidence and prevalence of RS in patients with immune dysfunction.[493,926,927,941]

CVID, specific antibody deficiency (SAD), X-linked hypogammaglobulinemia, and several other disorders of humoral immunity are frequently referenced as contributing factors to chronic or recurrent recalcitrant RS.[40,928,931,932,939,942-944] A number of selective Ig deficiencies, specifically those involving IgG3 subclass, IgA, and IgM, have been consistently identified in this group of patients.[492,493,804,927,929,930,933,936,938-942,945-949] Pre-immunization antipneumococcal titers have shown to be decreased as well, particularly in patients with the more severe forms of immunodeficiency such as CVID; patients with refractory RS can also demonstrate poor functional antibody responses to immunization.[492,493,941,943] Treatment with IV immunoglobulin (IVIG) for Ig replacement in subsets of patients with humoral immunodeficiency has shown some benefit in clinical outcomes.[931,948-951]

The studies in this literature review demonstrate the significance of PID in the development of chronic sinus disease, with up to 50% of those with recalcitrant CRS found to have primary immune

dysfunction.[938] Conclusions drawn from the included studies are somewhat limited given the relatively inferior aggregate grade of evidence. Areas of further study include the degree to which the severity of hypogammaglobulinemia results in clinically significant RS, the cross-interaction of immunodeficiency and CRS endotypes, and the identification of CRS patients who would benefit most from further diagnostic investigation and treatment of immunodeficiency. Additional research may also define optimal medical and immune supplementation therapy in those with PID and CRS.

Immunodeficiency as a Contributing Factor for CRSsNP

Aggregate Grade of Evidence: C (Level 3: 1 study; level 4: 34 studies)
Benefit: Identifying patients with PID allows for the opportunity to treat a subset of patients who will respond to Ig replacement therapy. Morbidity associated with CRS may be minimized.
Harm: There is a potential for increased cost associated with unnecessary or premature testing.
Cost: Associated costs consist of the direct costs of laboratory testing; high costs of Ig replacement therapy.
Benefits-Harm Assessment: The benefits of identifying patients with immune dysfunction outweigh any associated risks.
Value Judgments: Otolaryngologists are often the first providers to see these patients given the frequent co-existence of immunodeficiency and RS. This provides the opportunity to identify patients with a treatable underlying disorder. "Refractory CRS" is not well defined.
Policy Level: Recommendation in cases of refractory CRS.
Intervention: PID should be considered in patients with refractory CRS.

Table IX-18. Evidence for immunodeficiency as a contributing factor for CRSsNP

Study	Year	LOE	Study Design	Study Group	Clinical Endpoints	Conclusions
Quinti[40]	2007	3	Prospective cohort	Italian CVID followed for a mean of 11 years; age 2-73; n=224	Prevalence of CRS, CLD and other co-morbidities in patients with CVID at the time of diagnosis and after IVIG therapy	It is possible that both IVIG treatment and better diagnostic and therapeutic strategies have had a great impact on CVID mortality. There is a need to develop international guidelines for the prevention and therapy of CLD, CRS, and other chronic diseases in patients with immunodeficiencies.
Khokar[947]	2019	4	Case series	Adults with primary selective IgG subclass deficiencies; n=78	Upper and lower respiratory tract infections Proportions and absolute numbers of specific CD-type T cells	IgG3 subclass deficiency is the most common IgG subclass deficiency. The majority of patients treated with Ig responded by reduction in the frequency of infections and the requirement for antibiotics.
Pimenta [930]	2019	4	Cross-sectional	Patients with hypogammo globulinemia; age 16-65; n=8	Clinical and laboratory characteristics	In patients with hypogammoglobulinemia, the main infections were RS and pneumonia, and airway manifestations prevailed.

Keswani[952]	2017	4	Case-control	Adults with CRS; n=595	Humoral status (Ig levels, antibody titers) Clinical characteristics (Lund-Mackay, endoscopy/CT scores, asthma severity)	Stratification of SAD by severity demonstrates a significant increase in the comorbid severity of asthma and infections in CRS patients with moderate-to-severe SAD compared with those with mild SAD and those without SAD.
Walsh[931]	2017	4	Case series	27 adults with CVID; 4 adults with SAD; age 18-83	Lund-Mackay scores Frequency sinus & pulmonary infections requiring antibiotics	Ig replacement therapy has a positive impact on the frequency of RS and pulmonary infections in adult patients with CVID and SAD.
Odat[936]	2016	4	Case-control	Adults with refractory CRS; n=257	Measurements of serum IgM, IgA, IgG, and IgG subclasses (compared to matched controls)	There is a high prevalence of subtle humoral immunodeficiency in medically resistant CRS. There are also no unique clinical and demographic characteristic of these patients. Routine screening of major immunoglobulins and IgG subclasses recommended for the group of CRS patients who failed medical treatment.
Kashani[946]	2015	4	Case series	Adults with CRS; n=239	Quantitative Ig levels Pre- and post-antibody titers to PPV	23.4% of CRS patients with normal IgG levels evaluated for immunodeficiency had SAD. A subset of patients with SAD benefit from Ig replacement.
Gabra[953]	2014	4	Case-control	67 Adult low CD8+ CRS patients ; 480 controls with CRSwNP	Serum CD8+ T-lymphocyte levels Bacteriology on endoscopically-obtained sinus culture Antibiotic use Severity of disease as assessed by the need for sinus surgery	Patients with CD8+ T lymphocytes lymphopenia express disease similar to patients with conventional CRS. These patients may occasionally benefit from antibacterial therapies.
Magen[935]	2014	4	Retrospective Case-control	226 children and adults with low IgE; matched controls (1:4)	Serum total IgE, IgM, IgG and IgG subclasses	Undetectable serum total IgE may serve as a marker of immune dysregulation and autoimmunity.
Carr[943]	2011	4	Case series	Adult CRS patients who	Baseline antipneumococcal	Patients with medically refractory CRS may have a high prevalence of

			with retrospective review	had ESS and prior assessment for humoral immunodeficiency; n=129	titers Functional antipneumococcal response	low preimmunization antipneumococcal titers and SAD.
Alqudah [941]	2010	4	Case series with retrospective review	Refractory CRS patients who had prior ESS; age 22-77; n=67	Quantitative Ig levels IgG subclass levels Functional antipneumococcal antibody response	There is an unexpectedly high prevalence of humoral immune dysfunction in patients with refractory CRS. An assessment of immune function should be undertaken routinely in refractory CRS, which should include serum Ig levels. If these are normal, then functional antibody responses may be performed.
Khalid [954]	2010	4	Case-control	22 patients with CRS associated immune dysfunction; 22 controls with CRS	Preoperative CT findings Pre-/postoperative endoscopic findings Disease-specific QoL	Immunodeficiency and autoimmune cases present with similar severity of disease when compared with controls with CRS. Patients with immune dysfunction may experience similar benefit from ESS.
Cui [804]	2009	4	Case-control	Adult Chinese patients with CRS; n=277	Quantitative serum Ig Serum mannose-binding lectin levels	Ig and mannose-binding lectin deficiencies are not associated with CRS.
Yel [927]	2009	4	Case control	Adults with IgM deficiency; age 39-79; n=374	Serum Ig and IgG subclass levels Pneumococcal antibody titers Lymphocyte response to mitogens and antigens	IgM-deficient patients who present with recurrent/severe infections may benefit from Ig treatment particularly in the presence of impaired pneumococcal antibody responses.
Bondioni [928]	2007	4	Case series	27 patients with CVID, 18 patients with agammaglobulinemia	CT evidence of CRS CT evidence of bronchiectasis	Pulmonary CT findings do not correlate with severity of sinus involvement.
Levin [934]	2006	4	Cross-sectional	Adult pregnant women; n=662	Serum total IgE levels in patients with CRS	Low serum IgE levels was not associated with CRS.
Seppanen [937]	2006	4	Case control	48 CRS or RARS patients; 50 ARS patients;	Serum Ig levels Plasma C3/C4 levels	Multiple clinical and immunological parameters may need to be evaluated when searching for prognostic variables in patients with

				healthy controls; age 18-83		CRS and RARS.
Vanlerberghe [940]	2006	4	Case series / Retrospective review	Belgian patients with humoral immunodeficiency (261 adults, 46 children)	Serum Ig levels	Humoral immunodeficiency is present in a significant proportion of patients with refractory RS. The majority of these deficiencies are subtle IgG subclass deficits. Measurement of IgA, total IgG and IgG subclasses should be part of the evaluation of patients with refractory RS.
Yarmohammadi [926]	2006	4	Retrospective Case control	113 patients with immune deficiency, 124 patients without immunodeficiency; age 1-8	Immune deficiency-related scores	CRS, bronchitis, otitis media, and chronic diarrhea are conditions associated with immunodeficiency syndromes. A scoring system coupled with specific clinical indicators may provide a useful guide to the identification of immunodeficient patients in the outpatient setting.
Moin [939]	2004	4	Case series	Iranian XLA patients; age 2 mos - 30 yrs; n=33	Serum Ig levels (IgG, IgM, IgA) Circulating T- and B-lymphocyte levels Prevalence of co-existing infection in patients with XLA	It is important to consider hypogammaglobulinemia in any pediatric patient with a history of recurrent infections at different organ systems.
Plebani [944]	2002	4	Case series	Italian patients with XLA; age 2-33; n=73	Serum Ig levels % of circulating B cells BTK mutation analysis Duration of IVIG therapy	Despite early diagnosis and appropriate Ig replacement, CLD and CRS are common long-term complications in patients with XLA.
Chee [493]	2001	4	Retrospective review	Adult patients with CRS; n=79	Quantitative serum Ig Pneumococcal vaccine response Allergy skin testing T-cell function	There is a high incidence of immune dysfunction in patients with CRS.
Tahkokallio [938]	2001	4	Case control	25 patients with severe RARS or CRS and matched controls; age 19-64	Serum IgA levels Pneumococcal antibodies	Low serum IgA may be associated with a susceptibility to RS.
May [955]	1999	4	Case	CRS patients	Humoral antibody	Ig therapy does not appear to be

			series	not responding to antibiotics; age 4-79; n=245	levels Pneumococcal antibody response	effective in patients with CVID. For these patients, ESS is justified to restore mucociliary function and normal ventilation.
Sethi[492]	1995	4	Case series	Patients with refractory recurrent RS and immunologic abnormalities; age 3-71; n=20	Quantitative Ig levels Functional antipneumococcal antibody responses	Immune defects may exist in a significant percentage of patients with refractory CRS and RARS.
Armenaka[933]	1994	4	Case-control	30 CRS matched to 30 chronic rhinitis patients with normal CTs, and 30 healthy controls; age 16-75	Quantitative Ig levels IgG subclass levels	IgG3 levels are significantly decreased in adults with CRS.
Karlsson[942]	1985	4	Case-control	22 patients with CVID; 18 patients with selective IgA deficiency; 20 controls; age 22-58	Co-existence of CRS Incidence of sinus surgery	The development of CRS was only found in patients with CVID, indicating the more severe nature of this condition compared with selective IgA deficiency.
Manning[929]	1994	4	Case series	Patients with severe refractory RS and PID; age 27-59	Serum IgG subclass levels Pneumococcal vaccine responses Immunoglobulin A levels Response to Ig therapy	RARS may be the primary or only clinical manifestation of immunodeficiencies. The diagnosis should be considered in any patient failing routine management.
Scadding[948]	1994	4	Case series	Adult patients with CRS or RARS; age 15-60; n=74	Serum total IgG levels Serum IgG subclass levels	Ig replacement therapy has been shown to be efficacious in the treatment of IgG3-deficient individuals.
Snow[949]	1993	4	Case series	Patients with PID receiving IVIG therapy;	Sinonasal symptoms CT scores	Radiological changes can be widespread in patients with hypogammaglobulinemia. RS

				age 17-70; n=13		symptoms do not resolve with IVIG, but early treatment may prevent chronic changes in sinus mucosa.
Williams[956]	1991	4	Case series	Patients with primary hypogammaglobulinemia; age 15- 65; n=17	Symptom scores pre- and post IVIG therapy Measured and corrected sinus washout return fluid IgG concentrations	Poor clinical responses do not appear to be due to lack of penetration of antibodies to the required sites of action. The addition of antibiotics at high dosage may be a more economical therapeutic alternative to high dose IVIG therapy.
Roifman[951]	1988	4	Case series	Patients with hypogammaglobulinemia; age 7-50; n=12	Serum IgG levels Sputum cultures Chest and sinus radiographs PFTs	High dose therapy with IVIG appears to be the treatment of choice in patients with sinopulmonary disease.
Watts[932]	1986	4	Case series	Patients with common variable hypogammaglobulinemia; age 11-53; n=32	Pulmonary function tests chest radiographs pulmonary symptom questionnaire	Pulmonary function and chest radiograph scores remained stable while CVH patients received adequate therapy.
Roifman[950]	1985	4	Case series	Patients with hypogammaglobulinemia; age 7-49; n=7	Serum IgG levels Clinical and radiographic (CT) evidence of RS PFTs	The administration of increased amount of IVIG is of benefit in patients with chronic sinopulmonary disease.
Buckley[945]	1972	4	Retrospective review	Adult patients with chronic respiratory disease; n=688	Serum immunoglobulin measurements	Humoral immune surveillance may be important in the pathogenesis of chronic respiratory disease.

IX.C.15. Contributing Factors for CRS: Genetics and Epigenetics

Because of limited data, CRSsNP and CRSwNP are combined in this analysis.

IX.C.15.a. Genetics in CRS

The first identified genetic disorders were discovered because they showed a clear pattern of heritability, with well-defined disease phenotype. These well-characterized genetic disorders implicated a single gene with a high penetrance and strong effects. In contrast, CRS is considered to be a more complex disease process with multiple genes all having weak effects and therefore contributing varying

degrees of penetrance. This has made the identification of candidate genes in CRS much more difficult. In the late 1990s, the goal of the Human Genome Project was to revolutionize medicine by sequencing the genome, identifying single nucleotide polymorphisms (SNPs) to allow identification of the genetic basis of diseases, and future treatments to be based on personalized genetic makeup.[957] Experience since has shown that while associations can be identified, interpreting these and transposing them for clinical use can be difficult. For a number of genetic findings, biological plausibility may not be evident, as the role these genes play in normal function may not yet be described. Alternatively, identified genetic factors may not so much modify the structure of a cellular organelle, but may instead increase susceptibility to an environmental influence, such as infection with undesirable bacteria like *Staphylococcus aureus.*[958] Lastly, clinical phenotype does not necessarily originate from a unique genetic variation, but may instead reflect differently located variations in a single gene, or any number of key genes in a pathway. Also problematic for genetic association studies in CRS is the high risk of spurious association from multiple testing. Studies thus require large populations, explaining the high costs of such studies. For these reasons, caution must be used when interpreting CRS genetic studies in the literature.

Strong evidence supports a hereditary (genetic) component to CRS. Known genetic diseases that have a demonstrated association with CRS indicate the presence of a genetic component to CRS. These include cystic fibrosis (CF), where homozygous mutations in the CFTR gene lead to defects in chloride transport, and the ciliary dyskinesias, where a mutation in one of 31 different genes coding for a different portion of the structural arm of the cilia causes ciliary dysfunction.[959]

Recent work demonstrates the heritability of CRSwNP and CRSsNP. In a study by Oakley *et al.* of 1638 patients with CRSwNP and 24,200 CRSsNP patients, first-degree relatives of affected subjects are 4.1 times more likely to develop CRSwNP and 2.4 times more likely to develop CRSsNP.[960] This is complemented by work from Sweden in which 13.4% of relatives of patients with nasal polyposis had CRSwNP compared to 2.7% in a Swedish control group, yielding a relative risk of the first-degree relatives having nasal polyps of 4.9.[961]

Published genetic association studies in CRS have increased in number over the past decade, increasing the number of potential gene candidates (Table IX-19) and repeatedly implicating certain genes, supporting their relevance to the disease process (Table IX-20). Gene candidates are categorized by location and function, grouped loosely into regulation of immune function, barrier function, and a broad category of SNPs in which effect on CRS pathophysiology is not yet known. Note that the high percentages of identified genes related to immune function may reflect a selection bias of candidate genes studied rather than their actual level of implication.

These findings improve our understanding of the disease process and open potential new targets for therapy. In an example of this from Desrosiers *et al.*, "hypothesis-free" association studies suggested candidate genes associated with epithelial and basement membrane structure and function. This led to exploration of barrier function in CRS patients, culminating in the recent identification of a defect in tissue repair and regeneration as an unexpected feature of CRS,[962] opening up the possibility of new drug treatments such as rho-kinase (ROCK) inhibitors to promote repair and regeneration.

Other insights still waiting to bear fruit may become clearer as we better understand the role and functions of identified putative candidate genes.

Taste receptors - Predicting Gram-Negative Carriage: TAS2R38 polymorphisms have been associated with CRS.[611] TAS2R38 codes for a type of bitter taste receptor, which is expressed in the airway and is implicated in innate immune defense. Activation of T2Rs by bitter stimuli are followed by secretion of antimicrobial peptides, production of nitric oxide, and increased ciliary beat frequency. In CRSsNP, the non-tasting (or non-protective) TAS2R38 genotype is associated with a higher rate of gram-negative bacterial carriage and a poor outcome. The effect may not be similar in patients with CRSwNP, however. Additional taste receptors may also play role or have predictive value in CRS, notably the taste receptor TAS2R19 (rs10772420).[963,964] This remains to be validated and replicated in other populations.

Staphyloccus aureus Carriage in CRSwNP: Genes associated with culture-positivity for *Staphylococcus aureus* in CRSwNP patients have been assessed in an agnostic 'hypothesis-free' fashion using a pooling-based genome-wide association study. *S. aureus* carriage was associated with a number of genes loosely organized along reduced engulfment of bacteria, modulation of inflammatory response, and genes of barrier elements (Table IX-21)**.** This supports that CRS patients colonized with *S. aureus* may be subject to immune impairment and dysfunction of the epithelial barrier and may thus be exquisitely sensitive to low level chronic bacterial infection with *S. aureus*.

IX.C.15.b. Epigenetics in CRS

Transmissible variations in gene function may also be induced by exposure to outside agents in a process termed epigenetic regulation, or epigenetics. Epigenetics deals with changes in organisms brought about by modifications in gene expression not resulting directly from alteration of DNA sequences.[965] This can lead to the modification of gene expression which can then be transmitted both intra-generationally and inter-generationally. It is of significant interest that cigarette smoking and *S. aureus*, factors associated with increased severity of CRS, are both implicated in epigenetic modification. Evidence of epigenetics *in-vivo* is still limited, but nevertheless, the concepts suggested by these studies are intriguing and hold promise for the future.[853,966-969] Most studies assessing blood and/or nasal epithelia have identified that epigenetic changes are more pronounced in epithelium than in circulating blood, supporting the importance of contact with the external environment for their development. This suggests that pathogens might be playing a role in adapting the environment for evolutionary advantage.

In summary, the current knowledge base in the genetics of CRS is still very limited. However, as our understanding and appreciation of interactions of the immune system, microbiome, and epithelial barrier improve, it offers the promise of further identification of novel pathogenic mechanisms and markers that identify predisposing factors and predict disease evolution. This could then elucidate optimal response to therapy and allow customization of therapy to a patient's disease profile, improving clinical care.

Table IX-19. CRS-associated genes reported in more than one study. Genes are grouped according to putative biological role: a. Immune system-related, b. Epithelial barrier related, c. Difficult to categorize.

Gene	Reference
Immune System	
ALOX5AP	Al-Shemari;[970] Henmyr [971]
AOAH	Bossé;[972] Zhang [973]
IL1A	Karjalainen;[974] Erbek;[975] Mfuna[976]
IL1B	Erbek;[975] Bernstein [977]

IL10	Kim;[978] Bernstein;[977] Zhang [979]
IL22RA1	Endam;[980] Henmyr [971]
IL33	Buysschaert;[981] Kristjansson[982]
IRAK-4	Tewfik;[983] Zhang[984]
NOS1	Castano;[985] Zhang;[973] Henmyr[971]
NOS1AP	Zhang;[973] Henmyr[971]
TAS2R38	Adappa;[611] Mfuna Endam;[964] Purnell[963]
TGFB1	Kim;[986] Henmyr[971]
TNFA	Erbek;[975] Bernstein;[977] Batikhan[987]
Barrier and Structural	
None	*None*
Not Easily Categorized	
DCBLD2	Pasaje;[988] Henmyr[971]
PARS2	Bossé;[972] Henmyr[971]
RYBP	Bossé;[972] Zhang;[973] Cormier[958]

Table IX-20. CRS-associated genes reported in a single study. Genes are grouped according to putative biological role: a. Immune system-related, b. Epithelial barrier related, c. Difficult to categorize.

Gene	Reference
Immune System	
ALOX15	Kristjansson[982]
ALOX5	Al-Shemari[970]
BDKRB2	Cormier[958]
CD58	Pasaje[989]
CD8A	Alromaih[990]
CIITA	Bae[991]
CNTN5	Cormier[958]
COX2	Sitarek[992]
CYSLTR1 (X)*	Al-Shemari[970]
FOXP1	Kristjansson[982]
HLA-DQA1	Kristjansson[982]
HLA-DQB1	Schubert[993]
HLA-DRA	Bohman[994]
IGFBP7	Cormier[958]
IL1RL1	Castano[985]
IL1RN	Cheng[995]
IL18R1	Kristjansson[982]
IL4	Zhang[979]
MET	Sitarek[992]
MET1	Castano[985]
OSF-2 (POSTN)	Zielinska-Blizniewska[996]
PDGFD	Cormier[958]
PRKCH	Cormier[958]
RAC1	Cormier[958] C

SERPINA1	Kilty[997]
TAS2R19	Purnell[963]
TNFAIP3	Cormier[998]
TP73	Tournas[999]
TSLP	Kristjansson[982]
VSIR	Bohman[994]
Barrier and Structural	
BICD2	Bohman[994]
CACNA1I	Bossé[972]
CACNA2D1	Cormier[958]
CACNG6	Lee[1000]
CDH23	Cormier[958]
K6IRS2	Cormier[958]
KCNAM1	Purkey[1001]
KCNQ5	Purkey[1001]
K6IRS4	Cormier[958]
LAMA2	Bossé[972]
LAMB1	Bossé[972]
LF	Zielinska-Blizniewska[996]
MMP9	Wang[1002]
MSRA	Bossé[972]
MUSK	Bossé[972]
NARF	Cormier[958]
NAV3	Bossé[972]
RPGR	Bukowy-Bieryłło[1003]
Not Easily Categorized	
C13orf7	Cormier[958]
CYP2S1	Kristjansson[982]
DPP10	Kim[1004]
FAM79B	Cormier[958]
GFRA1	Cormier[958]
GNB2	Purnell[963]
HLCS	Bohman[994]
KIAA1456	Bossé[972]
MYRF	Kristjansson[982]
PHF14	Cormier[958]
PIGT	Cormier[958]
SLC13A3	Cormier[958]
SLC22A4	Kristjansson[982]
SLC5A1	Bohman[994]
TOMM34	Cormier[958]
TRHDE	Cormier[958]
TRIP12	Bossé[972]
UBE3A	Cormier[958]

UBE3C	Pasaje[1005]
10p14	Kristjansson[982]

Table IX-21. Genes associated with *S. aureus* carriage in CRSwNP patients. (*Cormier et al., 2014*)

Immune System
BDKRB2
CNTN5
IGFBP7
PDGFD
PRKCH
RAC1
Barrier and Structural
CACNA2D1
CDH23
GFRA1
K6IRS2
K6IRS4
TOMM34
Not Easily Categorized
C13orf7
FAM79B
NARF
PHF14
PIGT
RYBP
SLC13A3
TRHDE
UBE3A

IX.C.16. Contributing Factors for CRS: Viruses

Because of limited data, CRSsNP and CRSwNP are combined in this analysis.

Beyond the role of acute respiratory infection-related inflammatory edema, the pathogenic roles of respiratory viruses in the development of CRS or CRS exacerbations are largely unknown.

Several cross-sectional or case-control studies have examined the prevalence of respiratory viruses in patients with CRS. Most commonly, nasal swabs, nasal lavage, or mucosal scrapings were collected and screened for multiple viruses, frequently including: parainfluenza 1, 2, and 3; respiratory syncytial virus; human metapneumovirus; adenovirus; rhinovirus (RV); coronavirus; bocavirus; cytomegalovirus; and influenza A and B.

Several studies found an increase in viral detection in CRS patients compared to control[753,754,1006] or high viral prevalence in CRS in cross-sectional studies.[1007,1008] However, several studies did not replicate these

findings.[1009-1013] Many of the studies which did not show increased viral detection were limited by small patient numbers or seasonal sample collection. This is important, as many respiratory viruses have seasonal increases in prevalence.

Goggin *et al.* in 2019 was the largest study, reporting results from 288 patients. Nasal brushings were taken, and PCR was utilized to evaluate for adenovirus, bocavirus, coronavirus, enterovirus, influenza, metapneumovirus, parainfluenza 1-4, respiratory syncytial virus, and rhinovirus. Viral species were isolated from 7% of controls, 20% of CRSsNP, and 15% of CRSwNP. RV species and coronavirus species were the most frequently isolated viruses. Peak viral isolation was found in samples collected in winter and spring. Only 20% of CRSsNP patients were positive for viral DNA/RNA at time of sampling; however, this group had significantly worse objective measures of disease severity compared to CRSsNP patients who were negative for a virus. Viral presence was not associated with increased objective disease severity in CRSwNP or virus-positive controls.

Among the epidemiologic studies which showed differential viral recovery in CRS versus control patients,[753,754,1006,1007] a consistent finding was that RV is either the most prevalent or one of the most prevalent viruses. A recent systematic review[1014] identified five studies that met a multi-component quality review for potential bias. Three studies reported an association between RV and CRS,[1006,1015,1016] while two studies reported no association.[1009,1010] Three additional epidemiologic studies evaluated RV in CRS (among other respiratory viruses) since this systematic review. Two of these[753,1013] found no association of RV with CRS status, but the largest[754] found that RV species and coronavirus species were the two most commonly isolated viruses from CRS samples. One epidemiologic study[1016] sequenced RV to determine the species. Only RV-A was detected in the control group. Both RV-A and RV-B were detected in CRS patients. The results may have been skewed, however, because subjects with active URI symptoms were excluded from their analyses.

These studies suggest a trend toward greater prevalence of viral infections, particularly RV, in CRS patients. However due to the heterogeneity of the studies and mixed results, the relationship of viral infection to CRS is unclear. One possibility is that CRS patients may have persistent viral infections with chronic local inflammation. Further longitudinal studies and repeated samplings of positive viral infections are necessary to test this hypothesis.

Several factors may explain the heterogeneity of epidemiologic findings. Viral detection rates in CRS patients may vary seasonally.[1008] This could lead to seasonality of sample collection influencing viral prevalence rates in CRS, even if the patient is asymptomatic. Collection of specimens over at least one full year may minimize any potential bias. Differences in sampling technique may also explain some observed differences, as various methodologies were used. Additionally, the site of collection may influence viral recovery, demonstrated by the lack of concordance between viruses recovered from the inferior and middle meatus of individuals.[1013] While studies utilizing prospective viral challenges have been useful in delineating many of the immunologic responses to respiratory viral infection in acute URI, these have involved healthy controls or patients with lower respiratory disease such as asthma, making direct application to CRS problematic.

In vitro studies with sinonasal epithelial cells derived from CRS patients can elucidate the response to respiratory viral infection. In one study,[1017] sinus air-liquid interface epithelial cells were differentiated from patients who underwent ESS for CRS. Cultures were challenged with RV-A, RV-B, and RV-C species. Viral yield, cytokine/chemokine production, and markers of cellular cytotoxicity were measured. RV-B strains had lower viral yield, decreased host immune viral response, and were less cytotoxic compared

to RV-A and RV-C strains. This supports clinical observations that RV-A and RV-C result in more severe upper respiratory infections than RV-B. Another group[383] inoculated commercial ALI cultures from nasal polyp cells with RV-A, RV-B, and RV-C species. RV-A and RV-C species again provoked greater epithelial response, as characterized by decreased MCC, cytokine secretion, and induced gene expression compared to RV-B. These data suggest that identification of RV species at the time of RS infection could help to predict disease severity. Another group[386] also derived nasal epithelial cells from CRS patients and controls. The cultures were infected with RV-16. While no difference was found by this study in IL-6 and IL-8 levels when comparing CRS and control cultures following RV infection, IFN-β induction was not noted in the CRS group. The authors speculate that this could lead to delayed viral clearance.

Overall, *in vitro* studies support the idea that rhinovirus can lead to alterations in the nasal epithelial cell immunologic homeostasis in CRS and that different RV species may have differential severity.

In summary, the epidemiologic data predominantly support an association between higher rates of viral infection in CRS patients than in controls; however, the data is inconsistent, particularly regarding genus of virus isolated and association with polyp status. The *in vitro* studies suggest that infection by RV leads to alterations in immunologic homeostasis, but additional studies are needed to clarify the extent to which viral insults are an antecedent factor, chronically present, or merely result in exacerbations of a patient's underlying sinonasal symptoms. Recent findings[754] suggest that CRSsNP patients with viral infection have worse endoscopic and radiographic measures of disease severity. Combined with previous studies such as the identification of a missense mutation in *CDHR3* (the viral receptor for rhinovirus-C) as a risk factor for development of CRS.[1018] These data suggest that additional research is needed to elucidate the potential for virome-host genome interactions as a risk for development of CRS.

Viruses as a Contributing Factor for CRS

Aggregate Grade of Evidence: C (level 3: 1 study; level 4: 12 studies; level 5: 5 studies)

Table IX-22. Evidence for viruses as a contributing factor for CRS

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Goggin [754]	2019	3 *	Case-control	Healthy controls, CRSwNP, CRSsNP	Viral presence, Lund-Mackay & Lund-Kennedy scores, symptom scores	Viral positivity significantly greater in CRSsNP; Objective scores significantly worse in virus (+) compared to virus (-) CRSsNP; RV, coronavirus, and influenza were isolated.
Hwang [1012]	2019	4	Case-control	Healthy controls, CRSwNP, CRSsNP	Viral presence; IFN-β and gamma	No difference in viral rates between control and CRS; decreased expression of IFN-β and gamma in CRS, but no data regarding effect of viral infection.
Goggin [1013]	2018	4	Case-control	Adult controls and adults with CRSwNP or CRSsNP	Viral presence	Virus present in 75% of patients; poor correlation between inferior and middle meatus.
Abshirini [1007]	2015	4	Cross-sectional	Adults undergoing ESS for CRSwNP or CRSsNP	RV prevalence 29%; RSV 12%	Higher than expected prevalence for rhinovirus.
Divekar [1010]	2015	4	Case-control	Adults	43% in CRSwNP; 55% in control	No statistically significant difference.
Hardjojo [367]	2015	4	Case-control	Infants separated into prolonged/recurrent rhinitis vs typical duration	RV incidence: 14% in rhinitis group; 13% in control	No significant difference between groups.
Lee [1016]	2015	4	Case-control	Adults	36% RV in CRS; 21% in control	
Lima [1008]	2015	4	Cross-sectional	Adults	19% prevalence of RV in CRS patients	
Ro	2015	4	Case-	Healthy	Viral presence, Lund-	24% viral recovery from CRS group;

wan[753]			control	controls, CRSwNP, CRSsNP	Mackay & Lund-Kennedy scores, symptom scores	0% from controls.
Liao[1009]	2014	4	Case-control	Adults	PCR detection of viruses; RV 36% for CRSwNP; 28% for CRSsNP; 49% in control	No significant difference between groups.
Cho[1006]	2013	4	Case-control	Adults and children	PCR for virus detection; 44% RV in CRSwNP; 20% in control	Rhinovirus 2x more prevalent in CRSwNP than control.
Wood[1011]	2011	4	Case-control	Adults with CRS and controls undergoing sinus surgery	Presence of respiratory viruses	No viruses detected by PCR.
Jang[1015]	2006	4	Case-control	Adults	21% RV prevalence in CRS; 0% in control	Rhinovirus more likely to be isolated from CRS.
Essaidi-Laziosi[383]	2017	5	*In vitro* rhinovirus challenge	Healthy controls; nasal polyp epithelium	IL-8, rantes, IP-10, IFN γ, IL -1, IL -6, GM-CSF	Significant change after rhinovirus inoculation.
Alves[385]	2016	5	*In vitro* rhinovirus challenge	Healthy, CF, COPD - inferior surface of middle turbinate	IFN-β, IFN-γ, il-6, IL-8	Significant change after rhinovirus inoculation.
Lee[1019]	2016	5	Murine model; rhinovirus challenge	Murine model of chronic allergic RS	IL-6, MIP-2, IL -13, TNF-α, IFN-γ	
Kim[386]	2015	5	*In vitro* rhinovirus challenge	Healthy control, CRS at inferior turbinate	IL-6, IL-8, IFN-β	Significant change after rhinovirus inoculation.
Nak	2014	5	*In vitro*	Undergoi	CCL, CXCL8/10/11,	

ago me [1017]			rhinovi rus challe nge	ng ESS - residual epithelial tissue	IFN-α2, IFN-β, IFN -l1, and IL-6	

* case-control study, but upgraded due to including radiographic, endoscopic, and symptom data as well as viral detection, with larger sample size

IX.C.17. Contributing Factors for CRS: Occupational and Environmental Factors

Because of limited data, CRSsNP and CRSwNP are combined in this analysis.

Occupational and environmental exposures can contribute to the development of CRS and lead to worsening disease severity.[1020-1022] Mucosa lining the nasal cavity and paranasal sinuses is the first area to interact with smoke, pollutants, or toxins during respiration.[1023] Exposure to particulates in upper airway diseases may relate to alterations of the sinonasal barrier, microbiome changes, and/or propagation of inflammation.[156,1021]

There is high-level evidence that cigarette smoke contributes to CRS, in addition to lower airway diseases such as asthma.[1023-1025] Tobacco smoke reduces MCC by altering chloride secretion and CBF, and tobacco smoke inhibits ciliogenesis in animal models.[896,1026] Both active and passive smoking have been shown to contribute to the development of CRS throughout childhood and adulthood.[15,1023,1025,1027] In a large, population based analysis, current smoking was associated with increased odds of several symptoms of CRS, including facial pain and pressure (odds ratio (OR) 1.52, 95% confidence interval (CI) 1.03-2.24) and smell loss (OR 1.8, 95% CI 1.01-3.11), and former smoking was associated with smell loss (OR 1.9, 95% CI 1.24-2.89).[13] A case control study showed that an increased likelihood of CRS was associated with passive smoke exposure at work (OR 2.81, 95% CI 1.42-5.57) and at private functions (OR 2.60, 95% CI 1.74-3.89).[1027] Further, the odds of having CRS increased with second-hand smoke exposure in multiple venues, including at home and work.[1027] To the best of our knowledge, smoking has not been reported to be associated with reduced therapeutic efficacy of recommended treatment for CRS nor failure of ESS. Limited research into the impacts of non-conventional cigarette smoking exists, including on electronic cigarettes, however cannabis in combination with tobacco smoke appears to further worsen CRS severity compared to tobacco smoke alone.[1028] Public health interventions that limit smoking would likely serve to reduce the morbidity of CRS.

Beyond tobacco smoke exposure, fewer conclusions on other occupational and environmental factors could be drawn until recently. A 2015 systematic review on CRS and occupational and environmental exposures assessed 41 studies.[1020] There was substantial heterogeneity in the definition of CRS used and reporting of exposures was subject to bias in the form of self-report or industry/job title extrapolation. The authors concluded that limited conclusions can be drawn regarding the role of occupational or environmental exposures in CRS. Further and more recent work has, however, suggested a link between occupational and environmental exposures and CRS.

Additional studies since this review often continue to in adequately define their cohort with accepted diagnostic criteria, while also failing to specifically differentiate ARS from CRS. Further, self-reported outcomes are common, introducing a strong recall bias to these results. Consequently, the conclusions regarding the impact of these exposures and their effect on ARS or CRS should be tempered.

Nevertheless, several cross sectional studies have demonstrated a significant and independent association between environmental and occupational exposure and CRS.[1029-1031].

A cross-sectional study from Denmark showed that female blue-collar workers had higher rates of CRS compared to white-collar workers (adjusted risk ratio 1.64, 95% CI 1.10-2.43), and that occupational exposures elevated the risks of CRS.[1032] Large cross-sectional studies of individuals in the U.S. and in South Korea identified associations between CRS and air quality, including pollution with particulate matter 10 (PM10).[1033,1034] Recent cross-sectional studies using a symptom-based diagnosis of CRS completed in China in 2016 and in Norway in 2018 determined that factors such as dust, poisonous gas, cleaning agents, animals, mildew and physically strenuous work were associated with CRS.[1029,1030] In general, statistically significant odds ratios for associations between these factors and CRS range from 1.2 to 2.7.[1029,1030,1034] A 2018 case-control study of textile and retail workers incorporating nasal endoscopy to diagnose nasal polyps identified significantly more nasal polyposis ($p=0.001$), polypoid degeneration of the middle turbinate, ($p=0.001$) and poorer Lund-Kennedy score (LK, $p<0.001$) than those not exposed to dust.[1031] A 2015 case-control study demonstrated that higher serum levels of cadmium and nickel were associated with nasal polyposis, however these findings may have been confounded by smoking status.[1035] Research by the same group using atomic absorption spectrometry demonstrated a higher amount of heavy metals, including nickel, chromium, and arsenic, in nasal polyp tissue compared to non-polyp nasal mucosa from the same subjects, though again smoking status may have confounded these results.[1036]

Further study using novel techniques has corroborated that exposures contribute to CRS. Following the World Trade Center attack, dust exposure has been linked to increased prevalence of CRS.[1037] A 2018 investigation employed spatial monitoring techniques to estimate environmental exposures in individuals with confirmed diagnoses of CRSsNP and CRSwNP. The study correlated exposures of particulate matter 2.5 (PM2.5) and black carbon with measures of CRS severity and treatment, such as corticosteroids and ESS.[1038] When exposed to PM, this cohort of patients had a significantly greater likelihood to require ESS and revision ESS in a dose dependent relationship ($p=0.015$). Additionally, BC was shown to be a significant predictor of SNOT-22 scores in a subgroup of patients that otherwise did not demonstrate sufficient mucosal inflammation to warrant surgery. These data showed that air pollutants correlated with symptom severity and that this may be influenced by exposure levels in patients with CRSsNP.[1038] A subsequent study in 2020 showed that occupational airborne exposures to vapors, gases, dusts, fumes, fibers, and mists correlated with increased rates of ESS and need for corticosteroids in individuals with CRS, while there was no correlation between pollutant levels and disease severity measures.[1039] These two studies employed guideline definitions to diagnose CRS in included subjects, strengthening the conclusions that can be drawn from these reports.[1038,1039] Interestingly, occupational exposure to several agents like hypochlorite, dust, cleaning agents and irritants have been associated with negative outcomes after ESS for CRS, as self-reported exposure to multiple irritants increased with the number of revision surgeries.[1040] The mechanisms of action of occupational agents leading to chronic sinonasal inflammation are most likely linked to epithelial barrier dysfunction with/without immune activation of the innate and adaptive immune system.[156] although the level of evidence linking pollution to CRS is limited, the existing literature does suggest that air pollution may play a role in the pathogenesis of CRS.[1041] Indeed, *in vivo* studies in mice have shown that air pollution results in eosinophilic RS in mice, highlighting an area for futher investigation and further lending credence to the theory that environmental pollutants may contribute to the development of CRS.[1042] Also, environmental irritants like hypochlorite in swimming pools have been associated with chronic inflammation and nasal hyperreactivity.

Overall, these data suggest that environmental and occupational exposures contribute to CRS. Further studies are needed to refine this association and establish causality. Ultimately, additional studies with larger patient population sizes and control groups, using current diagnostic criteria for ARS or CRS, and objective disease outcome measures (*i.e.*, SNOT-22, LM, LK, etc), are needed to establish the association between sinonasal disease and environmental/occupational allergens, while allowing for subgroup analyses. Ideally, accomplishing this will lead to an investment into well-designed and randomized studies that can then be employed to explore the potential underlying pathogenesis between exposure and disease.

Table IX-23. Aggregate grades of evidence for occupational and environmental factors

Item	Explanation
Smoking	Level C, multiple case-control and cross-sectional studies identify smoking as a contributing factor for CRS. This is also supported by animal studies.
Pollutants	Level C, observational studies identify associations between pollutants and CRS severity and need for treatment. Limitations in prior studies regarding diagnosis and design have been improved in recent studies.

Table IX-24. Evidence for environmental triggers as a contributing factor for CRS

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Velasquez[1039]	2020	4	Case series (n=234)	CRSwNP (n=113), CRSsNP (n=96), AERD (n=25)	Impact of exposure to airborne vapors, gases, dusts, fumes fibers, mists (VGDFFiM) or diesel fumes on sinonasal disease severity as measured by LM, systemic steroids, need of ESS.	Patient's with CRSsNP had a significantly higher exposure to levels >30% of VGDFFiM compared to CRSwNP and AERD (p=0.03). Exposed patients require significantly more systemic steroids (p=0.015 and p=0.03, respectively) and are more likely to require ESS (p=0.04) than controls. However, there is no difference in LM between the two groups. At higher levels of pollutant exposure (*i.e.*, >30%), there is a trend demonstrating increasing prevalence of CRSsNP.
Clarhed[1029]	2018	4	Cross-sectional (n=16,099)	Random sample population in Telemark, Norway was surveyed (n=48,142). CRS defined according to EPOS criteria.	Prevalence of CRS and occupational exposure (self-identified on survey).	Occupational exposure to metal and paper dust, cleaning agents, animals, moisture/mold/mildew, and physical labor is independently associated with CRS.
Geramas[1041]	2018	3	Systematic review	30 studies (12 living/working environment conditions, 14 use of toxins/drugs, 11 SES, 5 diet/exercise, 1 family/martial	Association between CRS, which is variably defined in the included studies, and SES, education level, drug/toxin use,	There appears to be an association between prevalence of CRS and smoking status, low SES, and living/working environment with pollutant exposure. Heterogeneity of defining CRS across

				status)	smoking status, diet/exercise, family life, and living/working environment.	the investigations that were included in this review limits the interpretation of the results.
Mady[1038]	2018	4	Case series (n=234)	CRSsNP (n=96), CRSwNP (n=138)	Impact of air pollutants (PM and BC) on sinonasal disease severity as measured by SNOT 22, LM, systemic steroids, number of ESS	Both groups had similar exposure to air pollutants. CRSsNP cohort with PM exposure is significantly more likely to require ESS and revision ESS in a dose dependent relationship (p=0.015). BC exposure is predictive of significantly worse SNOT 22 scores (p=0.008). These significant trends are not seen in the CRSwNP cohort.
Steelant[1043]	2018	4	Cross-sectional (n=66)	Competitive swimmers (n=38); indoor athletes (n=13); age-matched controls (n=15).	Baseline upper airway symptoms (*i.e.,* SNOT-22, VAS), amount of nasal fluid generated, neurogenic and inflammatory mediators in nasal fluid, *in vitro* effect of hypochlorite on nasal epithelial cells	Baseline SNOT-22 and VAS (nasal itch and impaired smell) were significantly worse in swimmers compared to controls. Similarly, swimmers demonstrated more nasal inflammation compared to indoor athletes and controls. The authors hypothesized that this may be due to greater exposure among swimmers to hypochlorite, which is present in chlorinated pools. Using *in vitro* experiments, the authors demonstrated that hypochlorite decreased nasal epithelial cell integrity.

Veloso-Teles[1031]	2018	4	Cross sectional (n=316)	Random sample of textile workers (n=215) and retail store workers (n=101). CRS defined according to EPOS criteria.	Prevalence of nasal polyposis, sinonasal specific QoL, and LK.	Sinonasal specific QoL was significantly poorer in the textile group (p=0.005). The textile group (dust exposure) also demonstrated significantly more nasal polyposis (p=0.001), polypoid degeneration of the middle turbinate (p=0.001) and LK (p<0.001).
Gao[1030]	2016	4	Cross-sectional (n=10,633)	CRS (n=850), non-CRS control (n=9,783). CRS defined by EPOS criteria.	Prevalence of various occupational exposures in CRS vs control population.	Risk factors for CRS in this large population study on multivariate analysis include: clearance job, occupational exposure to dust, poisonous gas, having a pet or carpet.
Weakley[1037]	2016	4	Case series (n=9848)	High risk exposure (n=1623), moderate risk exposure (n=7025), low risk exposure (n=1200).	Incidence of CRS by exposure group post World Trade Center attack on 9/11/01	Among those exposed to dust from the World Trade Center attack, the relative risk of developing CRS in high risk exposure group was greater than the moderate or low risk exposure group (p<0.0001). RS was not defined according to any accepted diagnostic criteria, limiting interpretation of study results.
Hox[1040]	2012	4	Case-control (n=536)	ESS (n=467), control (n=69)	Number of ESS procedures	Occupational exposure (assessed using a questionnaire) was associated with an increased likelihood to require more than one ESS (OR 1.64) or more

						than two ESS (OR 1.97) on logistic regression analysis.
Bhattacharyya[1033]	2009	4	Cross-sectional (n=313,982)	Hay fever and RS; weak/failing kidneys control.	Prevalence of disease (self identified on survey) and air concentrations of pollutants.	Improving air quality is associated with a decrease in prevalence of hay fever and RS. RS was not defined according to any accepted diagnostic criteria, limiting interpretation of study results.
Sundaresan[1020]	2004	4	Systematic review	41 studies (37 occupational risk, 1 enviornmental risk, 3 both).	Self reported exposures. CRS not adequately defined.	The limited quality of evidence in the literature hinders the ability to make any definitive conclusions regarding the impact of occupational or environmental exposure on CRS.
Zuskin[1044]	2004	4	Cross-sectional (n=311)	Pharmaceutical workers (n=198); matched control workers (n=113).	Chronic respiratory symptoms, pulmonary function test.	Pharmacetuical workers have a significantly higher level of RS, nasal mucus, and dyspnea compared to matched controls. Employment and smoking are significant independent predictors of symptoms. RS was not defined according to any accepted diagnostic criteria, limiting interpretation of study results.
Duclos[1045]	1987	4	Cross-sectional (n=15 hospitals)	Information from patient visits to 15 hospital ER's most affected by the 1987 California wildfire was abstracted	ER visit diagnosis	In contrast to non-respiratory conditions, ER visit diagnoses at each of these 15 hospitals impacted by wildfires increase for asthma ($p<0.001$), COPD ($p<0.02$) , upper respiratory infection

				during the fires and for 2 separate reference periods.		(p<0.001), RS (p<0.05) and laryngitis (p<0.02). These increases are more than expected based on the two reference periods. RS was not defined according to any accepted diagnostic criteria, limiting interpretation of study results.
Hox[1022]	2014	5	Non-systematic review	CRSwNP (n=113), CRSsNP (n=96), AERD (n=25)	A review of existing literature on occupational upper airway disease with a focus on pathophysiology and a suggested diagnostic work up.	The authors highlight the limitations of the current literature on this topic, including small sample sizes, a lack of standardized diagnostic criteria for CRS and retrospective nature of the investigations. The authors highlight the link between occupational exposures and adult-onset asthma, suggesting a potential link between these exposures and CRS as well, due to the close association of upper and lower airway. The authors propose a classification scheme based on size and pathophysiology of occupational agents. The authors also present a diagnostic work flow to better identify occupational upper airway disease.

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IX.D. Chronic Rhinosinusitis without Polyps: Management

IX.D.1. Management of CRSsNP: Saline (Spray and Irrigation)

In an updated search since the ICAR-RS-2016, fourteen RCTs, three systematic reviews and one cohort study were identified. Three RCTs were excluded due to the inclusion of mixed ARS/CRS patients.[439,442,1046] One RCT was excluded due to unusable data.[1047] A Cochrane review[1048] was discussed in the section of CRSwNP as it extracted data from participants with mixed ARS/CRS[442] and CRSwNP.[1049] Finally, the data from ten RCTs, two systematic reviews and one cohort were extracted for assessment.

To address the duration of saline treatment, 4 studies were evaluated. A study by Heatley *et al.*[1050] and a systematic review by Harvey *et al.*[1051] assessed disease-specific QoL at two weeks and did not show difference between the saline treatment and the control. A cohort study by Perkasa *et al.*[1052] assessed the outcomes at 6 weeks and showed no difference in QoL between the saline irrigation group and the control. Finally, a randomized trial by Taccariello *et al.*[1053] evaluated outcomes at eight weeks, and demonstrated significantly greater improvement in the QoL and endoscopy in two study groups: nasal saline irrigation and seawater nasal spray, compared to the non-saline group.

To address the differential benefits, if any, of isotonic versus hypertonic saline, a systematic review by Kanjanawasee *et al.*[445] was identified. Pooling the data, a greater benefit of hypertonic over isotonic saline was revealed (mean difference in total nasal symptoms scores -0.37, 95%CI -0.58, -0.15). Ural *et al.*[1054] demonstrated improvement in MCC after ten days in the group receiving hypertonic saline irrigation, but the improvement was not shown by isotonic saline irrigation treatment. Two RCTs by Berjis *et al.*[1055] and Culig *et al.*[1056] evaluated the effects of tonicity on symptoms score and hypertonic showed better improvement in congestion over isotonic saline solution.

An RCT by Nimsakul *et al.*[1057] studied the effects of temperature on saline treatment and concluded that warming up saline was not necessary. At 1 hour after the intervention, MCC improved in both room temperature and heated saline irrigation (40°C) without a difference between the two temperatures. In addition, there were no differences in peak nasal inspiratory flow, nasal volume change, nasal resistance, and symptoms score. There was no adverse event reported.

Different devices give different volume and pressure of saline delivery which may impact the penetration of the saline solution into the posterior part of the nasal cavity and postoperative cavity. Pynnonen *et al.*[441] demonstrated greater improvement on disease-specific QoL and symptom scores in patients using large volume (240 ml) isotonic saline irrigation, compared to saline spray. When a large volume (240 ml) of a pot was compared to a medium volume of a bulb syringe (around 60-90 ml), Heatley *et al.*[1050] demonstrated that both devices improved symptom scores without a difference in patient preference, satisfaction and bacterial colonization. Taccariello *et al.*[1053] compared a medium volume (60 ml) of nasal saline irrigation by cupped hand and seawater nasal spray and found that 60 ml of nasal saline irrigation did not bring greater benefit over seawater spray for QoL score, symptom scores, MCC and rhinomanometry test results.

Adverse effects of saline irrigations are minor and quite rare. These include local irritation, nasal burning, nausea, itching, pain, otalgia, and epistaxis.[445,1051] A higher risk ratio (2.38, 95%CI 1.05, 5.40) for adverse effects was reported in hypertonic saline use, especially for nasal burning and irritation.[445] However, these adverse events subsided spontaneously and did not affect their high satisfaction among patients.[442]

Nasal Saline for CRSsNP

Aggregate Grade of Evidence:

- Saline irrigatons (≥60 ml): B (Level 1: 2 studies, level 2: 1 study; level 3: 4 studies)
- Saline irrigatons (<60ml): B (Level 1: 2 studies; level 2: 1 study; level 3: 1 study, level 4: 1 study)
- Saline sprays: B (Level 2: 2 studies; level 3: 2 studies)
- Saline drops: N/A (Level 3: 1 study)

Benefit: Improvement in QoL, endoscopic appearance for CRSsNP, and role in maintenance therapy. Benefit over the control were shown with saline irrigiatons (≥60 ml) and at eight weeks duration.
Harm: Minor and rare adverse effects. Nasal burning and irritation are more reported with hypertonic irrigation (see Table II-1).
Cost: Minimal
Benefits-Harm Assessment: Preponderance of benefit over harm.
Value Judgments: Topical management is essential for treating a chronic inflammatory disease of the nose and paranasal sinuses. Regimen and delivery method impact the penetration of saline and its ability for mechanical removal of thick mucus. The use of saline irrigation (≥60 ml) is recommended as an adjunct to standard treatment. Saline irrigiatons (<60 ml), saline spray and drop show less benefit but could be an alternative.
Policy Level: Recommendation
Intervention: Saline nasal irrigation improves symptoms, QoL and nasal endoscopy for patients with CRSsNP. Duration of treatment should be greater than eight weeks. Hypertonic saline is more effective but may be more irritating than isotonic saline. There is no advantage of heated saline (40°c) over room temperature saline. Devices with volume greater than 60 ml bring greater benefits.

Table IX-25: Evidence for CRSsNP management with nasal saline

Study	Year	LOE	Study Design	Study Groups (N)	Device	Clinical Endpoint	Conclusions
Kanjanawasee [445]	2018	1	SR	Any sino-nasal disease (hypertonic focused)	Any mode of delivery	QoL Symptoms	Hypertonic saline brings greater benefits on symptom improvement over isotonic saline nasal irrigation in RS.
Harvey [1051]	2007	1	SR	Persistent sino-nasal disease	Any mode of delivery	QoL Symptoms Radiology Endoscopy	Saline irrigations improve CRS symptoms as a sole modality and as an adjunct to INCS. Not as effective as INCS.

Friedman [1058]	2012	2	RCT, DB	Dead sea salt solution irrigation and spray (59) Hypertonic saline irrigation and fluticasone spray (55)	20ml/side irrigation (syringe), spray	QoL (SNOT-20) UPSIT Acoustic rhinometry	Dead sea salt irrigation alone was equally as effective as hypertonic saline irrigation plus fluticasone spray.
Friedman [1059]	2006	2	RCT, DB	Dead sea salt solution (22) Hypertonic saline (20)	Irrigation (volume not reported), spray	QoL (RQLQ) Symptoms	Dead sea salt irrigations are more effective in reducing QoL and symptom score than hypertonic saline irrigations at 1-month time.
Bachmann [1060]	2000	2	RCT, DB	Ems salt hypertonic solution (20) Isotonic saline (20)	200 ml irrigation (nasal irrigator)	Symptoms Endoscopy MCC Nasal airflow Olfactometry Radiology	No difference between Ems salt hypertonic solution and isotonic irrigation at 7 days.
Nimsakul [1057]	2018	3	RCT, SB	Heated isotonic saline (12) Room-temperature isotonic saline (11) Healthy control (9)	250 ml irrigation (squeeze bottle)	MCC PNIF Nasal resistance Nasal volume Symptoms Adverse event	Warming saline is not necessary and adds no additional benefit to room-temperature saline irrigation.
Berjis [1055]	2011	3	RCT, UB	Hypertonic saline (57) Isotonic saline (57)	Drop	Symptoms Patient satisfaction	Hypertonic saline irrigation is more effective than isotonic saline in symptoms reduction and patient satisfaction.
Culig [1056]	2010	3	RCT, UB	Hypertonic seawater (30) Isotonic seawater (30)	Spray	Symptoms	All symptoms improved in the group of patients using

							hypertonic seawater solution. While only congestion and rhinorrhea improved in the group of isotonic seawater solution.
Ural [1054]	2009	3	RCT, SB	Hypertonic saline (18) Isotonic saline (24)	4ml/side irrigation (syringe)	MCC	Mucociliary clearance improved after irrigation with hypertonic saline but did not with isotonic saline.
Pynnonen [441]	2007	3	RCT, UB	High volume, low-pressure isotonic saline (64) Low volume spray isotonic saline (63)	240 ml irrigation (squeeze bottle), spray	QoL (SNOT-20) Symptoms Medication use	High-volume low-pressure irrigation is more effective than saline spray in a reduction of SNOT-20 and symptom score at 8 weeks.
Heatley [1050]	2001	3	RCT, UB	Isotonic saline in bulb syringe (43) Isotonic saline in pot irrigation (39) Reflexology as control (46)	Bulb syringe irrigation, pot irrigation	QoL (RSOM-31) Patient satisfaction Medication use	RSOM-31 improved in all groups. There was no difference between the two irrigation groups and reflexology after 2 weeks.
Taccariello [1053]	1999	3	RCT, SB	Alkaline nasal douche (19) Seawater spray (21) Standard treatment (22)	60 ml irrigation (cupped hand), spray	QoL (RQLQ) Symptoms MCC Endoscopy Cross-sectional area Volume	Both treatment groups showed significant improvements in endoscopic appearances and QoL scores, while improvement

							did not reach a significant level in the control group at 8 weeks.
Perkasa [1052]	2016	4	Prospective cohort	Antibiotic/ Oral steroid + isotonic saline Antibiotic/Oral steroid	20 ml/side irrigation	QoL (SNOT-20) Radiologiy	At 6 weeks, SNOT-20 improved in both groups while CT score improved only in the group with saline irrigation.

IX.D.2. Management of CRSsNP: Topical Corticosteroids

Topical corticosteroids may be delivered using standard sprays or using irrigations and other nonstandard methods. These two broad delivery methods will be discussed separately.

IX.D.2.a. Topical Corticosteroids: Standard Delivery (Sprays)

INCS have been used extensively in the treatment of CRSsNP, however clinical evidence supporting their use in this patient cohort has been variable both in quality, delivery mechanism and type of corticosteroid. The majority of studies included mixed populations such as chronic rhinitis, CRSsNP, and CRSwNP limiting the ability to make strong recommendations for or against the intervention. Variability in clinical and radiographic diagnosis for this diagnostically heterogeneous population is an additional challenge, particularly in trials recruiting from primary care. Finally, newer trials have found more pronounced results comparing novel devices and high-volume irrigations with both placebo and traditional nasal sprays.

Three high quality systematic reviews with meta-analyses address INCS in CRSsNP. Kalish *et al.*[1061] in 2009 combined 5 trials reporting overall response to treatment.[504,1062-1065] When evaluated as a single group, there was no benefit found, with significant variability among studies noted (aggregate data: RR=0.75, 95% CI 0.50-1.10, p=0.14). It is worth noting that three trials[1062,1063,1066] reported change in symptom scores, and showed a standardized mean difference favoring INCS use (RR 0.63, 95% CI 0.16-1.09, p=0.009). In a second high quality review, Snidvongs *et al.*[1067] published a Cochrane review in 2011 that combined 5 trials[1062,1063,1066,1068,1069] reporting symptom scores in patients treated with INCS compared to placebo. A significant improvement in standardized mean difference of symptom scores was found in the treatment arm (SMD=-0.37, 95% CI -0.60 to -0.13, p=0.002), with no evidence of significant heterogeneity. Two of the studies administered steroids following sinus surgery,[1066,1068] one study included only surgically naïve patients,[1069] one included a mixed population of surgical and non surgical patients[1062] and the remaining study did not specify surgical status of the included patients.[1063] Four trials[1062,1063,1070,1071] in patients with CRSsNP were identified and concluded there was little effect of INCS on HRQL and disease severity with a small improvement seen in a general health subscale indicating a limited role for INCS.

Since the Kalish and Snidvongs systemic reviews, two additional randomized trials were published showing mixed results. Mosges *et al.*[1070] randomized 60 CRSsNP patients in a double-blinded study to receive either mometasone furoate spray 200 µg BID or placebo for 16 weeks. Less than 10% of included patients had a history of sinus surgery, and none had surgery within 6 months leading up to the start of the study. Total symptom scores improved in both groups during treatment, with no significant difference seen (-7.27 vs -5.35, p=0.51). A significant improvement was seen in endoscopy scores in the treatment arm (p=0.002). The authors noted their small sample size may limit the ability to detect a significant difference, and no power calculation was reported. Zeng *et al.*[1072] randomized 43 patients with no history of sinus surgery in a single-blinded treatment comparison study to receive either mometasone furoate 200 µg daily or clarithromycin 250 mg daily for 12 weeks. Significant improvements in both symptom and endoscopy scores were seen in both treatment groups, with no significant difference noted between the groups. The lack of a placebo control, and small sample size weakened the quality of this study.

The literature examining the efficacy of INCS for CRSsNP is less robust than that of CRSwNP which does limit generalizability of results. Minimal, though consistent improvements are seen in both surgical and non-surgical patients.

All included studies utilized spray as a delivery method for INCS. No studies meeting inclusion criteria were identified utilizing drops.

Intranasal Corticosteroid (Standard Delivery) for CRSsNP

Aggregate Grade of Evidence: A (Level 1: 3 studies, Level 1: 9 studies).
Benefit: Improved symptom scores, improved endoscopy scores.
Harm: Epistaxis, headache (see Table II-1).
Cost: Low to moderate (USD$0.61-USD$4.80 per day depending on medication).
Benefits-Harm Assessment: Possible mild benefit over harm.
Value Judgments: Direct sinus delivery methods showed greater effects on symptom scores, therefore should be considered in more complex cases of CRS or following failure of treatment with simple sprays.
Policy Level: Option.
Intervention: Standard metered dose INCS could be used in treatment of CRSsNP, particularly if primary symptoms are that of rhinitis.

Table IX-26. Evidence for CRSsNP management with topical nasal corticosteroids (standard delivery with sprays).

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Chong [1073]	2016	1	Meta-analysis (n=269 CRSsNP)	INCS Placebo/No treatment	HRQL Disease severity	Slight improvement with steroid for general health subscale, no effect on other HRQL or disease severity for CRSsNP.
Snidvongs [1067]	2011	1	Meta-analysis	INCS Placebo (or	Symptom scores QoL	INCS improved symptom scores.

			(n=590)	antibiotics)	Adverse events	No change in QoL. No adverse events.
Kalish [1061]	2009	1	Systematic review (n=657)	INCS Placebo (or antibiotics)	Overall response to treatment Symptoms	Insufficient evidence to demonstrate a clear benefit with INCS. Possible improvement in symptom scores.
Mosges [1070]	2011	2	DBRCT (n=53)	Mometasone furoate 200mcg BID Placebo	Total symptom score Patient evaluation treatment response Endoscopy score Adverse events	No difference in total symptom score between groups. Significant improvement in endoscopic score.
Zeng [1072]	2011	2	RCT – single-blinded, treatment comparison study (n=43)	Mometasone furoate 200mcg daily Clarithromycin 250mg daily	Symptom score Endoscopy score Overall symptom burden score	Improvement in symptom scores and endoscopy scores in both groups.
Jorissen [1068]	2009	2	DBRCT (n=99)	6 month course, starting 2 weeks post-surgery Mometasone furoate 200mcg BID Placebo	Endoscopic score Symptom scores Adverse events	No significant difference in total endoscopic score or symptom scores between groups.
Dijkstra [1064]	2004	2	DBRCT (n=162)	Following ESS Fluticasone propionate 400mcg BID Fluticasone propionate 800mcg BID Placebo	Symptom scores (VAS) Endoscopy score CT score (Lund-McKay)	No reduction in recurrence rate of CRS following ESS.
Lund [1063]	2004	2	DBRCT (n=167)	20 week course 1. Budesonide 128mcg BID 2. Placebo	Combined symptom scores Individual symptom score HR-QoL (SF36) Peak nasal flow	Budesonide improved combined symptom score, individual symptom scores and peak nasal flow. No change in HRQoL.
Giger [1065]	2003	2	DBRCT (n=112)	Beclamethasone dipropionate 200mcg BID Beclamethasone	Symptom score Active anterior rhinometry Acoustic rhinometry	Significant reduction in symptom scores in both groups as compared to

				400mcg morning, saline placebo evening	Morning serum cortisol Adverse events	placebo.
Parikh [1062]	2001	2	DBRCT (n=22)	Fluticasone propionate 200mcg BID Placebo	Symptom score Acoustic rhinometry Endoscopy scores Middle meatal swabs Blood tests	No difference between groups in any outcome measures.
Qvarnberg [504]	1992	2	DBRCT (n=40)	Budesonide 200mcg BID Placebo	Symptom scores X-ray changes Microbiology	No significant differences in treatment outcomes between groups.
Sykes [1074]	1986	2	DBRCT (n=50)	1. 20µg dexamethasone + 120mcg tramazoline + 100mcg neomycin 2. 20µg dexamethasone, 120µg tramazoline 3. Placebo	Proportion of patients with improved symptoms Nasal airway resistance Mucociliary clearance Sinus x-ray Bacteriology	Significant increase in patients with improved symptoms in both treatment arms. No difference between active treatment groups.

IX.D.2.b. Topical Corticosteroids: Nonstandard Delivery

Penetration of nasal sprays beyond the nasal cavities into the paranasal sinuses has been shown to be limited, particularly in patients who have not previously undergone ESS.[1075,1076] This has led to an increased use of novel delivery devices to improve corticosteroid deposition, and clinical outcomes.

Five papers addressing the use of corticosteroid sinus irrigations met inclusion criteria, 3 prospective cohort studies and two high quality RCTs. In a 12 month follow up study, Harvey *et al.* compared high dose mometasone spray (2mg) with a similar dose of large volume mometasone irrigation in post-operative ESS patients.[1077] Steroid irrigations improved patient reported symptoms, radiographic scores and endoscopy appearance as compared to the steroid spray. The study included both CRSwNP (77%) and CRSsNP (33%), limiting generalizability regarding CRSsNP. Tait *et al.* compared budesonide irrigations with saline alone in patients with primarily CRSsNP administered over 30 days and concluded improved subjective and objective outcomes in the budesonide group with an average difference of 7 points on the SNOT-22 and improved endoscopic scores, however the results did not reach statistical significance.[1078] Snidvongs *et al.*[1079] published a prospective cohort of 111 patients, 49 who had a diagnosis of CRSsNP (analyzed separately). Treatment was once daily irrigations of 1 mg budesonide/betamethasone in 240 ml of normal saline in the immediate post-operative period. Significant improvements were seen in SNOT-20 (2.3 +/- 1.1 vs 1.2 +/- 0.9), symptom (2.5 +/- 1.1 vs 1.4 +/- 1.0) and Lund-Kennedy endoscopy scores (4.3 +/- 2.0 vs 1.9 +/- 1.6). Two smaller studies were published by Sachanandani *et al.*[1080] and Steinke *et al.*,[1081] of 9 and 8 patients respectively. Improvements in disease specific QoL (SNOT-20), symptom and endoscopy scores were shown, but the small patient numbers limits conclusions. There have been concerns about the potential for increased

systemic absorption with subsequent adrenal suppression with corticosteroid irrigation use, yet two studies have shown no evidence to date.[1082,1083]

A novel exhalational delivery device developed using fluticasone has shown promise in case series,[1071,1084,1085] although no comparisons with steroid sprays or topical steroid irrigations have been performed. Two single arm, prospective studies included CRSsNP patients. Sher *et al.* enrolled 603 CRSsNP patients and noted an average improvement in SNOT-22 scores of 23.2.[1084] EXHANCE-12, a 12 month prospective single arm design included 189 CRSsNP patients and noted SNOT-22 scores decreased by an average of 21.1 with improved Lund-Kennedy endoscopy scores.[1085] Using a similar device, Hansen *et al.*[1071] published a double-blinded RCT of 20 patients using a bi-directional spray device. Patients received a 12-week course of either fluticasone propionate 400 µg or placebo twice daily. Significant improvements in subjective patient symptom scores were seen in the corticosteroid group. Overall RSOM-31 and endoscopy scores showed no statistically significant changes. The main weakness of this study was the small sample size.

One paper investigated mucosal atomization devices (MAD). Thamboo *et al.*[1086] randomized 20 patients in an unblinded comparison study to a 12-week course of either 1 mg budesonide via MAD or budesonide irrigations. Clinically significant improvements in SNOT-22 scores were seen in both arms, although only in the MAD group did this reach statistical significance. Importantly a statistically significant difference in stimulated cortisol was seen in the MAD group at 60 days, although this did not reach threshold for diagnosis of adrenal suppression. A long-term safety follow up in 2017[1087] raised some concerns about elevated intraocular pressure and adrenal suppression with this device and recommended screening with long-term use.

Finally, three studies have examined the role of sinonasal catheters for steroid delivery.[1066,1069,1088] All studies were small with 20, 13, and 25 patients, respectively. Furukido *et al.*[1069] reported a single-blinded RCT utilizing the YAMIK sinus catheter. Twenty-five patients were treated with a one-month course of weekly irrigations of betamethasone (0.4 mg/ml) or saline. No difference was seen between treatment groups in symptoms or sinus x-ray scores. Lavigne *et al.*[1066] randomized 20 patients to receive either 256 mcg budesonide or placebo via a unilaterally placed maxillary sinus antrostomy tubes (MAST) for 3 weeks. The budesonide treatment group had a significant improvement in clinical scores, as well as significant reductions in tissue biopsy eosinophil counts and IL-4 and IL-5 levels compared with placebo. Moshaver *et al.*[1088] reported a case series of 13 patients who had bilateral MAST tube placement and daily irrigations of tobramycin (10 ml of 0.8 mg/ml) and 0.4 ml of a mixture containing ciprofloxacin (2 mg/ml) and hydrocortisone (10 mg/ml). Significant improvements in both SNOT-16 and endoscopy scores were seen and maintained at 16-week follow-up. Given the invasive nature of catheter placement with epistaxis as a common side effect and the limited clinical uptake of these methods, the authors would not recommend their use in clinical practice.

Intranasal Corticosteroids (Nonstandard Delivery) for CRSsNP

Aggregate Grade of Evidence: Irrigations – A (Level 1: 1 study, Level 2: 5 studies; level 3: 1 study; level 4: 3 studies), Atomizer/exhalational device – C (Level 2: 2 studies; level 3: 2 studies), Irrigation tubes – C (Level 2: 2 studies, Level 4: 1 study),
Benefit: Irrigations – Improvement in HR-QoL, subjective symptom scores and endoscopic appearance in postoperative patients. Atomizer/exhalational device – Improved subjective symptom scores and endoscopy scores,

Harm: Irrigations – minor (epistaxis, nasal irritation). No evidence of adrenal suppression using irrigation delivery. Atomizer devices – possible adrenal suppression; MAST – invasive insertion, epistaxis. See Table II-1.
Cost: Moderate to high (from USD$2.50 per day for budesonide respules, unknown costs of atomization/exhalational devices. MAST tube USD$100 for each tube + variable costs associated with insertion).
Benefits-Harm Assessment: Irrigations – Preponderance of benefit over harm, with increased cost compared to nasal sprays. Atomizer/exhalational device – Possible benefit, possible long-term harm. MAST – Limited evidence balancing harm and benefit.
Value Judgments: Evidence for irrigations good with best evidence in post-operative patients.
Policy Level: Irrigations – Recommended in postoperative patients, option for use in non-surgical/medical therapy patients. Atomizers/exhalational devices - Option. MAST – No recommendation.
Intervention: Corticosteroid nasal irrigations are recommended in CRSsNP in postoperative patients and an option in nonsurgical/medical therapy patients. The use of atomizers/exhalational devices is an option. No recommendation for MAST.

Table IX-27. Evidence for CRSsNP management with topical nasal corticosteroids (nonstandard delivery).

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Grayson [1089]	2019	1	Systematic Review	Steroid irrigation Steroid spray Placebo	SNOT-22 Endoscopy score	Best outcomes with large volume, low pressure devices.
Harvey [1077]	2018 (n=44)	2	DBRCT	12 month follow up; mometasone irrigation vs spray (both 2mg) post-ESS	VAS SNOT-22 Radiographic LM scores	Improved nasal blockage and LM score with fewer recurrences with irrigation.
Tait [1078]	2018 (n=61)	2	DBRCT	30 day course of budesonide vs. saline irrigations	SNOT-22 Clinical Global Impressions Endoscopy score	Improved SNOT-22 scores in budesonide group, particularly among CRSsNP, results not significant.
Thamboo [1086]	2014 (n=20)	2	RCT - unblinded	1 mg budesonide via mucosal atomization device 1 mg budesonide in 120 ml saline	SNOT-22 ACTH stimulation test Plasma cortisol levels	MAD-delivered budesonide improved SNOT-22. A slight

				via large volume irrigation		reduction in ACTH stimulated cortisol levels was seen.
Hansen [1071]	2010 (n=20)	2	DBRCT	Bi-directional spray 12 week course of: - Fluticasone propionate 400µg BID - Placebo	RSOM-31 Subjective symptoms Nasal endoscopy Peak nasal flow Acoustic rhinometry MRI sinuses	Fluticasone improved nasal symptom scores, endoscopic nasal edema, and peak nasal airflow.
Furukido [1069]	2005 (n=25)	2	RCT – single blinded	1 month course of once weekly irrigations via YAMIK sinus catheter - Saline solution -Betamethasone (0.4mg/ml) solution	Clinical symptom score Radiologic (Sinus x-ray score) Sinus effusion cytokine levels	No difference between study groups' clinical or radiological scores.
Lavigne [1066]	2002 (n=13)	2	DBRCT	Unilateral MAST catheter with 3 week daily irrigation with either: - 256µg budesonide - Placebo	Nonvalidated clinical response score Tissue eosinophil counts Tissue IL-4 and IL-5 levels	Treatment improved clinical response scores and reduced eosinophil counts and IL-4/5 levels.
Steinke [1081]	2009 (n=8)	3	Prospective, pilot, cohort study	3 month course of twice daily budesonide irrigations (500 µg into >100 ml saline)	Endoscopy score	Budesonide irrigations may improve endoscopy scores.
Sher [1084]	2020 (n=603)	4	Prospective, case series	Twice daily EDS-FLU exhalational device with 372 µg fluticasone BID x 12 weeks	Endoscopy score SNOT-22 PGIC	90% improvement on PGIC, significant reduction in SNOT 22, improved endoscopy scores.

Palmer [1085]	2018 (n=189)	4	Prospective case-series	12 month use of EDS-FLU 372mcg fluticasone BID	SNOT-22 Endoscopy score PGIC	Improved SNOT-22, endoscopy scores, anterior and posterior rhinorrhea, good safety profile.
Manji [1087]	2017 (n=100)	4	Cross sectional observational study	Patients treated with MAD and budesonide x >6 months	ACTH suppression test Intraocular pressure	6% with elevated IOP, 3% with adrenal insufficiency.
Snidvongs [1079]	2012 (n=111)	4	Prospective case-series	Once daily irrigations of 1 mg budesonide/ betamethasone in 240 ml saline	Symptom score SNOT-22 Lund-Kennedy endoscopy score Need for revision surgery Need for oral corticosteroids	Improvement in symptom score and SNOT-22 scores in CRSsNP. High tissue eosinophilia predicted better response.
Moshaver [1088]	2010 (n=13)	4	Prospective case series	Bilateral MAST catheter insertion with 3 weeks' daily irrigation of Tobramycin (10 ml of 0.8 mg/ml) and CiproxinHC® (0.4 ml of ciprofloxacin 2 mg/ml and hydrocortisone 10 mg/ml)	HRQoL (SNOT-16) Endoscopy scores	Significant reduction in both SNOT-16 and endoscopy scores, continuing at 16 week follow-up.
Sachanandani [1080]	2009 (n=9)	4	Prospective case-series	30 day course of 250 µg budesonide diluted into 5 ml of isotonic saline each nostril QID	SNOT-20 Adrenal function	Topical budesonide improved SNOT-20 scores, and did not affect adrenal function.

IX.D.3. Management of CRSsNP: Oral Corticosteroids

There are six, level 4 studies and two, level 2 studies that evaluate the benefit of oral corticosteroids in patients with CRSsNP. All include oral corticosteroids with other interventions including oral antibiotics, topical INCS, and saline irrigations. Four of the six include both CRSwNP and CRSsNP patients. The two groups are separated as much as possible in the following summaries.

Liu 2018[1090] described 100 patients diagnosed with CRSsNP, treated either with oral antibiotics, oral corticosteroids or both. The corticosteroid agents used were either methylprednisolone for 6 days or prednisone for 20 days. All three groups showed significant post-treatment improvements of their Lund-Mackay scores ($P \leq 0.002$). All three groups showed improvement in symptoms to varying degrees but this was not analyzed statistically. The number of patients ultimately requiring surgery was not significantly different among the three groups.

Poetker 2013[1091] performed an iterative systematic review of corticosteroid use in CRS and evaluated four level 4 studies. They report data showing both subjective and objective improvements in CRSsNP patients treated with oral corticosteroids. The risks of corticosteroids are acknowledged but the authors felt there is a balance of benefit to harm and recommend oral corticosteroids as an option.

Young 2012[1092] reported on 80 patients with CRS, 28 of whom also had nasal polyps, treated with three weeks of oral antibiotics, a prednisone taper, topical budesonide spray (200 mcg to each nostril BID) and saline washes. Patient symptoms were assessed via visual analog scale before and three months after starting therapy. Results did not specify response in patients with or without polyps, however 30 patients reported sufficient improvement such that surgery was not offered. The presence of polyps was not found to be a predictive factor for the need for surgery.

Lal and Hwang 2011[1093] performed a systematic review of corticosteroid use in CRSsNP patients. They included 30 studies in their review, most of which were level 4 or 5 evidence. They identified no RCTs and no studies evaluating corticosteroids as a single therapeutic agent for CRSsNP. The single level 3 study included addressed the use in children. Lal and Hwang emphasized the widespread use despite the paucity of data on corticosteroid and encouraged more research be done.

Lal 2009[1094] reported on 145 patients, 82 of which were CRSsNP. All patients received 4 weeks of antibiotics, a 12-day corticosteroid taper, intranasal corticosteroid sprays, topical intranasal decongestant spray, and saline irrigations. Post-treatment, patients were followed for a minimum of 8 weeks. Of the CRSsNP cohort, 55% of patients were "successfully" treated, defined as complete resolution of symptoms. Forty-five percent "failed" medical therapy, defined as persistent symptoms, and 22 (31%) remained symptomatic enough to elect to pursue surgery. Combined therapy with oral corticosteroids, antibiotics and intranasal corticosteroid spray together did not allow assessment of benefit due to oral corticosteroids alone.

Hessler 2007[1095] prospectively followed CRS patients using the SNOT-20+1 (Sino-Nasal Outcomes Test-20 plus olfaction). Fifty of the patients that completed the study were CRSsNP. Patients were treated by a combination of medical therapy (antibiotics, oral corticosteroids, intranasal steroids, anti-histamines, anti-leukotrienes, herbal medications, saline) without a universal treatment algorithm. A non-significant improvement in the SNOT-20+1 scores was found in patients using prednisone for $\geq$11 days ($P=0.29$).

Subramanian 2002[1096] reported on 40 patients (23 CRSsNP) treated with a 10-day prednisone taper, 4-8 weeks of antibiotics, saline irrigations, and topical intranasal corticosteroid sprays. They reported significant improvements in symptom scores and Lund-Mackay CT scores post-treatment (P=0.0005); however no specifics were provided as to the timing of the post-treatment CT or symptoms scoring in these patients. Additionally, there was no way to determine the benefit from each component of the therapy.

Ikeda 1995[1097] evaluated the effect of oral corticosteroids alone on CRS symptoms. Twelve patients with CRSsNP based on nasal endoscopy and imaging, who had failed topical intranasal steroids, underwent olfactory testing before and after treatment with a 10-14 day taper of prednisone. The authors found significant improvements in both detection and recognition thresholds following the prednisone course (P <0.05, <0.01, respectively).

More recent data confirms what has been assumed in that corticosteroid use is associated with increased disease severity in CRSsNP. Yamasaki and colleagues evaluated CRSsNP patients and noted that when evaluated over a 12 month period, increased corticosteroid use reflected worse QoL.[28]

Despite the common use of oral corticosteroids for CRSsNP, high level evidence to support their use is lacking, even as part of a multi-drug regimen. Higher doses are associated with more side effects and though the cost of oral corticosteroids is low, potential costs due to adverse effects must be considered.[1098,1099] Given the potential risks of systemic corticosteroids, higher quality evidence supporting the use of steroids in CRSsNP patients is crucial to balance these risks.
There are no current studies evaluating the benefit of oral corticosteroids in the peri-operative period, representing a large gap in evidence and a potential area for future study.

Oral Corticosteroids for CRSsNP

Aggregate Quality of Evidence: C (Level 2: 2 studies; level 4: 6 studies).
Benefit: Subjective improvement in patient symptoms associated with CRS, objective improvement in imaging. May avoid need for surgery in some patients.
Harm: Risks of corticosteroids are well known (see Table II-1). Optimal duration and dosage have not yet been studied.
Cost: Low.
Benefits-Harm Assessment: Perceived balance of benefit to harm, but not objectively assessed adequately
Value Judgments: Improvement in patient symptoms is important.
Recommendation Level: Option.
Intervention: The use of oral corticosteroid in CRSsNP is an option and should be individualized based on patient preference and co-morbidities.

Table IX-28: Evidence for CRSsNP management with oral corticosteroids

Study	Year	Study design	LOE	Study group(s)	Clinical Endpoints(s)	Conclusion
Poetker [1091]	2013	Systematic review	2	4 level 4 studies involving oral corticosteroid use in		Subjective and objective improvements in

				CRSsNP patients.		CRSsNP patients from oral corticosteroids. Balance of benefit to harm and oral corticosteroids are an option for CRSsNP patients.
Lal [1093]	2011	Systematic Review	2	30 studies involving oral corticosteroid use in CRSsNP patients.		Very little data given the widespread use. More research is needed to measure outcomes of corticosteroid use in CRSsNP patients.
Liu [1090]	2018	Case Series, retrospective	4	Antibiotics, mean 19 days N = 17 Methylprednisolone for 6 days OR prednisone for 20 days.; N = 28; both antibiotics and oral steroids N = 55	CT Lund-Mackay score Nasal symptoms Need for surgery	53% of antibiotic group, 46% of corticosteroid group, 40% of the combo group had improved LM scores. All had improved symptoms of varying degrees. 40 of 100 required surgery.
Young [1092]	2012	Case series, retrospective	4	Prednisone 30, 20, 10mg for 7 days each and oral antibiotics (roxithromycin or doxycycline) for 21 days.	Visual analog scale of sinus symptoms before and 3 months after onset of therapy.	35% had nasal polyps. 37.5% reported sufficient improvement that surgery was not required.
Lal [1094]	2009	Case series, retrospective	4	Prednisone 60, 40, 20, 10mg for 3 days each in conjunction with 4 weeks of oral antibiotic, INCS, nasal saline rinses, topical nasal decongestant spray (5 days on, 3 days off).	Persistent symptoms	55% of patients were "successfully" treated, defined as complete resolution of symptoms

Hessler [1095]	2007	Case series, prospective	4	Patients treated medically and followed weekly with SNOT-20+1. No protocol for oral steroids.	SNOT-20+1	Non-statistically significant trend toward improved outcomes with ≥ 11 days of oral steroids
Subramanian [1096]	2002	Case series, retrospective	4	Prednisone 20mg twice daily x 5 days then 20 mg daily x 5 days and oral antibiotics for 4-8 weeks. Adjunctive therapies included nasal saline irrigations, INCS, antihistamines and decongestants.	CT Lund-Mackay score Nasal symptoms Time to relapse	Statistically significant improvement of CT Lund-Mackay scores and symptoms.
Ikeda [1097]	1995	Case series	4	Prednisolone, starting dose between 40-60mg for 10-14 days with a quick taper	Olfactory acuity tests	Significant improvement of olfactory detection and recognition.

IX.D.4. Management of CRSsNP: Antibiotics

IX.D.4.a. Antibiotics for CRSsNP: Oral Non-Macrolide Antibiotics for <3 Weeks

ICAR-RS-2016 found minimal evidence in this area and made no recommendations. For treatment of CRS with antibiotics for less than 3 weeks, the majority of the literature is focused on the treatment of AECRS. Despite the high utilization of this class of pharmacotherapy in CRS there is a surprising paucity of published evidence. High-quality prospective studies are lacking, but ICAR-RS-2016 evaluated several studies that addressed the short-term treatment of CRS with non-macrolide antibiotics.

Gehanno *et al.* observed 198 patients with diagnosis of CRS treated with ofloxacin for 12 days; however, these patients were not characterized by nasal polyposis.[1100] The study achieved a 93.7% improvement rate without any measurable objective outcome. There were a total of four double-blind randomized trials comparing two individual antibiotic regimens head-to-head without the inclusion of a placebo arm.[1101-1104] Clinical resolution of RS was the main endpoint in each study, and in none were there significant differences between treatment arms. None of these studies differentiated between CRSsNP or CRSwNP, and some treatment groups included AECRS and ABRS patients. Therefore, none of these studies was included in consideration of this updated EBRR.

Since ICAR-RS-2016 a single Cochrane review was published exploring systemic antibiotic usage in CRS.[1105] The authors found no studies that addressed this particular section's cohort. A literature search found only one new study evaluating the efficacy of non-macrolide antibiotics in CRSsNP with 3 weeks or less duration.

Liu *et al.* evaluated five years of patient data to compare patients with CRSsNP who were treated with 1) non-macrolide antibiotics, 2) steroids, or 3) a combination of the two.[1090] Patients were treated with a variety of antibiotics for a range of 10 to 21 days (median 21 days in the antibiotic only group and 14 days in the combination group) and/or a variable steroid regimen. The authors retrospectively evaluated improvement in CT Lund-Mackay score which necessitated that they exclude patients who did not have pre-treatment or post-treatment scans. They found that all groups had significant improvement in Lund-Mackay scores with no significant difference between the groups; the median pre-treatment score was 9 and improved to a median of 6. The authors found no difference in post-treatment need for surgery and they did not use a validated method of evaluating symptoms.

As of this update there continues to be minimal evidence on the efficacy of short-term (*i.e.,* <3 weeks) non-macrolide antibiotics in CRSsNP. Practitioners should use caution when prescribing these medications for this indication given the associated side effects. In the above studies the most common of these included gastrointestinal complaints, genitourinary infections, cutaneous rashes, and *Clostridium difficile* colitis (see Table II-1). The toll on patients and the cost on the healthcare system associated with these adverse events is significant. A review by Poetker and Smith found that medication errors were a common cause of medical litigation with antibiotics as the main source.[1106] In sum, the dearth of rigorous clinical studies and a focus on AECRS in most studies precludes the ability to make recommendations regarding the use of non-macrolide antibiotic for 3 weeks or less in CRSsNP.

Oral Non-Macrolide Antibiotics for <3 Weeks for CRSsNP

Aggregate Grade of Evidence: Not applicable

Table IX-29. Evidence for CRSsNP management with oral non-macrolide antibiotics for <3 weeks.

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Liu [1090]	2018	4	Retrospective cohort	Oral antibiotics Oral steroids Combination	Lund-Mackay score Symptoms Rate of surgery	Improvement in CT scores in all groups

IX.D.4.b. Antibiotics for CRSsNP: Oral Non-Macrolide Antibiotics for >3 Weeks

There has been no change in the literature on this topic since ICAR-RS-2016. While there is significant research on the role of prolonged treatment with macrolide antibiotics for CRSsNP, there are few studies evaluating non-macrolide therapies. Two early studies were observational, utilizing "maximal medical treatments" including antibiotics for 4 weeks in a total of over 240 patients, but neither distinguished outcomes between patients with polyps or without.[1096,1107] These studies were therefore not included in this EBRR.

A prospective study by Dubin *et al.* examined treatment duration with oral antibiotics in CRSsNP patients.[1108] A total of 35 patients with CT scan-confirmed CRSsNP were prescribed culture-directed antibiotics, clindamycin, or amoxicillin/clavulanic acid for a total of 6 weeks. Sequential CT scans were obtained at weeks 3 and 6 and compared to their baseline for any improvement using the Lund-Mackay (LM) scoring system. Only 45% of the patients (n=16) completed the full 6 weeks of therapy and obtained the 2 interval CT scans. The authors noted a significant improvement in average CT scores between the baseline scan (LM=8.9) and the interval scan at week 3 (LM=4.38). Although there were no

significant improvements between week 3 and week 6 (LM=4.125) the authors noted that a subset of patients (38%) did have a significant improvement in LM scores. The safety profile of the prolonged treatment was good; the only adverse event noted was gastrointestinal upset in 8% of patients. Based on this objective CT data the authors concluded that a longer course of therapy is safe and may be indicated to achieve radiographic improvement and disease resolution. Given the limitations of the study, however, they could not determine causation for the improvement in LM scores and therefore did not recommend prolonged antibiotics as a rule.

As of now there is only one study in the literature regarding this cohort and only 38% of the patient population in that study showing improvement with extended treatment duration. Lack of rigorous evidence therefore limits any recommendation of non-macrolide oral antibiotics for longer than three weeks in standard treatment of CRSsNP.

Oral Non-Macrolide Antibiotics for >3 Weeks for CRSNP

Aggregate Grade of Evidence: Not applicable

Table IX-30. Evidence for CRSsNP management with oral non-macrolide antibiotics for >3 weeks.

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Dubin [1108]	2007	5	Prospective case series	Oral antibiotics	Lund-Mackay score	Improvement in LM scores at 3 weeks and 6 weeks

IX.D.4.c. Antibiotics for CRSsNP: Macrolide Antibiotics

The presumed effects macrolides have on CRS are in reducing mucus production, inhibiting biofilm formation, producing oxidative species, inhibiting neutrophils, enhancing MCC, and lowering cytokine production.[1109]

In 2006, Wallwork *et al.*[1110] conducted an RCT on CRSsNP patients treated with roxithromycin for 3 months or with placebo. They found significant improvements in SNOT-20, nasal endoscopy, saccharine transit time, and IL-8 levels in lavage fluid. In contrast, Videler *et al.*[1111] published an RCT in 2011 evaluating the efficacy of azithromycin for recalcitrant CRS both with and without nasal polyps and found no significant benefit of long-term azithromycin over placebo in either QoL outcomes, endoscopy, peak nasal inspiratory flow, Sniffin' Sticks smell tests, or middle meatus culture.

Zeng *et al.*[1072] compared the efficacy of clarithromycin versus mometasone furoate in CRSsNP patients. After 4 weeks of therapy, they found improvements in symptoms and endoscopic findings were comparable across both groups. In an RCT, Jiang *et al.*[1112] compared the efficacy of erythromycin versus Chinese herbal medicine in the treatment of CRSsNP, demonstrating both groups had a significant but comparable decrease in SNOT-20 scores after 8 weeks of treatment.

Majima *et al.*[1113] examined the effects of clarithromycin in patients with CRSsNP or those with limited polyps in a cohort study and reported significant improvements in SNOT-20 and computed tomography scores. In comparing the combination of clarithromycin and budesonide spray with budesonide spray

alone for treatment of CRS patients, Deng *et al.*[1114] found that the improvement in SNOT-22, visual analog scale, CT and endoscopic scores that was seen did not significantly differ between the two groups. However, Amali *et al.* [1115 1115] found that azithromycin with nasal steroid showed significant improvement in SNOT-22 scores compared with nasal steroid alone in post-ESS CRS patients. Haxel *et al.*[1116] published an RCT in 2015 examining outcomes after three-month treatment with erythromycin in both CRS phenotypes following sinus surgery, demonstrating greater improvements in nasal endoscopy scores in CRSsNP patients when treated with erythromycin than in CRSwNP patients.

Several systematic reviews and meta-analyses have been conducted to assess the effect of macrolides in CRS. For instance, Pynnonen *et al.*[1117] systematically reviewed patient QoL outcomes after long-term macrolide therapy and, based on limited evidence from only 3 prospective clinical studies, did not recommend use in CRS patients. In a meta-analysis by Huang *et al.*[1118] in 2019, authors concluded that adding oral clarithromycin to intranasal steroid spray likely achieves better results than using intranasal steroid spray alone; however, evidence was insufficient to conclude that oral clarithromycin alone has similar efficacy as nasal spray alone. In two reviews evaluating the effect of macrolides in CRSsNP or CRSwNP, both ultimately concluded it is a treatment option, with one specifying it should only be used in select patients.[1119,1120] On a similar note, in 2019 Seresirikachorn *et al.*[1121] assessed prognostic factors that predicted favorable outcomes of low dose macrolides in treating CRS and found benefits in patients with CRSsNP as opposed to CRSwNP.

Gastrointestinal complaints are the most common side effects noted from use of macrolides in the CRS literature.[1111,1113,1114] Hepatotoxicity and ototoxicity may also occur.[1113] In addition, care should be taken when administering macrolides to patients with cardiac comorbidities.[1120] Concerns have also been raised about the development of antibiotic resistance with use of macrolides, particularly for long durations and at low doses.[1122] Videler *et al.*[1111] reported that one bacterial culture demonstrated resistance to macrolides after previous azithromycin treatment. In the Jiang *et al.* study, bacterial culture rate increased and growth of gram-negative aerobic bacteria was heavier in patients who took erythromycin than in patients who took Chinese herbal medicine.[1112] Finally, macrolides are metabolized in the liver and have known interactions with drug metabolism via the CYP450 system.[1120]

Briefly, there are a total of 3 RCTs investigating macrolides for CRSsNP.[1072,1110,1112] Others on this topic were cohort or observational studies without controls. Based on these studies, macrolides demonstrate benefits in selected CRS patients. Currently, there are no definitive biomarkers or prognostic factors for macrolide treatment selection in CRS. However, Seresirikachorn *et al.*[1121] found benefits of macrolides in treating patients with the CRSsNP phenotype, as opposed to CRSwNP. Oakley *et al.*[1123] reported that patients with low tissue and serum eosinophilia may reflect an endotype suitable for a trial of macrolide therapy.

Macrolide Antibiotics for CRSsNP

Aggregate Grade of Evidence: B (Level 1: 5 studies; level 2: 7 studies; level 3: 1 study).
Benefit: Some studies show reduction in endoscopy and symptom scores, others show no benefit.
Harm: Gastrointestinal side effects, ototoxicity, hepatotoxicity, cardiotoxicity, and drug-drug interactions; potential microbial resistance (see Table II-1).
Cost: Low.
Benefits-Harm Assessment: Mixed results about benefits and potential for harm make a balance unclear.
Value Judgments: Optimal drug, dosage, and treatment duration are not known.

Policy Level: Option.
Intervention: Macrolides are an option for patients with CRSsNP, especially for pateints at low risk of harm.

Table IX-31. Evidence for CRSsNP management with macrolide antibiotics

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Huang[1118]	2019	1	Meta-analysis	CRSsNP or CRSwNP 7 studies	TNSS, VAS, endoscopy score, CT score	Adding clarithromycin to INCS ± nasal saline irrigation may yield better results than INCS ± nasal saline irrigation alone.
Seresirikachorn[1121]	2019	1	Meta-analysis	CRSsNP or CRSwNP 10 studies	SNOT, symptom score, CT score, endoscopy score	Favorable outcomes in patients with CRSsNP. A half dose of macrolides should be given for a duration of 24 weeks.
Cervin[1120]	2014	1	Systematic review	CRSsNP and CRSwNP. 2 RCTs 22 Open/cohort studies		Long-term macrolide therapy is an option in selected CRS patients.
Pynnonen[1117]	2013	1	Meta-analysis of RCTs	CRSsNP and CRSwNP. 3 RCT	SNOT	Insufficient evidence to recommend long-term macrolide therapy.
Soler[1119]	2013	1	Systematic review of RCTs and cohort studies	CRSsNP or CRSwNP. 2 RCTs 1 case-control study 14 prospective observational		Recommendation level: Option

				studies		
Deng[1114]	2018	2	RCT	CRSsNP (n=32), CRSwNP (n=42) 1. Clarithromycin 0.25 g/d and budesonide nasal spray 256 μg/d) for 3 months 2. Budesonide nasal spray 256 μg/d.	SNOT-22,VAS,CT score, endoscopic score	No significant difference between the groups.
Haxel[1116]	2015	2	RCT	CRSsNP or CRSwNP after ESS 1.Erythromycin 250mg daily (n=29) 2.Placebo (n=29) for 3 months	Inflammatory parameters in nasal secretion, SNOT-20, VAS, olfaction, SCT, endoscopy score	Nasal endoscopy scores were significantly improved in the erythromycin group compared to the placebo group.
Amali[1115]	2014	2	RCT	CRSsNP (n=38) and CRSwNP (n=28). 1. Azithromycin postoperatively 250 mg daily and fluticasone nasal spray for 3 months (n=22) 2. Control: fluticasone nasal spray postoperatively (n=44)	SNOT	The intervention group showed a statistically significant improvement in SNOT-22 scores compared with controls.
Jiang [1112]	2012	2	RCT	Chinese herb medicine with erythromycin placebo (n =26) Erythromycin 250mg (n=27) q12H for 8 weeks.	SNOT-20, endoscopy, SCT, bacterial culture rate	SNOT-20 significantly decreased in both groups. The SCT was shortened in more patients in the Chinese herbal medicine group than in patients in the

						erythromycin group.
Videler[1111]	2011	2	RCT	CRSsNP (n=29) and CRSwNP(n=31); 1. Medical group (n=30): azithromycin 500mg daily for 3 days at week 1, then weekly for 11 weeks. 2. Placebo (n=30).	SNOT-22,VAS, SF36, endoscopy, PNIF, Sniffin' Sticks smell tests, middle meatus culture	Azithromycin showed no benefit over placebo.
Zeng[1072]	2011	2	RCT	CRSsNP without ESS Mometasone furoate 200mcg daily (n=21) vs Clarithromycin 250mg daily (n=22) for 12 weeks	VAS, endoscopy scores	Mometasone and clarithromycin had comparable effect on CRSsNP.
Wallwork[1110]	2006	2	RCT	CRSsNP without ESS Roxithromycin 150mg/d (N=29) vs control (N =35) for 12 weeks	SNOT-20, patient response scale, peak inspiratory flow, SCT, endoscopic score, olfaction, nasal lavage assays	Improved SNOT-20, patient response scale, nasal endoscopy, SCT, and IL-8 level in lavage fluid.
Majima[1113]	2012	3	Cohort study	Clarithromycin 200mg daily (n=212) Clarithromycin 200mg daily + S-carboxymethylcysteine daily (n=213)	SNOT-20, subjective symptom score, CT score, nasal examination	SNOT-20 and CT scores were significantly improved in both groups. Clinical effectiveness was higher in the combination group than monotherapy group at 12 weeks.

IX.D.4.d. Antibiotics for CRS: Intravenous Antibiotics

Because of limited data, CRSsNP and CRSwNP are combined in this analysis and recommendations.

There have been no new publications in this area since ICAR-RS-2016. The evidence for IV antibiotics in the treatment of CRS is limited, with no differentiation of CRSsNP versus CRSwNP in the literature. In the literature, the use of IV antibiotics has been suggested in: 1) patients who are not surgical candidates, 2) cases in which oral antibiotic therapy has failed, 3) pediatric patients, 4) cases in which the infection being treated has no oral equivalent, 5) cases in which serious extra-nasal complications are present, and 6) as an adjuvant or alternative to surgery. Only one review of the literature from 2004 was identified; Tanner *et al.* reviewed four case series of which three were retrospective and one prospective.[1124]

Gross *et al.* reported outcomes of 13 patients receiving culture-directed IV antibiotics following ESS and one patient receiving IV antibiotics as an alternative to surgery.[1125] Indications for IV therapy included 1) pathogen resistance to effective oral antimicrobial agents, 2) patient intolerance or allergy to effective oral antimicrobial agents, and 3) extranasal complications of CRS (*e.g.*, orbital cellulitis, frontal osteomyelitis). The duration of outpatient therapy was four weeks delivered via peripherally inserted central catheter. Clinical endpoints examined response to therapy; of the 14 patients treated, 79% were noted to show a partial or complete response. Adverse events were reported in five patients (35%), including three catheter-related events (two patients with thrombophlebitis and one patient with deep vein thrombosis) and two allergic drug reactions.

Fowler *et al.* reported a retrospective case series of 31 CRS patients who failed three courses of oral antibiotics and were subsequently treated with 4-8 weeks of culture-directed IV antibiotics.[1126] Only 29% of patients were noted to have resolution of disease on CT scan or nasal endoscopy following treatment. Of these responders, 89% relapsed at an average of 11.5 weeks after cessation of therapy. Complications occurred in 10 patients (32%) including thrombophlebitis, peripheral venous thrombosis, catheter infection, red man syndrome, diarrhea, and neutropenia.

Anand *et al.* reported a prospective case series of 52 non-surgical patients, all with evidence of osteitis of the paranasal sinuses on CT scan.[1127] However, 45 of these patients were enrolled based on subjective symptomatology alone without report of endoscopic findings nor mucosal thickening on imaging. All patients were treated with culture-directed antibiotics for a period of 6 weeks; a wide variety of antibiotics were utilized. Clinical endpoints included patient-reported symptom scores and RSDI scores; there was significant improvement in patient-reported symptom scores noted at 3 weeks after completion of therapy. RSDI was only recorded from a subset of 7 patients, and thus, despite a trend toward improvement, significance could not be calculated. Minor complications were reported in 7 patients (13%) and included rash, elevations in liver enzymes, neutropenia, septicemia, and bleeding at the peripherally inserted central catheter (PICC) insertion site.

Tabaee *et al.* performed a retrospective analysis of CRS patients with endoscopic cultures positive for MRSA who then underwent 6-8 weeks of IV antibiotics.[1128] Of the 6 patients that the authors treated, 5 had improvement in SNOT-20 scores with pretreatment median of 62 dropping to a post-treatment median of 43. Interestingly, the one patient whose SNOT-20 scores did not improve had negative cultures post-treatment. Five of 6 patients were culture negative at follow-up (median follow-up 1.3 years). Adverse reactions were recorded in 4 of 6 patients (67%) and included allergic reactions and neutropenia.

There is some limited literature regarding use of IV antibiotics in the pediatric CRS population. Don *et al.* published a retrospective case series of 70 pediatric patients who had failed a 3-4 week course of oral antibiotics.[1129] All patients had post-treatment CT scans with disease, underwent operative nasal endoscopy with maxillary aspiration/irrigation, and then had culture-directed, outpatient IV antibiotics for at least one week. Adenoidectomies were performed at the surgeon's discretion. The primary endpoint was symptomatic improvement. The mean duration of therapy was 17 days (range 7-42 days). Immediately following IV antibiotics, the authors report that 62 patients (89%) were improved. After six months, there was data on 52 patients, of whom 44 (88%) were improved. However, the majority of patients (67%) were also placed on oral antibiotics after their IV courses (range 4-16 weeks). Ten patients (14%) developed complications, mostly related to the catheter.

This protocol was repeated by Adappa *et al.* with the addition of concurrent adenoidectomy for all patients.[1130] Immediately following cessation of culture-directed antibiotics (mean 5 weeks, range 1-10 weeks) all 22 pediatric patients were symptomatically improved (100%). After twelve months, 17 of 22 patients were symptom free (77%). Two patients (9%) had line-related complications. Criddle *et al.* reviewed the charts of pediatric CRS patients who had failed a 3-week course of oral antibiotics.[1131] Twenty-three patients underwent adenoidectomy and maxillary irrigations and afterward were placed on culture-directed, oral double-therapy antibiotics. Four patients did not improve after 4 weeks of oral treatment and were placed on 3-4 weeks of outpatient IV antibiotics. All four patients achieved short-term resolution of symptoms but 3 had recurrent symptoms in follow-up that responded to oral antibiotics. All four patients were later tested and found to have various immune deficiencies. One of the four had diarrhea requiring hospitalization and change in antibiotic (25%).

The high rates of complications associated with use of IV antibiotics noted above was also reported in a subsequent larger patient series. In a 2005 chart review, Lin *et al.* examined 177 patients who underwent IV antibiotic therapy for CRS.[1132] The majority receiving some combination of ceftriaxone, clindamycin, and/or vancomycin. The overall complication rate was reported at 18%, with 16% antibiotic-related adverse events (*e.g*., neutropenia, elevated LFTs, and rash) and 2% catheter-related adverse events (*e.g*., thrombosis).

The current literature regarding the treatment of CRS with parenteral antibiotics is sparse. One challenge is that IV antibiotics are frequently used as a "last resort" and therefore standardization and guidelines of appropriate use are not well established. The published studies are case series, often with subjective endpoints, resulting in data that are difficult to evaluate and compare. In addition, there is a substantial rate of adverse events noted with both PICC placement and antibiotics (9-67% in the reviewed studies). Further, practitioners may need to take into account the patient's time and cost burden of PICC placement, antibiotics, and home health care. A large review by Mitchell *et al.* found conflicting evidence on the cost-efficacy of long-term IV antibiotics.[1133] For these reasons, we recommend against the use of IV antibiotics for standard therapy in CRS. However, for a subset of patients with CRS complications, extranasal manifestations of CRS, or lack of response to standard oral therapy the benefits of treatment may outweigh the cost and risk of possible adverse events.

Intravenous Antibiotics for CRSsNP

Aggregate Grade of Evidence: C (Level 4: 7 studies).
Benefit: Potential improvement in patient-reported symptoms in case-series studies.
Harm: Thrombophlebitis, neutropenia, sepsis, deep vein thrombosis, elevated liver enzymes, allergic events, rash, bleeding, gastrointestinal disturbance (see Table II-1).

Cost: High.
Benefits-Harm Assessment: Preponderance of harm over benefits.
Value Judgments: Lack of evidence, risk of adverse events, and cost of treatment outweigh the possible benefit for routine use in CRS.
Policy Level: Recommendation against.
Intervention: Intravenous antibiotics should not be used for routine cases of CRS. For extenuating circumstances such as nonoperative patients, those who have failed oral/topical therapy, or those with extranasal manifestations of CRS the benefits of treatment may outweigh the risks.

Table IX-32. Evidence for CRS management with IV antibiotics

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Criddle [1131]	2008	4	Case series (pediatric)	IV antibiotics (4 patients)	Short-term response	100% symptomatic improvement
Tabaee [1128]	2007	4	Case series	IV antibiotics (MRSA) (6 patients)	SNOT-20 Culture response	83% symptomatic improvement and culture negativity
Adappa [1130]	2006	4	Case series (pediatric)	IV antibiotics (culture-directed) (22 patients)	Short-term response One-year response	100% symptomatic improvement initially, 77% at one year
Anand [1127]	2003	4	Prospective case series	IV antibiotics (culture-directed) (52 patients)	Symptom scores RSDI	Significant improvement in symptom scores
Fowler [1126]	2003	4	Case series	IV antibiotics (culture-directed) (31 patients)	Resolution (defined by CT or endoscopy) Relapse rate	29% with resolution 89% with relapse at average of 11.5 weeks
Gross [1125]	2002	4	Case series	IV antibiotics following surgery (13 patients)	Short-term response	50% showed complete resolution
Don [1129]	2001	4	Case series (pediatric)	IV antibiotics (70 patients)	Short-term response	89% symptomatic improvement

IX.D.4.e. Antibiotics for CRS: Topical Antibiotics

Because of limited data, CRSsNP and CRSwNP are combined in this analysis and recommendations.

The goal of topical antibiotic therapy in CRS is to deliver a high concentration of antibiotics directly to the diseased sinonasal mucosa, thereby increasing efficacy and decreasing systemic absorption and associated side effects compared to oral antibiotics. Disadvantages to topical antibiotic therapy include user-dependent variations in delivery technique, local adverse effects, and limited long-term data. Studies on topical antibiotic delivery do not distinguish between those with CRSwNP and CRSsNP. Additionally, the majority of studies focus on the subpopulation of recalcitrant CRS patients after ESS. However, post-ESS patients seem to be an appropriate target for topical therapy as studies have shown that very little irrigation penetrates native paranasal sinuses and that ESS greatly improves penetration,

especially into the frontal and sphenoid sinuses.[1076,1134,1135] Carlton *et al.* published a review of this topic in 2019 which includes the majority of updates since the first iteration of these guidelines.[1136] Seven RCTs and nine systematic reviews have examined topical antibiotics in CRS.

Videler *et al.* performed a randomized, placebo-controlled, double-blind, cross-over pilot study in 14 people with refractory CRS post ESS having persistent *Staphylococcus aureus* after two treatments of oral antibiotics and nasal saline irrigations.[1137] Patients were randomized into groups of high-dose nebulized bacitracin-colimycin (8 weeks) and oral levofloxacin (2 weeks) or nebulized saline (control) and oral levofloxacin (2 weeks). Although nebulization improved CRS symptoms, it did not show benefit of bacitracin/colimycin over the nebulized saline. Authors acknowledge that this study was underpowered and may have been confounded by levofloxacin.

Sykes *et al.* investigated the additive effective of neomycin with a nasal spray of trazoline and dexamethasone compared to saline placebo.[1074] They studied 50 patients with symptoms of chronic purulent nasal drainage although there was no mention of prior surgical therapy. Comprehensive outcome measures were used including nasal MCC, imaging, rhinomanometry, bacterial cultures, and endoscopy. Both therapy groups showed improvement in objective measures of disease and no added benefit was seen with topical neomycin.

Desrosiers *et al.* looked at twenty patients with a history of post-ESS recalcitrant CRS who were randomized to nebulized tobramycin with saline compared to saline placebo alone for a total of 4 weeks.[1138] Tobramycin was found to improve pain more quickly than saline, but led to the side effect of nasal congestion. Both groups showed similar improvement in symptoms and QoL, and overall, tobramycin did not offer any significant benefit over saline.

Head *et al.*[1105] performed a Cochrane systematic review of topical antibiotics for CRS and did not find any RCTs that met inclusion criteria, which were studies comparing topical antibiotic treatment to (a) placebo or (b) no treatment or (c) other pharmacological interventions with at least 3 month follow-up, indicating that the available evidence could be stronger. Eight systematic reviews have nonetheless summarized the available evidence on topical antibiotics in CRS. The most comprehensive systematic review[1139] inclusive of four systematic reviews[1119,1140,1141 1142] concluded that topical antibiotics were not recommended due to lack of clear benefit, but made special mention that there may be a role for topical mupirocin in recalcitrant cases of *Staphylococcus aureus*. Kim and Kwon[1143] performed systematic review of this subgroup of patients with recalcitrant staphylcoccal CRS treated with topical mupirocin. Evidence of two RCTs, two prospective studies, and two retrospective reviews indicate a short-term effect on reducing staphylococcal infection, however high level studies are needed to evaluate the durability of eradication and assessment of long-term risk. Jervis-Bardy *et al.*[1144] report low rate of mupirocin resistance, and Carr *et al.*[1145] reported changes to the sinonasal flora after mupirocin treatment with an increase in gram-negative species and more *Corynebacterium species*. The clinical implications of this shift in the microbiota are unknown.

Existing high-level evidence of topical antibiotics in CRS fails to consistently demonstrate benefits and routine use cannot be recommended. Some lower-level studies have reported effectiveness, particularly in recalcitrant cases of CRS after ESS or in CF patients,[1146-1154] suggesting there may be a role in unusual cases, but higher level studies in these subgroups are needed. New ciprofloxacin-eluding stents have shown potential in-vitro and in a rabbit model, however they have not been studied in humans.[925]

Topical Antibiotics for CRSsNP

Aggregate Grade of Evidence: A (Level 1: 7 studies; level 2: 7 studies; level 3: 2 studies, level 4: 3 studies).
Benefit: Systematic reviews and RCTs failed to show benefit from the use of topical antibiotics in CRS.
Harm: Nasal congestion, irritation, epistaxis. Theoretical possibility of systemic absorption with topical aminoglycosides. Possibility of developing bacterial resistance.
Cost: Moderate to high (USD$2.64 to USD$7.64) per dose, need for compounding pharmacy depending on antibiotic and formulation.
Benefits-Harm Assessment: Relative harm over benefit
Value Judgments: Topical therapy may be a preferable alternative to IV therapy for infections caused by organisms resistant to oral antibiotics.
Policy Level: Recommendation against.
Intervention: Topical antibiotics are not recommended for routine CRS. They may be beneficial in unusual circumstances.

Table IX-33. Evidence for CRS management with topical antibiotics.

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Head [1105]	2016	-	Cochrane systematic review			No studies met inclusion criteria. No recommendation.
Kim [1143]	2016	1	Systematic Review and meta-analysis			Topical mupirocin is an effective short-term treatment for recalcitrant staphylococcal CRS.
Rudmik [1139]	2015	1	Systematic review of RCTs with heterogeneity			Routine use not recommended. High volume mupirocin may be beneficial in recalcitrant *S. aureus.*
Lee[1155]	2014	1	Systematic review with heterogeneity			Topical antibiotic therapy not recommended as first-line therapy, but may be considered for recalcitrant CRS.
Rudmik [1141]	2013	1	Systematic review with heterogenei			Recommend against topical antibiotic due to

			ty			insufficient clinical research.
Soler [1119]	2013	1	Systematic review with heterogeneity			Use of topical antibiotics recommended against due to lack of evidence.
Woodhouse [1156]	2011	1	Systematic review of RCTs with heterogeneity			Nebulized antibiotics cannot be recommended due to lack of evidence.
Lim [1140]	2008	1	Systematic review with heterogeneity			Topical antibiotics may be effective, but further high-level studies are required.
Mainz [1150]	2014	2	DBRCT	Patients with CF 1. Nebulized 80 mg tobramycin 28 days (n=6) 2. Nebulized saline 28 days (n=3)	*P. aeruginosa* colony count QoL Symptoms Otologic/renal safety	Nebulized tobramycin in CF may reduce *P. aeruginosa.* Higher level studies needed.
Huang [1157]	2013	2	Review with heterogeneity			Additional studies required to evaluate efficacy of topical antibiotics
Jervis-Bardy [593]	2012	2	DBRCT	Post-ESS recalcitrant infection with *s. aureus* 1. Mupirocin rinses + PO placebo (n=9) 2. Saline rinses + PO amoxicillin/clavulanate (n=13)	Bacterial culture Symptoms QoL Nasal endoscopy	Short-term effect on *S. aureus* clearance with mupirocin, but no effect on long-term outcomes
Wei [1158]	2011	2	DBRCT	Pediatric CRS 1. 6 weeks saline rinse + gentamicin (80mg/1000ml) (n=21) 2. 6 weeks saline rinse (n=19)	CT QoL	No benefit of topical antibiotic compared to saline.
Videler [1137]	2008	2	DBRCT cross-over pilot study	Post-ESS recalcitrant infection with *S. aureus* 1. Nebulized	Symptoms QoL questionnaire Nasal endoscopy	No benefit seen with topical antibiotic.

				bacitracin-colimycin + 2 weeks PO levofloxacin 2. Nebulized saline + 2 weeks PO levofloxacin (Total n=14)		
Desrosiers [1138]	2001	2	DBRCT	Post-ESS recalcitrant CRS 1. Tobramycin-saline nebulization TID for 4 weeks 2. Saline-quinine nebulization TID for 4 weeks (Total n = 20)	Symptoms QoL Nasal endoscopy	No benefit seen with topical antibiotic.
Sykes [1074]	1986	2	DBRCT	Neomycin, tramazoline, dexamethasone (n=20) Tramazoline, dexamethasone (n=20) Placebo (n=10)	Nasal MCC Sinus X-ray Nasal rhinomanometry Bacterial cx Nasal endoscopy	No benefit seen with topical antibiotic.
Ezzat [1151]	2015	3*	Prospective, controlled trial	Topical ofloxacin drops 12 weeks (n=15) No antibiotics (n=25)	Symptoms Nasal endoscopy CT scan Culture SEM	Ofloxacin may reduce biofilm in recalcitrant CRS cases.
DiCicco [1152]	2014	3	DBRCT pilot study	Patients with CF 1. Hyaluronate nasal spray (N=13) 2. Hyaluronate-tobramycin nasal spray (N=14)	Symptoms Nasal endoscopy Bacterial load Tolerability	Hyaluronate-tobramycin spray failed to improve symptoms or bacterial load in CF patients.
Lee [1153]	2016	4	Retrospective case series	Recalcitrant CRS high volume culture-directed antibiotics BID for 1 month (N=58)	Symptoms Nasal endoscopy Culture	Topical culture-directed antibiotics may be beneficial in recalcitrant CRS. Higher-level studies are needed.
Carr [1145]	2016	4	Case series	Recalcitrant CRS BID mupirocin irrigations for at least 1 week (n=22)	Culture	Topical therapy did not reduce bacteria but may lead to overgrowth of

						Corynebacterium and gram-negative bacteria.
Maniakas [1154]	2014	4	Retrospective case series	Recalcitrant CRS after ESS and failed BID budesonide. Added azithromycin TIW (N=12)	Symptoms Nasal endoscopy	Azithromycin added to budesonide irrigations may reduce symptoms of CRS.

*insufficient information, high risk of bias, downgraded to 3

IX.D.5. Management of CRS: Antifungals

Because of limited data, CRSsNP and CRSwNP are combined in this analysis and recommendations.

At the end of the 1990s, the use of topical antifungals for CRS started to rise in popularity with the publication of studies such as those by Ponikau *et al.*[616] To date this remains a controversial area due to data from studies of both topical and systemic antifungal agents that both support and refute their usage in CRS.[1159] A 2018 Cochrane review therefore considered the evidence for both oral and topical antifungals in CRS.[618] The review considered a mixed group of eight studies with either CRSsNP, CRSwNP, CRS in which NP was not recorded or CRSwNP and CRSsNP in the same study. These two sections provide the opportunity to revisit the evidence and consider new additions since 2018.

IX.D.5.a. Antifungals for CRS: Oral Antifungals

Searches revealed only one study for CRS patients with or without polyps when allergic fungal RS was excluded. This study by Kennedy *et al.*[1160] used an oral antifungal in the form of terbinafine tablets (625 mg/day) for six weeks. This study included 53 adult CRS patients in which the phenotype for with or without polyps was not distinguished, were entered into a double blind RCT of terbinafine (n=25) versus placebo (n=28). The above dose used in the trial appears to be a high dose in accordance with prescribing guidelines such as the British National Formulary which recommends 250 mg/day. Patients who had undergone ESS within 3 months prior to recruitment, were not included in the study. Outcome measures included percentage change in Lund-Mackay scores (primary) and QoL scores and patient and clinician rating of their CRS and therapeutic response (secondary). Nine patients failed to complete the study – four in the terbinafine and five in the placebo group.

There was no statistically significant difference observed between active and placebo treatment with respect to QoL (Rhinosinusitis Disability Index), CT scores or patient symptoms, albeit with limited data reported and the data spread indicating very large variations in the results. A key limitation of this study was the use of the CT scan scores as the primary outcome measure as radiological changes correlate poorly with symptom scores.[1161] Of the participants in the terbinafine group, one had elevated liver enzymes and another experienced gastrointestinal disorders and in the placebo group three participants experienced gastrointestinal side effects.

On the basis of the one available study, there is no evidence to support the use of systemic antifungal treatment in the routine management of CRSsNP.

Oral Antifungals for CRSsNP

Aggregate Grade of Evidence: not applicable.

Table IX-34. Evidence for CRS management with oral antifungals

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Kennedy [1160]	2005	1	RCT	Terbinafine 625 mg/day Placebo	Lund Mackay score QoL score rating of CRS and response to treatment	No benefit of systemic antifungal over placebo

IX.D.5.b. Antifungals for CRS: Topical Antifungals

Few studies on topical antifungals in CRS separated CRSsNP and CRSwNP. Due to the limitations of the studies identified within the Cochrane review, the results here are presented as a summary of all studies for topical antifungals in both CRSsNP and CRSwNP. Some studies defined inclusion as unresponsiveness to previous medical therapy for CRS.[1162,1163] Liang *et al.* definitively excluded CRSwNP cases[1164] and one study did not provide details about whether participants had NPs.[1163] Five studies cited NPs as an inclusion criterion;[1165-1169] the remaining four studies reported polyps in 20%,[1170] 35.6%,[1171] 43.8%[1162]and 81.9%[1172] of participants. Four studies excluded patients with AFRS[1165-1167,1172] and one study reported on double density signs and positive fungal cultures being present in 29% and 30% of cases, respectively, but did not definitively diagnose AFRS.[1168] The remainder failed to report any evidence for AFRS. One study had aspirin sensitivity present in 77% of participants.[1165]

From the eleven studies that investigated the use of topical antifungal agents, amphotericin B was used in ten studies and fluconazole in only one study. The Cochrane review of 2018 summarized the evidence for topical antifungals[618] and there were three additional RCTs published after the review that have been included here.[1168,1170,1171] The delivery methods varied among the studies with nasal irrigations being most popular, [1164,1168,1170-1172] followed by syringe delivery[1163,1165,1166]; Weschta *et al.* and Gerlinger *et al.* used a spray delivery method[1167,1169] and Hashemian *et al.* formulated the fluconazole as nasal drops.[1162]

Inclusion criteria were variable with some studies being mixed and some included participants having had prior ESS. Outcome measures assessed included endoscopic scores, radiological scores, generic and disease specific HRQoL scores, serum IgE levels and side effects. In the study by Zia *et al.*, participants had not undergone any previous nasal surgery but underwent ESS and were then randomized in a 1:2 ratio of amphotericin to placebo due to a lack of funding.[1168]

Seven studies reported the results of nasal endoscopy and four studies assessed the extent of nasal polyps on a scale of 0 to 4 for each side[1162,1163]or 0 to 3 each side.[1167,1169] Other studies used a generic endoscopic score[1164,1172] and one study simply reported on polyp recurrence.[1165] Five studies measured CT score either using the percentage change in opacification and or variations of the Lund-Mackay score.[1162,1163,1167-1169]

Validated HRQoL scores were used in six of the studies; RSOM-31,[1172] Chinese RSOM-31,[1164] Persian RSOM-31,[1170] SNOT-20,[1162,1163] SNAQ-11[1169] and Taiwanese SNOT-22.[1171] There was however little consistency among these studies, and the other studies did not use a validated HRQoL score at all.[1165-1167] The studies also varied in the way the data from these scores were both reported and analyzed with a non-normal distribution in three of the four studies. Nonetheless in all studies with symptom scores, there were no reported differences between the groups. In two studies where only CRSwNP patients were recruited, disease severity was reported as the sum of five individual symptom scores.[1167,1172] Ebbens *et al.* also reported SF-36 scores but without evidence of any significant differences.[1172] Side effects of treatment were not fully reported by all studies. Ebbens *et al.* reported on epistaxis and headache symptoms.[1172] Four other studies reported on local discomfort.[1163,1165,1166,1170] Overall it was noted that there was a lack of standard reporting of outcome measures across the studies in the Cochrane review.

In contrast with the one oral administration study, the daily doses of topical antifungals used were lower than expected. This may reflect a lack of specific guidance in prescribing authorities however, typical rhinology clinical practice dose regimens for amphotericin B would be approximately 20 mg per day. The studies involving Amphotericin B used 10 mg/day or less in six out of ten, which may be considered to be half of the 'usual' daily dose or less; it ranged from 0.5 mg/day to 20 mg/day and notably with varying concentrations, dosing regimens and delivery methods. In the one study using fluconazole, the dose used was 1.2 mg per day, also considered to be low.

Nonetheless disease-specific and generic HRQoL and disease severity showed no significant difference between the topical antifungals and placebo/no treatment groups. Endoscopy and CT scores similarly did not show any significant differences. Variable reporting of adverse events left uncertainty about any adverse effects, although the studies suggest that local irritation may be the most common adverse effect associated with topical antifungals. Other adverse effects included epistaxis and headache;[1162,1163,1166,1167,1172] one study reported a hypersensitivity reaction to amphotericin B.[1168]

The Cochrane Review concluded that the evidence was of *low* or *very low quality*. The risk of bias in the studies was low and although they were considered to have been well conducted, only one study had more than 80 participants. These studies were generally small. Also, these studies have often sampled mixed CRS populations or failed to define cases of AFRS for exclusion; the context of AFRS should be considered separately. Although two studies appeared to have evidence of improvement on CT[1163] or polyp scores,[1165] neither study found evidence of symptomatic improvement and thus the clinical significance of these findings is likely to be negligible. There were variable delivery methods used in the studies, but this did not result in any major differences in the outcomes. On the basis of the available studies, there is no evidence to support the use of topical antifungal treatment in the routine management of CRSsNP or CRSwNP. No further studies should be conducted without strict eligibility criteria and use of the Core Outcome set for RS.[1173]

Topical Antifungals for CRSsNP

Aggregate Grade of Evidence: A (Level 1: 1 study; level 2: 11 studies)
Benefit: No apparent benefit from using topical antifungals
Harm: Treatment generally well tolerated with potential for local irritation; possible epistaxis and headache less common
Cost: 50 mg of Amphotericin B is £3.88 or USD$4.86 – given maximum daily dose seen in these studies was 20 mg/day, 4 weeks of treatment would cost USD$54.43

Benefits-Harm Assessment: Minimal risk of harm but no apparent potential for benefit
Value Judgments: The role in selected cases of AFRS is not considered here.
Policy Level: Strong Recommendation Against
Intervention: Topical antifungal agents are not recommended for CRSsNP or CRSwNP

Table IX-35. Evidence for CRS management with topical antifungals

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Head[618]	2018	1	Systematic review with meta-analysis	Topical antifungal therapy Placebo	Collated symptom scores QoL Adverse events	No benefit of topical antifungal over placebo.
Zia[1168]	2019	2	RCT	20mg amphotericin B daily (n=29) Placebo (n =58)	CT scans	Authors report improvement of CT scores. Unclear approporiateness of metric use.
Jiang[1171]	2018	2	RCT	20 mg amphotericin B (n=37) Placebo (n=36)	Taiwanese SNOT-22 Endoscopic score Smell test Saccharin test Acoustic rhinometry	No benefit of topical antifungal over placebo.
Yousefi[1170]	2017	2	RCT	4 mg amphotericin B (n=40) Placebo (n=40)	Persian RSOM-31 VAS CT and MRI scans Endoscopic score Cytokine levels	No benefit of topical antifungal over placebo.
Hashemian[1162]	2016	2	RCT	1.2 mg fluconazole daily (n=27) Placebo (n=24)	SNOT-20 score CT score Endoscopic score	No benefit of topical antifungal over placebo.
Gerlinger[1169]	2009	2	RCT	4 mg daily amphotericin B (n=16) Placebo (n=17)	Lund-Mackay CT score SNAQ-11 Generic QoL score Endoscopic score	No benefit of topical antifungal over placebo.
Liang[1164]	2008	2	RCT	20 mg amphotericin B daily (n=51) Placebo (n=46)	Chinese RSOM Endoscopic scores	No benefit of topical antifungal over placebo.
Ebbens[1172]	2006	2	RCT	10 mg amphotericin B (n=59) Yellow colored placebo (n=57)	Total and individual symptom VAS RSOM-31 SF-36	No benefit of topical antifungal over placebo.

					PNIF	
Corradini[1165]	2006	2	RCT	0.8 mg amphotericin B daily for 1 month then 0.5 mg daily either after ESS (n=16) or after triamcinolone (n=23) Two additional groups had no amphotericin (ESS = 25, triamcinolone = 16) All groups received lysine aspirin 4mg/day	Polyp recurrence at 20 months	Reduction in nasal polyp recurrence.
Ponikau[1163]	2005	2	RCT	20 mg amphotericin B daily (n=15) Placebo (n=15)	CT score SNOT-20	Improvement in CT over placebo. No improvement in symptom score.
Shin[1166]	2004	2	RCT	4 mg daily amphotericin B (n=16) 2 mg daily amphotericin B (n=14) placebo (n=11)	Cytokine levels	No benefit of topical antifungal over placebo.
Weschta[1167]	2004	2	RCT	4.8 mg daily amphotericin B (n=39) Placebo (n=39)	CT score (modified Lund Mackay) RQLQ Endoscopic score	No benefit of topical antifungal over placebo.

IX.D.6. Management of CRSsNP: Biologic Therapy

Following an extensive literature search, only one study of biologic therapy included CRSsNP subjects. Pinto, *et al.* conducted a randomized, double-blind, placebo-controlled trial of omalizumab, an anti-IgE biologic for 6 months, in 14 patients with severe, refractory CRS.[1174] Only two subjects had CRSsNP, and both were in the placebo arm. Based on a lack of data, omalizumab is not recommended for standard treatment of CRSsNP.

While some CRSsNP patients may also have eosinophilic inflammation,[1175,1176] biologics such as dupilumab may have a role in some CRSsNP but given that current evidence is lacking, further study in the CRSsNP population is needed in this specific subgroup.

The current literature demonstrates an absence of a well-designed investigation that has examined the role of biologics in the management and treatment of CRSsNP. No recommendation can be given based on currently available data.

Biologics for CRSsNP

Aggregate Grade of Evidence: Not applicable.

IX.D.7. Management of CRSsNP: Anti-Leukotriene Therapy

There have been few studies examining the therapeutic efficacy of anti-leukotriene (LT) therapy in CRSsNP, and no systemic reviews or meta-analyses. Furthermore, the existing studies often group CRS and AR together into the same study group, making it difficult to determine which subgroup of patients might derive the most benefit. An early case series of patients with allergic and non-allergic uncontrolled CRS suggested that the addition of montelukast to INCS may improve subjective symptom scores.[1177] There has been one RCT of 128 patients with severe allergic CRS that compared montelukast plus INCS to placebo plus INCS,[1178] and assessed outcomes with a QoL questionnaire and symptom scales. After 1 and 2 months of treatment, both the symptom and QoL scores were significantly more improved in the montelukast group compared with the placebo group, with additional improvements noted in allergy symptoms as patients in the montelukast group required significantly fewer rescue antihistamines to control allergic symptoms during the study period. Two additional randomized open-label studies of 30 patients[1179] and 100 patients[1180] with AR compared montelukast alone to INCS alone to montelukast plus INCS, for either a 1 month or a two-week study period, respectively. The Dalgic study specifically investigated the effects of the interventions on olfactory function in patients with AR and found that INCS alone or with montelukast improved olfaction as measured with Sniffin' Sticks, but montelukast alone did not, and the addition of montelukast to INCS offered no further benefit. The Chen study evaluated the effects of the interventions on symptom scores, fractional exhaled NO (FeNO), and nasal cavity volume, and found that all 3 treatment arms improved symptoms from baseline, and that the combination of montelukast plus INCS produced greater improvements in nasal congestion than either drug alone. One prospective open-label study of 75 AR patients [1181] compared the efficacy of montelukast to the antihistamine levocetirizine for the control of nasal and eye symptoms for 2 weeks, and reported that each drug and their combination were equally effective in controlling symptom scores.

In summary, one DBRCT of AR patients has shown benefit with the addition of montelukast to INCS for symptom improvement, though the patient symptoms were largely allergic in nature, without a clear diagnosis of true CRS. Three other studies, also largely of AR patients, demonstrated no or very limited symptom improvement with the use of montelukast. Montelukast may provide some benefit in AR, but it is unclear whether anti-LT therapy would provide benefit in non-allergic CRSsNP.

Anti-Leukotriene Therapy for CRSsNP

Aggregate Grade of Evidence: C (Level 2: 2 studies; level 3: 2 studies; level 4: 1 study)
Benefit: Improvement in symptoms for patients with comorbid AR, lack of evidence for utility in non-allergic CRSsNP.
Harm: Limited risks. Montelukast has been associated with rare neuropsychiatric events in postmarketing reports (see Table II-1).
Cost: Moderate.
Benefits-Harm Assessment: No clear benefit in undifferentiated patients with CRSsNP though there appears to be benefit in patients with comorbid allergy.
Value Judgements: Montelukast may be beneficial for allergic patients with CRSsNP who are not

sufficiently responsive to INCS.
Policy Level: No recommendation for non-allergic CRSsNP; Option for CRSsNP with comorbid allergy
Intervention: Montelukast is an option for CRSsNP patients with an allergic component to their disease, as an adjunct to INCS.

Table IX-36. Evidence for CRSsNP management with anti-leukotriene therapy

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Chen [1180]	2018	2	Randomized open-label study of 100 pts assigned to 2 wks of 256ug budesonide nasal spray, 10mg montelukast, or 128ug budesonide + montelukast	Seasonal Allergic Rhnitis	Symptom scores nasal cavity volume FeNO nasal mediator levels	All 3 treatment arms improved symptoms from baseline but the ½ dose budesonide + montelukast combo produced greater improvements in nasal congestion than either drug alone. FeNO was also more decreased by the combination than by either drug alone.
Goh [1178]	2014	2	RDBPCT of 128 patients: INCS + placebo vs INCS + montelukast	Allergic Rhinitis	Symptom scores QoL scores Medication usage	Improvements in symptom scores and QoL scores after 1 and 2 months were significantly greater in the montelukast + INCS than the placebo + INCS arm, with less rescue antihistamine use in the montelukast arm.
Dalgic [1179]	2017	3	Randomized open-label of 30 patients to 1 months of either montelukast or INCS or both	Seasonal Rhinitis	Olfactory function with Sniffin' Sticks	The two arms with INCS showed significant improvements in olfaction, but the arm with montelukast alone did not and the addition of montelukast did not further improve.
Andhale [1181]	2016	3	Prospective open label trial of 75 patients for montelukast vs levocetirizine for 2 weeks (I	Allergic Rhinitis	VAS for nasal and eye symptoms at night and during the day	Montelukast, levocetirizine and their combination was equally effective in controlling symptoms, with equivalent

			think no one was on INCS)			improvement in symptom scores.
Wilson [1177]	2001	4	Case series of 32 pts with uncontrolled CRS, despite INCS, for whom montelukast was added	CRS, allergic and non-allergic.	Symptom improvement PNIF PFTs	Addition of montelukast showed improvements in subjective symptom scores but no changes in PNIF or PFTs.

IX.D.8. Management of CRS: Probiotics

Because of limited data, CRSsNP and CRSwNP are combined in this analysis and recommendations.

Microbial communities encode millions of genes and associated functions which act in concert with those of human cells to maintain homeostasis.[1182] Numerous studies have now established the microbiota as an important contributor to essential mammalian functions such as metabolism,[1183] biosynthesis,[1184] neurotransmission[1185,1186] and immunomodulation[1187,1188] The perturbation of the healthy microbial ecology, referred to as microbial dysbiosis, has now been linked to many chronic diseases including RS.[1183] Theoretically it is postulated that restoration of a healthy or physiological microbiome through the use of pre or probiotic therapy, may reverse the disease process and reestablish health.

As defined by the World Health Organization, probiotics are "live microorganisms, which when consumed in adequate amounts confer health and benefit to the host".[1189] Proposed mechanisms of action include maintenance of the epithelial barrier, production of anti-microbial substances, competitive inhibition of pathogenic organisms, and modulation of the immune system.[1190] Numerous studies have been performed assessing probiotics as a treatment option in allergic rhinitis with mixed outcomes,[1191] however, research in CRS treatment is limited.

Oral probiotics have been investigated in the treatment of CRS and RARS in three clinical studies. Two of the studies demonstrated that oral administration of *Enterococcus faecalis* in the treatment of recurrent acute and chronic RS conferred a benefit.[1192,1193] In a double-blind placebo-controlled study, Habermann *et al.* showed a reduction in the frequency and time to recurrence of acute exacerbations of CRS in patients who received a 6-month course of oral *Enterococcus faecalis* and that this benefit was sustained for 8 months post treatment.[1192] Kitz *et al.* also demonstrated a reduction in frequency and duration of RARS in children who received 8 weeks of oral probiotic *Enterococcus faecalis* in suspension post standard oral antibiotics and intranasal decongestant treatment in a non-randomized controlled study.[1193] In contrast, a randomized controlled trial in by Mukerji *et al.* did not identify any improvement of sinonasal QoL scores with oral *Lactobacillus rhamnosus* for 4 weeks.[1194]

There is a paucity of data regarding the use of topical probiotics in the treatment of CRS with only one placebo controlled trial in the literature.[1195] In this double-blind study, CRSsNP patients were randomized to receive topical nasal *Honey bee microbiome* spray or placebo sprays for 2 weeks. The authors could not identify a statistically significant change in sinonasal symptom scores, microbiologic flora, or local inflammatory markers.[1195] A recent *in vitro* study evaluating the effect of a commercially available probiotic suspension on *Pseudomonas aeruginosa* clinical isolates has also shown concerning

signs with the rinse inducing the growth of a virulent isolate when co-cultured with the probiotic suspension.[1196]

Results from the studies in the current literature revealed mixed and limited success with oral probiotics in CRS treatment while topical probiotics have not yet shown clinical benefit in human studies. In summary, no recommendation for the use of probiotics in CRSsNP and CRSwNP is possible at this time.

Probiotics for CRS

Aggregate Grade of Evidence: not applicable.

Table IX-37. Evidence for CRS management with probiotics

Authors	Year	LOE	Type of Study	Patient Groups	Clinical Endpoints	Conclusions
Martensson [1195]	2017	2	Double-blind randomized, crossover, sham-controlled trial	20 patients with CRSsNP 14/20 patients had previous ESS 1. mixture of 9 lactobacilli and 4 bifidobacteria (Honeybee microbiome) topical nasal spray 2. Sham solution After 4 weeks of wash out, the subjects were crossed over to the other arm	SNOT-22, Microbiome, Inflammatory proteins in nasal lavage fluid	Duration 14 days No statistically significant change in SNOT-22 scores, microbiologic flora, or local inflammatory markers
Mukerji [1194]	2009	2	Randomized double-blind placebo-controlled trial	77 patients with CRS 1. oral probiotic *Lactobacillus rhamnosus* (500 million active cells/tablet twice daily) 2. oral placebo twice daily	SNOT 20	Duration 4 weeks No improvement of sinonasal QoL scores with oral probiotics
Habermann [1192]	2002	2	Double-blind placebo-controlled trial	157 patients with chronic recurrent RS 1. Oral bacterial + immunostimulant (3 × 30 drops / day), comprised of cells and autolysate of human *Enterococcus faecalis* bacteria	Time to recurrent ABRS; Relative risk of ABRS; Severity of ABRS; Use of antibiotic therapy; side effects;	Duration 6 months therapy Reduction in frequency and time to recurrence of RS episodes in the treated

				2. Placebo	laboratory tests	group
Kitz [1193]	2012	3	Prospective phase IV controlled trial (not randomized)	204 children with RARS (4-6 episodes/yr) Standard RS treatment (amoxicillin 7 days, nasal anticongestants TID) followed by: 1. 8 weeks of oral probiotic *Enterococcus faecalis* in suspension 2. no probiotic treatment	Mean duration of RS episodes, Frequency of RS episodes	Probiotic treated group had reduction in number and duration of RS episodes

IX.D.9. Management of CRS: Decongestants

Because of limited data, CRSsNP and CRSwNP are combined in this analysis and recommendations.

For CRSsNP, no evidence exists to support the use of topoical or oral decongestants. Surveys report that less than half of otolaryngologists recommend the use of decongestants[1197,1198] Duration of use and development of rebound nasal congestion (rhinitis medicamentosa) is unclear though reported. Given the possible harm of rebound nasal congestion and lack of known benefit, we recommend against the use of decongestants in CRSsNP.

For CRSwNP one RCT has shown benefit of topical nasal decongestants when used in combination with INCS.[1199] They did not find any patients who developed rhinitis medicamentosa. While there appears to be a balance of benefit and harm, because of the limited amount of evidence, decongestants are an option when used as an adjunct to incs in CRSwNP. No recommendation is given for its use as monotherapy.

Decongestants for CRS

Aggregate Grade of Evidence: not applicable.

Table IX-38. Evidence for CRS management with decongestants

Study	Year	LOE	Study Design	Study Groups	Clinical End-point	Conclusion

Kirtsreesakul [1199]	2016	2	Randomized control trial (n=68)	CRSwNP	Nasal symptom score. Peak inspiratory flow index. Nasal MCC time. Total nasal polyps score.	The use of nasal steroids with oxymetazoline was more effective over 6 weeks than nasal steroids. There was no evidence of rebound congestion after 4 weeks of oxymetazoline treatment.
Passali [1198]	2006	5	survey	CRSsNP CRSwNP		32% of experts use nasal decongestants for CRS. 6% use nasal decongestants for CRSwNP.
Kaszuba [1197]	2006	5	survey	CRS		38% of respondants use topical decongestants for 1 week. 47% of respondants use oral decongestants for 2 weeks

IX.D.10. Management of CRS: Mucolytics

Because of limited data, CRSsNP and CRSwNP are combined in this analysis.

CRS is frequently associated with an increase in the volume and viscosity of sinonasal mucus.[1200] The clinical manifestations of some phenotypes (such as CRS secondary to cystic fibrosis) are a direct result of changes in the physical characteristics of the mucus produced. One of the histopathological hallmarks of CRS is mucus gland hyperplasia.[1201] Chronic rhinorrhea or post nasal drip are some of the most troubling and difficult to treat symptoms of this condition.

There are few clinical studies of mucolytic agents. Dornase-alfa, which degrades the DNA in mucus that is largely derived from neutrophils, and thiol-derivatives such as N-acetyl cysteine, which target the di-sulphide bridges between mucopolysaccharides, are the most thoroughly investigated mucolytics.[1202,1203] Guaifenesin is readily available and frequently taken by patients troubled by thick respiratory tract mucus. It is believed to act by stimulating the volume of mucus secretion and reducing its viscosity,[1204] so it is not strictly a mucolytic. There are however no clinical studies supporting its efficacy for the treatment of CRS. Agents that remove nasal mucus by sheer force (such as saline lavage) or by acting as a surfactant are addressed in separate sections of this document.

A recent systematic review concluded there is moderate quality evidence to show the benefit of inhaled Dornase-alfa, determined by improvements in functional expiratory volume within 1 second (FEV1) and

a decrease in pulmonary exacerbations, in trials lasting up to two years.[1205] A review of the efficacy of Dornase-alpha for non-CF respiratory disease found no improvement in lung function or QoL in patients with bronchiectasis, but some benefit was seen in patients with severe asthma.[1206,1207]

A Cochrane review found no evidence supporting the clinical efficacy of thiol-derivatives such as N-acetylcysteine for patients with CF.[1208] Nonetheless, more recent studies have shown that thiol-based agents have not only mucolytic effects but also have anti-inflammatory and anti-bacterial properties, and further research is warranted.[1209]

There is a surprising dearth of studies investigating the efficacy of mucolytics for the treatment of CRS. Most of the recent literature describes their use in the treatment of CRS in patients with CF in which topical Dornase-alfa led to some improvement in nasal symptom scores.[1210,1211]

Due to insufficient evidence, no recommendation can be given regarding the use of mucolytic agents in either CRSwNP or CRSsNP. The one subgroup that may derive some benefit from nebulized Dornase-alpha are patients with CRS secondary to CF. However, the cost-benefit ratio requires further study.

IX.D.11. Management of CRS: Herbal Medications

Because of limited data, CRSsNP and CRSwNP are combined in this analysis and recommendations.

Phytotherapy, as defined in EPOS 2012,[31] is "the use of plants or herbs to treat diseases". In spite of the huge number of preparations marketed over the counter in Europe, the position paper, based on the revised literature, stated that herbal medicines were not recommended for the treatment of CRSsNP (grade of evidence D) because of lack of reliable clinical trials and, in some cases, even unknown composition of the herbal medications.

Since then, a growing amount of scientific evidence has suggested that herbal medicine may be helpful as an adjuvant treatment in RS.

One systematic review aimed to assess the effectiveness and safety of herbal preparations on CRS was published by Anushiravan in 2018. The initial search of the literature, up to August 2016, identified 936 publications, among which only 4 studies met the inclusion criteria (RCTs, placebo-controlled, published in English): Of the 4 articles selected, two were conducted in Sri Lanka, one in Taiwan, and one in Iran, all performed between 2010 and 2016 and included 244 patients, age range 18-78 years. One study[1112] was double blinded and the rest were single-blinded. Different herbal preparation were used in three studies, Vazifehkah's study used only one plant. Herbal preparations were administered either as decoction, capsules or nasal drops. A clinical improvement in symptoms was reported in all 4 studies as measured by the SNOT 22 questionnaire or by subjectively reported improvement by the patients. However, because of the bias (lack of standard questionnaires; lack of diagnostic tools and lack of long-term follow-up), the review's authors felt the effectiveness of medicinal plants in the treatment of CRS needs to be further proven in the future through additional studies.

"Phytoneering" from "phyto-engineering" is a method for the extraction of the phytopharmaceuticals contained in herbs. The method uses three biochemical and analytical phases, allowing the optimization of the extracts and enhancing their pharmaceutical effects. Herbal products developed using phytoneering techniques have shown improvements in performance compared with previous

formulations.[1212] BNO 1011 is a herbal compound containing the active pharmaceutical ingredients gentian root (Gentianae radix), cowslip flowers with calyx (Primulaeflos cum calycibus), sorrel (Rumicisherba), elderflower (Sambuciflos), and vervain (Verbenaeherba) at a ratio of 1:3:3:3:3. This extract has shown several pharmacodynamic properties such as antiviral, antimicrobial, anti-inflammatory and secretolytic effects in experimental animals.[915] It has also been found to be efficacious in reducing the symptoms of acute and recurrent RS in children and the adult population *in vivo*, while demonstrating a high level of tolerability and safety. Concerning CRS, Cho[915] tested BNO 1011 extract in 30 New Zealand white rabbits after development of CRS. Treatment groups were oral placebo (n = 10), BNO 1011 (low dose 25 mg/kg/daily) (n = 10), or BNO 1011 (high dose 125 mg/kg/daily) (n = 10); treatment duration was 4 weeks. Sinus opacification (Kerschner's rabbit sinus CT grade), transepithelial Cl^- transport (sinus potential difference assay), airway surface liquid depth using micro-optical coherence tomography, and submucosal gland density on histopathology were tested before and after treatment. Outcome parameters were analyzed by 2 blinded investigators. The results showed a statistically significant improvement in all radiologic, histologic and MCC (MCC) parameters in high dose treatment group vs placebo.

The current literature suggests that phytotherapy is an effective and safe form of ancillary treatment for RS. In particular, herbal drugs made with the technique of phytoneering have proven effective in ARS both in laboratory studies as well as in clinical trials in adults and children.

However, additional worldwide multicenter observational studies should be performed in order to overcome the bias shown in the available literature and the lack of RC clinical trial in chronic forms.

Herbal Medications for CRS

Aggregate Grade of Evidence: C (Level 2: 1 study; level 3: 4 studies; level 5: 1 study)
Benefit: Pytotherapy may be safe and effective for RS.
Harm: Cannot be currently assessed
Cost: Unknown
Benefits-Harm Assessment: Significant bias in current data making difficult to assess
Value Judgments: Bias in data limits value judgments.
Policy Level: No recommendation.

Table IX-39. Evidence for CRS management with herbal medications

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Anushiravani [1213]	2018	2	Systematic analysis	936 articles selected 4 eligible for review	Study and define the effects of medicinal plants on CRS	All included articles showed the effectiveness of the medicinal plants in the treatment of CRS. Because of several biases, the effectiveness of medicinal plants needs to be further proven through additional studies.
Ediriweera [1214]	2010	3	Randomized clinical trial	80 patients. Group A (40) treatment, Group B (40) Placebo	Evaluate the efficacy of this decoction in Kaphaja Shira Shula in CRS	Symptomatic relief and reduction in esinophil count in the blood were observe; decoction of KatuwelbatuDeduruKatukadiya can be used in treatment of CRS.

Maragalawaththa [1215]	2010	3	Randomized clinical trial	60 patients. Group A (30) treatment, Group B (30) Placebo	Efficacy of PitawakkaNavaya in treatment of CRS	Symptoms relieve only 10% of patients unchanged or aggravated. Traditional decoction PitawakkaNavaya is beneficial for CRS.
Jiang [1112]	2012	3	Randomized clinical trial	53 patients 26 Tsang-Erh-San extract granules and Houttuynia extract powder 27 erythromycin	Efficacy of Chinese herbal medicine in the treatment of CRSwNP in comparison with erythromycin treatment for 8 weeks	Efficacy similar to macrolides for CRSwNP. A placebo effect possible in both treatment groups.
Vazifehkah [1216]	2016	3	Randomized clinical trial	48 patients: first group 26 P. anisum–based herbal medicine second group 22 fluticasone nasal spray	Effectiveness of a Pimpinella anisum–based herbal medicine for treating CRSwNP in comparison to fluticasone nasal spray	May be an effective treatment for CRSwNP but needs further investigation.
Cho [915]	2019	5	Trial on animal model	CRS in 30 New Zealand white rabbits: Group 1 oral placebo 10, Group 2 BNO low dose 10, Group 3 BNO high dose 10	Effectiveness evaluated on: sinus opacification maxillary epithelial Cl− secretion, airway surface liquid and submucosal gland density on histopathology.	Herbal dry extract BNO 1011 improves radiographic, histologic, and MCC parameters in a rabbit model of CRS.

IX.D.12. Management of CRSsNP: Topical Alternative Therapies

IX.D.12.a. Topical Alternative Therapies for CRS: Surfactants

Because of limited data, CRSsNP and CRSwNP are combined in this analysis and recommendations.

The word surfactant is derived from 'surface' 'active' 'agent' and refers to a group of amphipathic (both hydrophobic and hydrophilic) compounds that can be solvent in both water and organic substrates. In the respiratory system, naturally occurring surfactants decrease the surface tension and viscosity of mucus. The orthopedic literature has established the benefits of chemical surfactants, commonly found in soaps and shampoos, as therapeutic detergents to break up and assist in the eradication of bacterial biofilms. These agents also have antimicrobial potential as a result of their ability to cause cell membrane disruption and loss of function. Therefore, in the setting of CRS, chemical surfactant may have a therapeutic benefit both as a mucoactive agent and a biocide with activity against planktonic and

biofilm associated microbes.[1217] The use of baby shampoo, citric acid zwitterionic surfactant and a novel proprietary sinus surfactant solution (Sinusurf®; NeilMed Pharmaceuticals, Santa Rosa, CA) have been evaluated *in vitro*, in animal models, and *in vivo*.[589,590,1218]

One percent baby shampoo in normal saline was determined to be the optimal concentration for inhibition of *Pseudomonas* biofilm formation, but it had no effect on the eradication of already formed *Pseudomonas* biofilms.[601] A prospective study using 1% baby shampoo irrigation in the post-ESS setting showed modest symptomatic improvement, with 2 of 18 patients (11%) discontinuing use due to nasal and skin irritation; there was no control group[601]. A RCT of 1% baby shampoo versus hypertonic saline showed no significant differences in post-treatment symptom scores; however, 20% of patients receiving the surfactant irrigation solution discontinued use due to side effects.[603] The Sinusurf® surfactant solution was withdrawn from the market in 2011 due to adverse effects, including olfactory disturbance.[1141] A subsequent prospective crossover trial of a reformulated low-concentration Sinusurf® solution showed tolerability issues in a non-CRS population and reversible reductions in olfactory acuity in a subset of participants.[604]

Data regarding the effects of surfactant irrigation on the respiratory epithelium/cilia is mixed, with evidence of both a transient increase in cilia beat frequency and an increase in MCC time.[1217,1219] The Sinusurf® surfactant solution did not elicit cellular toxicity in a mucosal explant model when used at the manufacturer's recommended concentration, but showed dose-dependent toxicity with higher concentrations.[1220]

In summary, one RCT has shown no benefit of baby shampoo over control and patients in the treatment group had higher rate of side effects and study discontinuation. The benefits of surfactants are clearance of thick secretions and interruption of biofilm formation. Harms include nasal irritation as well as negative effects on cilia morphology, ciliary beat frequency, olfaction, and MCC time. Cost of surfactant therapy is low. While there appears to be a balance of benefit and harm, because of the limited clinical data, no recommendation is given for the use of surfactants in CRSsNP and CRSwNP.

Surfactants for CRS

Aggregate Grade of Evidence: not applicable.

IX.D.12.b. Topical Alternative Therapies for CRS: Manuka Honey

Because of limited data, CRSsNP and CRSwNP are combined in this analysis and recommendations.

Manuka honey (MH, *Leptospermum scoparium*) and its active component methylglyoxal (MGO) have demonstrated antimicrobial capabilities against both the planktonic and biofilm forms of gram-positive and gram-negative bacteria including MRSA.[1221-1223] Kilty *et al.* demonstrated that higher effective concentrations of MGO are needed for biofilms of *S. aureus* and *P. aeruginosa* than for their planktonic forms.[1221] Jervis-Bardy *et al.* demonstrated that the biocidal activity against *S. aureus* biofilms is enhanced when in a honey solution suggesting a role for both the honey component and the MGO.[1222] Most recently, Yang *et al.* devised a novel platform that generates NO using MH and nitrite that produced a potent anti-biofilm effect on *P. aeruginosa*.[1224]

In vivo animal studies have confirmed the safety of Manuka honey in the sinonasal cavity. Kilty *et al.* treated New Zealand rabbits with up to 14 days of daily irrigations of 1.5 ml of 33% mixture of Manuka honey and saline and found no epithelial damage of the nasal respiratory mucosa under light and transmission electron microscopy.[1225] Paramasivan *et al.'s* sheep study also showed no damage to the nasal epithelium or cilia at concentrations of MGO up to 1.8mg/ml. They did however observe cilia denudation of the epithelium at MGO concentrations of 3.6mg/ml.[1226] Paramasivan *et al.* also examined the antibiofilm action of MGO on mature *S. aureus* biofilms established in the frontal sinus of the sheep. They observed no effect of the MGO on the *S. aureus* biofilm biomass at concentrations less than 0.5mg/ml and similar effects on biomass reduction at 3.6 and 1.8mg/ml. The authors concluded that Manuka honey/MGO with MGO concentrations around 1.8mg/ml is probably optimal in terms of safety and efficacy.

Clinical studies assessing the efficacy of Manuka honey in treatment resistant post-surgical patients have not demonstrated superior efficacy over saline alone.[1227-1232] Thamboo *et al.* evaluated 34 AFRS patients, randomized to receive 30 days of atomized MH saline solution to one side and saline alone to the contralateral side. No observable difference in symptoms and endoscopic scores was found between the treatment arms.[1227] Similarly, Lee *et al.'s* randomized control study comparing patients treated with saline irrigations and 10% (vol/vol) MH irrigations, also showed no statistically significant difference in SNOT-22 and Lund-Kennedy scores after 30 days of treatment.[1230] However, during acute exacerbation of their CRS, culture negativity was statistically better in patients who irrigated with MH solution.[1230] A 2019 single-blinded, placebo-controlled trial by Ooi *et al.* investigated MH with augmented MGO rinses in recalcitrant CRS patients.[1232] Twenty-five patients with CRS and positive bacterial culture sinus swab after ESS were randomized to receive 14 days twice daily 16.5% MH + 1.3mg/ml MGO sinonasal rinses or 10 days of culture-directed oral antibiotic therapy with concurrent topical or oral placebo. The authors found that the MH/MGO sinonasal rinse was safe but not superior to culture-directed antibiotics in terms of endoscopic and patient-reported symptom scores.

The *in vitro* potential benefits of MH and MGO has not yet translated into statistically significant clinical improvement in the few clinical studies in literature. However, there is a potential for cytokine expression modulation as demonstrated in the study by Manji *et al.*[1231] Although generally well tolerated, reported side effects do include nasal burning, irritation, and possible epithelial injury if higher concentrations of MGO or MH are used. Given the heterogeneity of the study population and variable MH and MGO concentrations as well as paucity of evidence, no recommendation for the use of Manuka honey in CRSsNP and CRSwNP is possible at this time.

Manuka honey for CRS

Aggregate Grade of Evidence: B (Level 2: 5 studies; level 4: 1 study)

Table IX-40. Evidence for CRS management with manuka honey.

Authors	Year	LOE	Type of Study	Patient Groups	Clinical Endpoints	Outcomes
Ooi [1232]	2019	2	Single-blind RCT	25 patients with CRS who had previous sinus surgery Treated with	Safety observation: UPSIT and AE reporting; Efficacy	Duration 14 days Safety observation: UPSIT and AE reporting Efficacy observation:

				- 16.5% MH + 1.3mg/ml MGO sinonasal rinses twice daily and concurrent 10 days placebo tablets - Saline sinonasal rinses twice daily and concurrent 10 days culture-directed antibiotics therapy	observation: Lund-Kennedy score, VAS symptom score, SNOT-22	Lund-Kennedy score, VAS symptom score, SNOT-22 symptom score Safety: no AE or changes in UPSIT MH augmented with 1.3mg/ml MGO sinonasal rinses alone is safe but not superior to culture directed oral antibiotics and saline rinses twice daily
Manji [1231]	2019	2	Randomized control trial	46 patients (CRSsNP or CRSwNP); biopsies taken: during ESS; at 5 and at 12 weeks MH sinus irrigations (5-7%) twice daily for 3 months Saline irrigations in control patients	Cytokine expression in tissue biopsies.	MH for 12-week vs saline: cytokines IL-6, IL-8, MCP-1, and MIP-1β were significantly increased and IL-13 was significantly reduced
Lee [1230]	2017	2	Single-blind RCT	42 patients with CRS who had previous sinus surgery treated with daily 1. 10% (vol/vol) MH irrigation ½ bottle twice daily 2. Saline sinus irrigation ½ bottle twice daily	SNOT 22; Lund-Kennedy Endoscopic score; Culture negativity	Duration 30 days Both MH and SAL improved outcomes No statistically significant difference in SNOT-22 scores, Lund-Kennedy endoscopic scores Culture negativity was statistically better with MH in patients who did not receive oral antibiotics/steroids
Chang [1229]	2011	2	Double-blind control trial	3 groups: 48 patients (16 each group) after ESS Budesonide	VAS Pain scale; Histopathologic analysis of mucosal biopsies to assess for	Duration 7 days No significant difference in discomfort and pain on the removal of

				(0.25 mg/ml), MH (50%) or gentamicin (40 mg/ml) soaked Merocel MMS Nonmedicated Merocel in contralateral side Biopsies also taken from the middle meati after packing removal and blinded pathologists rated the level of mucosal inflammation	inflammation.	the packings between groups; trend toward less pain for the MH-soaked Merocel MMS No statistically significant difference between the 2 groups but trend towards reduced mucosal inflammation in the MH group
Thamboo [1227]	2011	2	Single-blind RCT	34 patients with surgically recalcitrant AFRS treated with daily 1. MH saline spray in 1 nostril 2. placebo in the other	SNOT 22; Endoscopic grading; Sinus cultures	Duration 30 days No significant difference in symptom scores, endoscopy grades or culture results on both sides
Wong [1228]	2011	4	Case reports	2 patients after failing maximal management of AFRS MH in sinus rinse bottles 120 ml per side twice a day	SNOT 22; subjective symptoms; Endoscopic exam	Duration 12 weeks Patients 1 and 2: symptoms and endoscopic examination improved drastically; side effects: patient 1 had irritation symptoms and patient 2 had none

IX.D.12.c. Topical Alternative Therapies for CRS: Xylitol

Because of limited data, CRSsNP and CRSwNP are combined in this analysis and recommendations.

Xylitol is a 5-carbon sugar that has been shown to enhance the innate immune system. Its mechanism of action occurs via xylitol's effect on the thin layer of airway surface liquid, enhancing the activity of innate antimicrobial factors present in respiratory secretions. Brown *et al.* demonstrated that

simultaneous administration of xylitol with *P. aeruginosa* into the maxillary sinuses of rabbits produced an increase in bacterial killing after 20 minutes when compared to saline.[1233] However, they found that pre-administration of xylitol into the sinus or administration of xylitol in an infected sinus did not decrease bacterial counts when compared with saline. In an in-vitro study, xylitol was also found to significantly reduce biofilm biomass of *S. epidermidis* and inhibit biofilm formation of *S. aureus* and *P. aeruginosa*.[1234]

In a human study, Zabner *et al.* demonstrated that xylitol nasal spray administered for 4 days in normal volunteers resulted in greater reduction of coagulase-negative *Staphylococcus* colony forming units than did saline spray.[1235] A subsequent *in vitro* study demonstrated that xylitol significantly decreased the viscoelasticity and viscosity of wet mucus derived from CRS patients more than saline controls.[1236] In that same study, postoperative mucus crust dissolution was also measured. Xylitol was found to significantly reduce mucus crust border definition in CRS patients to a greater degree than saline, indicating its potential efficacy as a mucolytic agent.[1236]

Thus far, there have been 2 clinical studies evaluating the effect of xylitol in patients with CRS. The studies did not specify whether patients had CRSsNP or CRSwNP. Weissman *et al.*[1237] performed a prospective DBRCT crossover pilot study. The subjects were adults with a history of CRS who had undergone sinus surgery. After a 3-day washout period, subjects were given either xylitol or isotonic saline irrigations daily for 10 days. This was followed by another 3-day washout period, followed by 10 days of the other treatment. Ten subjects were allocated to each group; 15 (75%) completed the study. The xylitol group showed a greater improvement in SNOT-20 scores than the saline group. However, there was no difference in the visual analog scale (VAS) scores between the 2 groups. A systematic review by Rudmik *et al.*, evaluated the evidence of using topical irrigations with xylitol based on Weissman's study, and the authors concluded that the benefit-harm assessment was unknown.[1141]

Subsequently, Lin *et al.* performed an RCT comparing sinonasal symptoms (VAS and SNOT-22 scores) and nasal NO in CRS patients who had undergone sinus surgery.[1238] Patients were randomly assigned to a 30-day regimen of xylitol (n=15) or saline nasal irrigation (n=15) post-operatively. Twenty-five subjects completed the study. VAS and SNOT-22 scores were significantly reduced in the xylitol group compared to the saline group following the 30-day study period. There were no adverse events with use of xylitol rinses in either study apart from one patient who reported minor stinging.[1237]

In summary, there have been 2 RCTs with small sample sizes and 17-25% dropout that have shown limited significant symptom benefit with xylitol. *In vitro* studies have demonstrated enhancement of innate immunity and mucolytic properties. Potential harm is limited to minor irritation and cost of therapy is low.

Xylitol for CRS

Aggregate Grade of Evidence: B (Level 2: 2 studies)
Benefit: Symptomatic improvement in the 2 small RCTS conducted on postoperative CRS patients
Harm: Occasional local discomfort (stinging)
Cost: Low.
Benefits-Harm Assessment: Preponderance of mild benefit over harm.
Value Judgments: None
Policy Level: Option
Intervention: Xylitol is an option for treating CRS.

Table IX-41. Evidence for CRS management with xylitol

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Lin [1238]	2017	2	RCT	Adult CRS patients that had sinus surgery, irrigation with: 1. xylitol (n=15) 2. saline (n=15)	Symptom/QoL score (VAS and SNOT-22). Nasal NO	Xylitol vs. saline irrigation significantly reduced VAS and SNOT-22 scores.
Weissman [1237]	2011	2	DBRCT	Adult CRS patients that had sinus surgery 1. xylitol (n=10) 2. saline (n=10)	Symptom/QoL score (SNOT-20)	Greater improvement in SNOT-20 with xylitol vs. saline irrigation.

IX.D.12.d. Topical Alternative Therapies for CRS: Colloidal Silver:

Because of limited data, CRSsNP and CRSwNP are combined in this analysis and recommendations.

Silver is known to possess broad antimicrobial properties, with effectiveness against gram-negative and gram-positive bacteria, fungi, protozoa and some viruses. It is among the most toxic elements to microorganisms, many of which do not develop resistance to its effects. Because of this, silver is used in a number of medical and non-medical products including wound dressings, catheters, water purification devices and textiles.

Orally administered silver has been described to be absorbed in a range of 0.4-18% and seems to be distributed to all organ systems with the highest levels being observed in the intestine and stomach.[1239] Prolonged silver exposure may lead to deposition of silver particles in the skin leading to the hallmark blue-gray discoloration of the skin (argyria), eye (argyrosis) and internal organs, including the central nervous system. Consumption of large doses of colloidal silver (CAg) can result in significant morbidity including gastrointestinal ulceration, hemolysis, agranulocytosis and neural toxicity.

Colloidal silver (a colloidal solution of 33.23 ppm elemental Ag in 99.99% water) has been shown to cause a 99% reduction in biomass of a *S. aureus* biofilm compared to controls in an *in vitro* study.[1240] Likewise, in a sheep model, 30-ppm CAg solution administered to infected frontal sinuses for 14 days resulted in significantly greater reduction in *S. aureus* biofilm mass relative to controls (normal saline irrigations).[599]

There have been 2 clinical studies investigating the efficacy of topical CAg in CRS. In a DB randomized crossover trial by Scott *et al.*,[1241] 20 patients with recalcitrant CRSsNP were randomized to receive either 10 ppm CAg spray for 6 weeks followed by saline intranasal spray for an additional 6 weeks, or saline intranasal spray for 6 weeks followed by 10 ppm CAg spray for 6 weeks. There were no significant differences in the sinonasal symptom (SNOT-22) and endoscopic scores (LK) between the 2 groups. In terms of adverse events, one patient developed nasal congestion and another a sinus infection.

However, no systemic side effects were reported. No cases of argyria were encountered, and no bluish discoloration of the sinonasal mucosa was seen in any of the patients. Subsequently, Ooi *et al.* compared the outcomes of 22 CRS patients who were randomized into two treatment arms, the first group received twice daily saline irrigations and 10-14 days of culture-directed antibiotics (n=11) and the second treatment group received only a 10 day courseof twice daily CAg irrigation (0.015 mg/ml) (n=11).[1242] All patients had recalcitrant CRS, had undergone prior sinus surgery, and had signs and symptoms of a sinus infection with positive bacterial culture. The study did not specify whether the patients enrolled had CRSsNP or CRSwNP. Both arms showed similar improvement in sinonasal symptom (SNOT-22 and VAS) and endoscopic scores (Lund Kennedy), but the result was not statistically significant and there were no significant differences between CAg versus controls. In addition, there was no difference in post-treatment culture negativity between the 2 groups. No adverse events were reported, but 4 patients had transient increase in serum silver levels above the normal range within 24 hours of administration. However, follow-up testing after 10 days showed the serum silver levels had returned to normal parameters.

Despite its availability as an over the counter drug, colloidal silver is an unregulated alternative medicine. Colloidal silver products of unknown formulation were tested and found to vary from ineffective to dangerous to possibly life threatening. Due to these findings, in 1999, the United States Food and Drug Administration (US FDA) stated that all over the counter drug products containing colloidal silver ingredients or silver salts for internal or external use were misbranded, although they had previously been recognized as safe and effective.[1243] In addition to these safety concerns, no evidence exists regarding the efficacy of topical silver treatment in CRSsNP or CRSwNP. Consequently, topical silver is not recommended in CRSsNP and CRSwNP.

Colloidal Silver for CRS

Aggregate Grade of Evidence: B (Level 2: 2 studies)
Benefit: No benefit for the use of CAg in clinical studies
Harm: Potential increase in serum silver levels
Cost: low (commercially available) to high (compounding)
Benefits-Harm Assessment: No benefit in light of potential harm
Value Judgments: CAg appears to have anti-bacterial properties in-vitro, but lacks efficacy in clinical studies
Policy Level: Recommendation against use in CRS

Table IX-42. Evidence for CRS management with colloidal silver

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Scott [1241]	2017	2	DBRCT Crossover	Adults with recalcitrant CRSsNP - Nasal spray with saline, 4 sprays BID (n=8) - Nasal spray with CAg, 4 sprays BID (n=12)	Symptom/QoL score (SNOT-22) Endoscopic score (Lund Kennedy)	No significant differences between the 2 groups

Ooi [1242]	2018	2	RCT	Adults with CRS who had prior sinus surgery, active sinus infection and positive bacterial culture - Culture directed oral antibiotics (10-14 days) + NSI BID (n=11) - Nasal CAg irrigation (0.015 g/ml) BID for 10 days (n=10)	Culture negativity Symptom score/QoL score (VAS and SNOT-22) Endoscopic scores (Lund Kennedy)	No difference in culture negativity, symptom, and endoscopy scores between the 2 groups. Twice daily CAg irrigations is safe but not superior to culture directed oral antibiotics.

IX.D.12.e. Topical Alternative Therapies for CRSsNP: Furosemide

The current literature demonstrates an absence of a well-designed investigation that has examined the role of furosemide in the management and treatment of CRSsNP.

IX.D.12.f. Topical Alternative Therapies for CRS: Capsaicin

Because of limited data, CRSsNP and CRSwNP are combined in this analysis.

Capsaicin is the active ingredient in chili peppers (plant genus *Capsicum*) and produces a burning sensation on contact with tissues. This response is secondary to its binding to transient receptor potential vanilloid 1 (TRPV-1), an ion-channel type receptor. It has been used as a topical medication for chronic neuropathic pain[1244] and psoriasis[1245,1246], and is also considered a treatment option for non-allergic rhinitis[1247]. Capsaicin affects the unmyelinated sensory C fibers of the nasal mucosa. These nerve fibers play a role in the neurogenic reflex mechanisms in the nasal mucosa, which when stimulated lead to a local release of neuropeptides, including substance P, C-peptide, calcitonin gene-related peptide (CGRP), and vasoactive intestinal peptide (VIP)[1248-1250]. It is hypothesized that repeated administration of high doses of capsaicin to the nasal mucosa leads to degeneration of these unmyelinated sensory C fibers[1251].

The vasodilation and increase in nasal secretions triggered by stimulation of these nerves with capsaicin has been demonstrated to be higher in patients with non-allergic rhinitis compared to asymptomatic controls.[1250,1252] High tissue concentration of neuropeptides such as CGRP in nasal mucosa has been shown to be directly correlated with the intensity of nasal obstruction and rhinorrhea symptoms.[1252,1253] It is theorized that sensory neuropeptide release in the nasal mucosa may trigger hyperproliferation and hypertrophy of the mucosa that even contributes to polyp formation,[1254] such that downregulation of this response may lead to improvement. In the case of non-allergic rhinitis, a Cochrane database review involving 5 studies indicated that capsaicin has beneficial effects on overall nasal symptoms up to 36 weeks after treatment[1247].

Three studies were identified in the literature that assessed the effect of topical capsaicin on nasal polyposis. In a randomized, placebo-controlled trial, Zheng *et al.*[1255] reported a significant improvement in subjective nasal obstruction and endoscopic staging of polyps in patients treated with topical

capsaicin following limited ESS versus controls. In their double blind, placebo-controlled study, Filiaci *et al.*[1256] also showed significant improvement in subjective nasal symptoms such as obstruction, secretions, and sneezing, as well as improvement in objective findings, including endoscopic polyp scores and nasal airway resistance by anterior rhinomanometry. Similarly, Baudoin *et al.*[1257] reported an improvement in nose/sinus air volume, endoscopy scores, and subjective symptoms scores at 4 weeks post-treatment in patients with nasal polyposis in their case series. In all of these studies, an assessment of underlying CRS was not part of the study, but rather patients were included if they demonstrated nasal polyposis. In two of the studies, patients were excluded from the study group if they had a history of asthma, allergy, or atopy.[1255,1257] Treatment schedules varied between the studies from daily application of capsaicin to weekly, similar to the wide range of capsaicin doses, concentrations, frequencies, and durations seen in other studies involving the use of this topical medication for non-allergic rhinitis and other pathologies.

There were no studies found on the efficacy of capsaicin in CRSsNP, nor has any comparison been made between the efficacy of topical capsaicin and other medical management for CRS, such as topical steroids. Given that it has shown some benefit in limited studies and is well-tolerated with no long term side effects shown,[1247] it may be an option as an adjunct in CRS treatment.

Capsaicin for CRS

Aggregate Grade of Evidence: C (Level 2: 1 study, Level 3: 1 study, Level 4: 1 study)
Benefit: Improvement in subjective symptoms and objective findings in CRSwNP. No literature evaluating CRSsNP.
Harm: Well-tolerated with no long term side effects shown
Cost: Minimal
Benefits-Harm Assessment: Balance of benefits and harm
Value Judgements: Limited studies evaluating capsaicin treatment in CRSwNP and no studies comparing capsaicin to standard CRS treatments. Capsacin should not replace these treatments, but may be considered as an adjunct.
Policy Level: Option
Intervention: Use of topical capsaicin as an adjunct treatment for CRS

Table IX-43. Evidence for CRS management with capsaicin

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoints	Conclusions
Zheng [1255]	2000	2	Randomized, placebo-controlled	Cotton pellet soaked in capsaicin ($3x10^{-6}$mol in 70% ethanol) in middle meatus post-limited sinus surgery, Placebo (70% ethanol alone) with same application method.	Subjective evaluation of nasal obstruction and rhinorrhea by visual analog scale, Endoscopy staging of polyps. Evaluations performed at 1 week preop and monthly postop x 9 months.	Improvement in subjective NAR and endoscopy staging of polyps in treatment group. No difference in rhinorrhea.
Filiaci [1256]	1996	3	Double blind, placebo-controlled	Topical capsaicin (0.1ml of 30µmol/L) once weekly x 5 weeks, Placebo (0.1ml of physiological solution alone) with same application method	Symptom questionnaire, Endoscopy scores, Nasal resistance by anterior rhinomanometry Specific nasal provocation testing with cold water and rhinomanometric assessment of NAR. Evaluations performed before and after each treatment and at 1 and 3 months post-treatment.	Improvement in symptoms, Reduction in size of polyps compared to controls, Reduction in objective nasal resistance.
Baudoin [1257]	2000	4	Prospective, case series	Topical capsaicin 0.5ml (30µmol/L) x3 days, then 100µmol/L on days 4 and 5 in patients with NP.	Nose/sinus air volume (NSAV), Subjective scores, Endoscopy scores, ECP levels in nasal lavage. All reviewed pre- and post-treatment and weekly x 4 weeks.	Improved NSAV, subjective scores, and endoscopy scores. No change in ECP levels.

IX.D.13. Management of CRSsNP: Influence of Head Position, Device, Surgery, and Nasal Anatomy on Distribution of Topical Medications

A previous review by Orlandi *et al.*[1258] synthesized the findings of multiple EBRRs regarding CRS which is included in the recommendations of this statement. These EBRRs have evaluated sinus distribution of topical therapies from intranasal delivery as influenced by; surgery, delivery device utilized, head position during delivery, influence of nasal anatomy. The findings of the cumulative studies show that surgery followed by high volume delivery devices are critical for effective delivery of topical therapies within the paranasal sinuses.[1259]t[1077,1085] Head position appears to affect distribution[1260,1261] but neither position nor volume seems to overcome the influence of surgical state.[1262]

ESS is an important component in the management of medically refractory CRS, both primarily and for the long term through improved access of topicals.[1141] ESS improves delivery of saline irrigations to address hypersecretory mucin, compensates for impaired ciliary function, and facilitates delivery of pharmaceutical agents, all of which are goals of topical management of CRSsNP.

The Influence of Sinus Surgery. Numerous studies have examined the effect of sinus surgery on the distribution of topical therapies in the nose and sinuses in both CRSwNP and CRSsNP.[1259] Surgical interventions ranged from sinus ostium dilation to procedures that completely remodel the paranasal anatomy.[1263] Unoperated sinuses appear to receive little topical therapy, with more extensive procedures resulting in increasing distribution in general.[1134,1264-1266] Specifically, a minimum of 4-5mm ostial size is required to allow sinus penetration with high volume irrigators.[1134] Standard sinus surgery increases distribution of topical therapies to all sinuses, but has no impact upon nasal cavity delivery.[1265,1266] The removal of partitions in sinus surgery also improves the penetration of second generation topical spray treatments.[1267-1269] While there are both direct and indirect costs surrounding surgical intervention, there is a preponderance of benefit over harm to improve delivery of local topical therapies and avoid systemic therapies.[1259] The largest benefit with ESS in CRSsNP is that penetration of topical therapy is greatly enhanced post-ESS.

Delivery Device. Delivery appears to be best achieved with large volume devices.[1134] Previous studies have shown that low-volume devices do not reliably penetrate the sinuses, although delivery into the nasal cavity has been demonstrated. High-volume devices (>60ml, but generally >100ml) have been found to improve delivery into the sinuses.[1258,1270] The definition of "high-volume" is somewhat arbitrary but clinical evidence suggests it may assist with both mechanical cleaning or lavage and drug delivery. High-volume devices can unfortunately carry unwanted side effects with eustachian tube dysfunction and local irritation being reported in up to one fourth of patients. However, these are often mild and compliance is high.[1271] First generation, low-volume devices such as drops, sprays, and nebulizers are an acceptable alternative if nasal cavity or limited sinus delivery is needed, but should not play a significant role in the management of CRSsNP as they do not reliably reach within the sinuses and provide no mechanism for lavage. However, second generation systems using pulsating aerosols or exhalation delivery systems do appear to provide significant deposition of drug to operated sinuses, but do not provide the additional benefit of lavage.[1267-1269,1272-1278]

Head Positioning. Head position improves delivery in the previously operated patient, especially for low volume devices.[1260,1261] Very limited sinus delivery occurs in the unoperated patient regardless of head position. However, in the postoperative cavity, sinus delivery is improved with the head down and forward position, although the influence of head position is overcome with high-volume devices, especially to the frontal sinus.[1258,1270] The head down and forward position appears to be optimal for topical delivery but may be impractical or difficult for those with limited mobility. For high volume devices, proper head position is less critical for solutions to reach the sinuses in the post-operative

state, but to reach the sphenoid sinus consistently, patients will often need to irrigate in the nose-to-ceiling position.[1278,1279]

Local Nasal Anatomy. While it may seem axiomatic that correcting local septal and turbinate deformities would enhance local drug delivery, there is little evidence to support this assumption, although in second generation spray devices, it is most likely important.[1277] In evaluation of the potential benefits and harms of altering nasal anatomy and/or using longstanding decongestants to improve topical medication delivery, the evidence-based review did not find significant data supporting this practice.[1259] Despite this, level C evidence supports that high-volume irrigations are able to overcome minor anatomic variations in the nasal cavity and still achieve sinus delivery for those with prior sinus surgery. Nasal cavity delivery with low-volume devices can be overcome with pharmacologic decongestion or head position but this is of little benefit to patients with CRSsNP in whom mechanical clearance of mucus is a primary goal of the intervention. Nasal surgery or a chronic topical vasoconstrictor use, without documented airflow obstruction, is unproven and increases the risk for harm and cost.

Conclusion. The goal of topical therapy in CRSsNP is directed at clearance of mucus and correcting the mucostasis that characterizes this condition. Enabling sinus distribution of topical therapies, primarily corticosteroids, antibiotics and mucolytics, allows effective local pharmacologic management, and is best achieved through use of high-volume irrigations or second-generation spray devices. The mechanical shear force that is provided by high volume irrigations in the post-operative state may be a major factor to manage the mucostasis. Advantages of direct topical medical therapy include the potential for delivering higher local drug concentrations and minimizing systemic absorption. Current evidence suggests that optimal topical sinus delivery occurs after surgery and with high volume irrigation and second-generation spray devices.

IX.D.14. Management of CRSsNP: Immune Workup and Treatment

Because of limited data, CRSsNP and CRSwNP are combined in this analysis and recommendations.

Tas *et al.* performed a randomized controlled study using thymic hormone preparation thymostimulin (TP-1) and placebo in a cross-over trial. TP-1 was proven to be effective in patients with recurrent CRS who were immunologically deficient in cell-mediated immunity.[1280] However, TP-1 was taken off the market and a related therapeutic target, thymosin 1α (a 28 amino acid peptide isolated from thymosin fraction 5), is under study.[1281] Thymic hormone preparation thymostimulin was shown to be effective and safe in one study but it is now not available in the market. Thus, thymostimulin cannot be recommended.

There is debate on the role of Ig replacement. Roifman and Gelfand evaluated sinopulmonary disease frequency after high and low dose therapy with IVIG. High dose Ig achieved minimal trough serum IgG levels and decreased symptoms and frequency of major and minor infections.[951] However, after a long-term follow-up of a large cohort of patients with CVID, Quinti *et al.* found routine Ig administration, at a monthly dosage of 400 mg/kg weight of IVIG at intervals ranging between 2 and 3 weeks, was associated with increased prevalence of CRS and bronchiectasis.[951] This was supported by a study from Rose *et al.* in which the inflammatory cytokines were markedly elevated in nasal lavage which had a discrepancy with serum IgG level.[1282]

In a systematic review of 243 patients with activated phosphoinositide 3-kinase delta syndrome, the majority were placed on long-term Ig replacement therapy, with 12.8% ultimately receiving stem cell transplantation.[1283] High dose IVIG was used to treat autoimmune hemolytic anemia and immune

thrombocytopenic purpura in 38 (84.4%) patients.[1283] Another review noted that in patients with primary immunodeficiency and CRS, Ig replacement therapy, appears to be most effective when administered at high doses early in the disease course.[1284] Lucuab-Fegurgur *et al.* show that in a subset of patients with CRS with selective IgM deficiency (n=8), all but one patient had resolution of symptoms on high dose IVIG.[1285] Similarly, Khokar *et al.* describe 78 adult patients with IgG subclass deficiency who had reduction in infection frequency and antibiotic requirement after treatment with IG, with a mean dose of 436 mg/kg/4 weeks.[947] IG replacement therapy, at various dosing, was found to have a positive impact on the frequency of RS in 31 patients with CVID and SAD[931] An open-label , prospective multi-center single arm study which was conducted to assess the safety of a highly purified 10% polyvalent immunoglobulin preparation dosed from 0.22 to 0.97 g/kg every 3 to 4 weeks for 12 months, and was well tolerated by patients with primary immunodeficiency.[1286] The benefits of Ig replacement were discussed in several review articles as well, including decreasing the rate of sinopulmonary infections and acute hospitalizations in patients with CVID.[1287-1289] The effect of IG replacement is controversial and this is a challenging issue on which to provide guidelines, because IVIG carries the risk of significant side effects (petechial bleeding, fatigue, headache, nausea, dyspnea, tachycardia, abdominal pain, and even anaphylactoid reaction) and can be expensive. The long-term benefit of IG replacement in controlling CRS is less encouraging. Still, Ig replacement is an approved treatment for CVID as it can prevent pulmonary disease and complications from CRS, such as subperiosteal and intracranial abscesses, meningitis, and sepsis. The use of IG replacement in other immune disorders including SAD or IgG subclass deficiencies remains controversial.

Patients on immunosuppressive therapy are another important sub-group of patients with immune dysregulation. Papagiannopoulos *et al.* describe 15 patients with CRS on immunotherapy and compare their histopathology variables and treatment outcomes with other patients with CRSwNP and CRSsNP.[1290] CRS on immunotherapy patients exhibit histopathology and disease severity similar to CRSsNP. The authors note that, in the appropriate clinical context, discontinuing or changing a patient's immunosuppressive regimen may be a valid treatment option.[1290] Wang *et al.* present 28 patients on a TNF-α inhibitor diagnosed with RS. These patients had mainly CRSsNP and the authors suggest modification of anti-TNF-α therapy should be considered as an option in the medical management of these patients.[1291]

ESS results were compared in CRS with immune dysfunction or autoimmune disease vs. controls. The results were similar in both groups, which suggests that patients with immune dysfunction may experience similar benefit from ESS.[954] In a review of 21 patients with immunodeficiency undergoing ESS, the revision rate was 14%.[1292] Mazza *et al.* report in their systematic review that patients with immunodeficiency experience similar benefit after ESS when compared to immunocompetent patients in relation to symptoms and QoL.[1284] ESS may have a similar role as in patients with normal immune function, but a strong indication for surgery is not clear. Larger future studies will be required to confirm the safety and clinical benefit of these studies.

Prophylactic antibiotics and early culture-directed antibiotics were also recommended by expert groups.[947,1281,1289,1293-1296] Yet there are no consensus guidelines on the use of antibiotics in refractory CRS with immunodeficiency. Pimenta *et al.* report a cross-sectional study of 8 patients with hypogammaglobulinemia in which most received prophylactic antibiotic therapy, however, no therapeutic outcomes were discussed.[930] Prophylactic antibiotics may reduce infections in immunodeficient patients, but, there is an increased concern on antimicrobial resistance and alterations to the sinus microbiome. Early culture-directed antibiotics are theoretically advisable, but there is a lack of definitive evidence to support this. Overall, since the current studies were small in scale and not based on controlled trials, the balance of risk to benefit is unclear.

Table IX-44. Evidence for CRS management with immunodeficiency treatment

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Tas [1280]	1990	2	Randomized control trial Double-blind cross-over trial (n=20)	TP-1 then placebo Placebo then TP-1	Endoscopy, DTH skin test, lymphocyte subsets, MIF assay, and other laboratory tests.	Refractory CRS patients were successfully treated TP-1, restoring some laboratory parameters
Jamee [1283]	2019	3	Systematic review	243 patients with activated phosphoinositide 3-kinase delta syndrome (APDS)	Clinical manifestations, immunological phenotypes, treatment modalities examined.	APDS should be suspected in patients with history of recurrent respiratory infections, lymphoproliferation, and raised IgM levels. 25.9% patients had RS. The majority of APDS patients were placed on long-term Ig replacement therapy. Hematopoietic stem cell transplantation was used in 12.8% of patients.
Mazza [1284]	2016	3	Systematic review	39 studies, predominantly level 4 evidence, of patients with primary immunodeficiency and CRS met inclusion criteria.	Data was collected pertaining to immune dysfunction in patients with CRS, the clinical workup for these patients, and the effectiveness of medical and surgical treatments.	Medical therapy, particularly Ig replacement therapy, appears to be most effective when administered at high doses early in the disease course. The addition of surgery is less clearly supported, but may also provide benefit if performed early.
Quinti [40]	2007	3	Multicenter prospective study	CVID patients on IVIG for a mean of 11.5 years. (n=224)	Ig level, lymphocyte subsets, culture test,	IVIG is more effective in reducing lower respiratory

					CT	infections than reducing RS.
Roifman [951]	1988	3	Prospective cross-over study	6 months of: 1. High dose (0.6 g/kg/month) IVIG 2. Low dose (0.2 g/kg/month) IVIG	Endoscopy, sputum cultures, Ig level, chest and sinus radiographs, spirometry.	High dose IVIG therapy was more effective than low dose IVIG.
Khalid [954]	2010	4	Case-control study	CRS with immune dysfunction or autoimmune disease (n=22) CRS control (n=22)	QoL measurement nasal endoscopy, sinus CT.	Immune dysfunction CRS patients had similar outcomes as control CRS patients.
Rose [1282]	2006	4	Case-control study	CVID (n=13) Selective IgA deficiency (n=10) Control (n=14)	MRI. Blood and nasal lavage after IVIG tested for -IgG, IgA, IgM -ECP, IL-8, TNF-α.	In the sample patients, IVIG was not sufficient to prevent chronic sinus inflammation.
Lucuab-Fegurgur [1285]	2019	4	Case series	62 patients with selective IgM deficiency, varying clinical manifestations	Subset (n=22) on IVIG treatment, resolution of symptoms.	Of 8 CRS pts on IVIG treatment, all but 1 had improvement in symptoms.
Pimenta [930]	2019	4	Cross-sectional	8 patients with hypogammaglobulinemia (age 16-65)	Clinical and laboratory characteristics.	In patients with hypogammoglobulinemia, the main infections were RS and pneumonia, and airway manifestations prevailed. Most patients received prophylactic antibiotic therapy.
Khokar [947]	2019	4	Case series	78 adult patients with IgG subclass deficiency	Upper and lower respiratory tract infections. Proportions and absolute numbers of specific CD-type T cells.	IgG3 subclass deficiency is the most common IgG subclass deficiency. The majority of patients treated with Ig responded by reduction in frequency of infections and requirement of antibiotics.

Papagiannopoulos [1290]	2018	4	Retrospective review	15 CRS patients on immunotherapy, 36 CRSwNP, and 56 CRSsNP	Histopathology variables, Lund–Mackay score (LMS), and sinonasal outcome test 22 scores.	CRS patients on immunotherapy exhibit histopathology and disease severity more similar to CRSsNP with trends toward increased neutrophilia and reduced fibrosis. In the appropriate clinical context, discontinuing or changing a patient's immunosuppressive regimen may be a valid treatment option in patients with CRSi.
Miglani [1292]	2018	4	Retrospective review	Retrospective review of 424 adult CRS patients undergoing ESS with a single surgeon. 5% (n=21) with immunodeficiency.	Endoscopic sinus surgery (ESS) outcome, revision rate.	Revision ESS rate for patients with immunodeficiency were 14%. CRSsNP subtypes with immunodeficiency merit further investigation to optimize outcomes.
Chiarella [1289]	2017	4	Literature review			In those patients with frequent CRS exacerbations or who are refractory to treatment, an immunodeficiency evaluation should be considered. Treatment includes vaccination, antibiotic therapy, Ig replacement and surgery.
Krivan [1286]	2017	4	Multi-center, open-label, prospective, single arm study	A highly purified 10% polyvalent immunoglobulin preparation (IqYmune®) for IV administration in patients with primary immunodeficiency was administered	Annualized rate of serious bacterial infections/patient.	Overall, 228 infections were reported, most frequently bronchitis, CRS, nasopharyngitis and upper respiratory tract infection. IqYmune® was shown to be

				to 62 patients (aged 2–61 years) with X-linked agammaglobulinemia or CVID		effective and well tolerated in patients with primary immunodeficiency.
Wang [1291]	2017	4	Retrospective review	28 patients on a TNF-α inhibitor diagnosed with RS	Patient demographics, RS characteristics, and treatment course.	Anti-TNF-α therapy can be associated with new-onset RS, mainly CRSsNP. Modification of anti-TNF-α therapy should be considered as an option in the medical management of these patients.
Walsh [931]	2017	4	Retrospective review	31 patients with CVID and SAD	Pretreatment and post-treatment Lund-Mackay scores, and frequency of RS and pulmonary infections requiring rescue antibiotics.	Ig replacement therapy has a positive impact on the frequency of RS and confirm its positive impact on pulmonary infections in adult patients with CVID and SAD.
Nayan [1287]	2015	4	Literature review			High clinical suspicion of primary immunodeficiency must be maintained in the setting of refractory. Early diagnosis and management of PID has a significant impact on their overall morbidity and QoL.
Stevens [1288]	2015	4	Literature review			Diagnosis of antibody deficiency in patients with CRS is important because of the large clinical implications it can have on sinus disease management.
Buehring [1297]	199	4	Prospectiv	16 R-CRS treated	MRI	Treatment was of

	7		e case series (open trial)	with azithromycin, N-acetylcysteine, and topical intranasal beclomethasone	Nasal lavage for ECP, IL-8, TNF-α Nasal culture	little benefit in patients with R-CRS with an underlying immunodeficiency.
Ocampo [1293]	2013	5	Expert opinion			Recommended prophylactic antibiotics, Ig replacement if indicated, and early ESS.
Kuruvilla [1296]	2013	5	Commentary/ review			Approximately half of the therapeutic dose is proposed for prophylactic antibiotics, with rotation to avoid drug resistance.
Dalm [1281]	2012	5	Expert opinion			Thymosin 1α may have an effect on monocyte function, a possible new target for therapy in R-CRS.
Ryan [1294]	2010	5	Expert opinion			Recommended prophylactic antibiotics, early, aggressive, culture-directed antibiotic treatment; and possible use IVIG.
Fergusson [1295]	2009	5	Expert opinion			Culture-directed antibiotics should be administered more promptly than in patients with normal immunity.
Ryan [1298]	2008	5	Expert opinion			Advocated prompt treatment with culture-directed antibiotics and the use of IVIG.

IX.E. Chronic Rhinosinusitis without Nasal Polyps: Complications

Complications from CRSsNP can be considered according to anatomic location, pathophysiology, clinical course, or disease severity. Although these conditions can be indolent, acute exacerbations can be life-threatening and may require surgery, particularly in immunocompromised patients or those with altered sinus anatomy. The true incidence of these complications is not well described. Herein, major and minor complications of CRSsNP are reviewed.

Major complications of CRSsNP typically occur as a result of worsening infection that extends into the eye, brain and/or lungs. The microbiology of these complications differs from that of ARS.[1299] Direct extension of RS into the orbit or chronic inflammatory changes near the orbit may begin with minor signs (*e.g.*, preseptal cellulitis) but can rapidly lead to orbital cellulitis/abscess causing enophthalmos,[1300] epiphora,[1301] diplopia,[1302] proptosis,[1303] optic neuropathy[1304,1305] and vision loss[1306-1308]. A recent study reported increased risk of orbital complications in adults, specifically in patients with previous sinus surgery or dehiscence of the lamina papyracea [464]. This study found that older age was the only major risk factor when looking at both CRSwNP and CRSsNP combined. Invasive fungal (most often seen in immunocompromised individuals) or bacterial infection along the skull base can lead to an epidural abscess or cavernous sinus thrombosis[1309]. These conditions require prompt diagnosis and often multidisciplinary intervention. The chronic inflammatory response observed in CRSsNP can worsen existing airway hyperreactivity, but can also lead to adult-onset asthma.[164] While the paranasal sinuses may act as a reservoir for chronic pulmonary infections, this association has not been well documented. When CRS is present concomitantly with recurrent pneumonia, immunodeficiency should be suspected.

Minor complications associated with CRS tend to occur with local tissue alterations and include mucocele formation,[1310,1311] and intrinsic narrowing and tortuosity of the frontal recess appears to be a predisposing factor for mucocele formation.[1311] Tissue remodeling can also lead to neo-osteogenesis[648,649,665] bone erosion and expansion[1312,1313] as well as osseous metaplasia.[1314,1315] Sinonasal mucosal remodeling, at times irreversible, can occur.[1316,1317] The varied medical therapies to treat CRSsNP, including antibiotics and systemic corticosteroids, can also cause serious complications and add morbidity to the disease.[1318-1323] Interestingly, recent evidence suggests that CRSsNP can be precipitated by treatment with anti-tumor necrosis factor-alpha inhibitors for rheumatic conditions.[1291,1324,1325]

X. Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

X.A. Incidence and Prevalence of CRSwNP

The epidemiology of CRSwNP has been investigated utilizing various methods. In France, 2.11% of 10,033 subjects screened with a questionnaire were identified as having nasal polyposis.[20] In Finland, a survey of 4,300 adults found that 4.3% reported having been diagnosed with nasal polyps.[21] Patient-reported surveys, however, lack objective confirmation of polyposis and are at risk of recall bias. Surveys, therefore, may not accurately estimate the true prevalence of CRSwNP. Interestingly, between 26% to 42% of autopsy specimens contain NP.[24,25]

The most accurate method, of diagnosing CRSwNP requires the reporting of symptoms with objective confirmation.[1326] In Sweden, 1387 adults were surveyed regarding CRS symptoms and examined with nasal endoscopy. Within that cohort, 2.7% were found to have nasal polyps.[22] The largest study evaluating the prevalence of CRSwNP was the Korean National Health and Nutrition Examination Survey from 2008-2012 in which 28,912 subjects underwent nasal endoscopy. In that study, the prevalence of CRSwNP was 2.6%.[23]

The incidence of symptomatic CRSwNP was estimated by Larsen and Tos in Denmark at 0.627 patients per 1000 per year. The same study found an incidence of 0.86 and 0.39 patients per 1000 per year for males and females, respectively.[1327] Incidence can also be estimated by analyzing billing codes. In a population-based analysis of ICD-9 codes from patients at the Geisinger Clinic from 2007 through 2009, the incidence of CRSwNP was 83±1.3 cases per 100,000 person-years.[17]

X.B. Diagnosis of CRSwNP

CRSwNP is defined by greater than or equal to 12 weeks of a combination of subjective and objective metrics as outlined in Section V.B. In distinguishing CRS into CRSsNP and CRSwNP, the only difference in diagnostic criteria between CRSwNP and CRSsNP is the presence of polyps.

Definition of Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)
Sinonasal inflammation persisting for more than 12 weeks, with a combination of at least two of the following symptoms and confirmed by endoscopic or radiographic findings:
- nasal obstruction/congestion/blockage
- anterior or posterior (mucopurulent) nasal drainage
- loss or decreased sense of smell
- facial pressure/pain/fullness

AND
presence of polyps

Table X-1. Evidence for the diagnosis of CRSwNP

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusion
Rosenfeld[88]	2015	1	Systematic Review (5 guidelines, 42 systematic reviews, 70 RCTs)	Adults with RS	Evidence based recommendations for adult RS	The diagnosis of CRS should include the presence of sinonasal inflammation as seen on anterior rhinoscopy, nasal endoscopy or CT.
Kaplan[142]	2014	1	Clinical Practice Guidelines (Canada)	CRS	Clinical summary of practice guidelines for CRS	Diagnosis of CRS based on type and duration of symptoms + objective finding of nasal inflammation. CRS is categorized based on presence or absence of polyps.
Fokkens[31]	2012	1	Position Paper	Adults with RS	Consensus statement	CRSsNP and CRSwNPin adults defined as: - Nasal inflammation with 2 or more symptoms, one of which is either nasal blockage/obstruction/congestion or nasal discharge - Facial pain/pressure - Reduction/loss of smell This should be supported by endoscopic signs of nasal polyps, purulent discharge, or mucosal edema or CT changes.
Meltzer[479]	2011	1	Review of Consensus Statements	Rhinosinusitis and subtypes	Compare recommendations of Rhinosinusitis Initiative, Joint Task Force on Practice Parameters, AAO-HNS, EP^{3}OS CRSwNP 2007, British Society for Allergy and Clinical Immunology	CRS symptoms persist 12 weeks or longer. The guidelines outline similar diagnostic parameters that combine symptom assessment with objective findings. Require presence of 2/4 symptoms (nasal congestion, anterior/posterior mucopurulent drainage, facial pain/pressure, decreased smell). Diagnostic testing is key difference between CRS and ARS .
Cottrell[522]	2018	2	Literature review (3	Adult CRS pts Exclusion	Develop CRS-specific quality indicators to	Strong recommendation for the diagnostic criteria based on multiple clinical consensus

			guidelines, 1 consensus statement)	criteria: Pts <18 yoa, systemic diseases resulting in CRS, non-English guidelines	evaluate diagnosis and management	statements. Diagnosis of CRS entails at least 2 CPODS present for 8-12 weeks plus documented objective finding (CT or endoscopy) of inflammation of the paranasal sinuses/nasal mucosa.
Thomas [530]	2008	2	Clinical Practice Guidelines	CRSwNP	Evidence-based methodology to identify and grade recommendations for management of RS	CRS is defined as presence of 2+ symptoms for > 12 weeks, one of which must be nasal discharge or nasal obstruction in addition to presence of facial pain/pressure or hyposmia. Anterior rhinoscopy/endoscopy should be done to identify polyps.
Bhattacharyya [480]	2010	3	Prospective diagnostic cohort	202 adult patients who presented for evaluation of CRS.	Improvement in diagnostic accuracy of CRS with use of nasal endoscopy	For patients meeting symptom criteria for CRS, a nasal endoscopy can improve diagnostic accuracy (improves the specificity, PPV, and NPV to 84.1, 66, 70.3 from 12.3, 39.9, 62.5, respectively). Addition of nasal endoscopy was not shown to statistically improve diagnosis of CRS in patients who failed to meet guidelines.
Bhattacharyya [1328]	2006	3	Prospective double-blind diagnostic study	703 patients referred with CRS	Evaluate correlation between CRS symptoms and radiographic findings	Presence of polyps and dyssomnia can distinguish between normal and diseased patients. Failure of nasal steroids after 5 week trial suggest possible CRS and should prompt imaging confirmation.
Bonfils[1329]	2005	3	Prospective study	474 patients with CRS symptoms	Evaluate clinical significance of nasal symptoms in diagnosis of CRS	Anosmia and loss of taste are distinguishing features of CRS.
Stankiewicz [554]	2002	3	Prospective diagnostic study	CRS patients	Use of nasal endoscopy in diagnosis of CRS	Nasal endoscopy is a good predictor of CRS only if nasal polyps, purulence, or mucosal edema was present.

Hopkins[1330]	`	4	Review	CRSwNP	Describe diagnosis and management of CRSwNP	CRS is defined as presence of 2+ symptoms for ≥12 weeks, one of which must be nasal discharge or nasal obstruction as well as presence of facial pain/pressure or hyposmia. There must be 1 objective finding of polyps or pus on CT or nasal endoscopy.
Hirsch [517]	2017	4	Retrospective cohort study	479 CRS patients	Evaluate if eliminating pain symptoms improves diagnostic accuracy for adult CRS	Removal of facial pain, ear pain, dental pain, and headache increases specificity (37.1 to 65.1%) without significant loss of sensitivity (79.2 to 70.3%) for diagnosis of CRS.
Dietz de Loos [564]	2013	4	Retrospective Case-Control Study	97 CRSsNP 137 CRSwNP	Utilizing only clinical evaluation to identify between CRSsNP and CRSwNP	Unable to distinguish between CRSsNP and CRSwNP on symptoms alone. Pts with CRSwNP often have higher scores in sense of smell and rhinorrhea.
Tomassen [524]	2011	4	Review	CRSsNP and CRSwNP	Review the various pathological observations in CRS	Inflammation in CRSwNP may be amplified by S. aureus enterotoxin. Elevation of IgE is one hallmark of CRSwNP.
Marple [526]	2009	4	Literature Review	Adult CRS	Evaluate algorithms for the diagnosis and management of CRS	Diagnosis of CRS requires presence of symptoms > 12 months. Patients with CRS symptoms but normal physical exam should undergo nasal endoscopy.

X.B.1. Establishing the Diagnosis of CRSwNP

Because of limited data, CRSsNP and CRSwNP are combined in Section IX.B.1.

X.B.2. Differential Diagnosis of CRSwNP

Several space occupying lesions in the nasal cavity can appear like NPs and must be considered (Table X-2).[1331] Sometimes normal structural variants, such as concha bullosa and medialized uncinate process, are misdiagnosed as NPs. Severely hypertrophied turbinates may also be mistaken as NPs. Although NPs have a characteristic translucent gray-to-yellow colored, teardrop-shaped morphology, those characteristics could be seen in other benign or malignant lesions. Alternatively,

NPs may have different morphology involving a significant fibrous component, such that biopsy is needed to confirm the diagnosis. Common benign tumors shaped like NP include inverted papilloma, lobular capillary hemangioma, cavernous hemangioma and schwannoma.[1332] Juvenile angiofibroma should be suspected in adolescent males. Malignant tumors simulating polyps include squamous cell carcinoma, salivary gland-type carcinoma, olfactory neuroblastoma and lymphoma, among others. Key features distinguishing sinonasal tumors from NPs are unilateral disease,[1333] lack of sinus inflammation in some cases and surface features, such as easy bleeding and ulceration.

Encephaloceles can masquerade as NPs.[1334] This lesion typically arises in the midline nasal and anterior skull base and can cause nasal obstruction. Characteristic signs are pulsation and expansion of the mass with crying or compression of the jugular vein. Biopsy or nasal polypectomy based on the misdiagnosis as NP can cause intracranial complications. Intracranial connection should therefore be ruled out before any intervention in cases of a unilateral nasal mass, especially in pediatric cases. Unilateral nasal obstruction or rhinorrhea in the pediatric population should also raise suspicion for a foreign body.[534]

An antrochoanal polyp differs from other NPs in that it tends to be a large unilateral single mass comprised of cystic and solid components. Removal of the base may decrease the chance of recurrence. It usually originates from the posterior or inferior walls of the maxillary sinus and extends into the choana through an accessory maxillary sinus ostium.[1335]

NPs can be associated with comorbid diseases including aspirin intolerance, asthma, AR, CF, and PCD.[1336-1340] Because NPs are often secondary to continued inflammation caused by these comorbid diseases, the clinician should evaluate underlying conditions in order to more effectively treat NPs.

Table X-2. Differential diagnosis of nasal polyps

Benign
Mucus retention cyst
Antrochoanal polyp
Mucocele
Dacryocystocele
Nasal dermoid
Glioma
Encephalocele
Osteoma
Respiratory epithelial adenomatoid hamartoma (REAH)
Schneiderian papilloma
Juvenile nasopharyngeal angiofibroma
Hemangiopericytoma
Capillary hemangioma
Cavernous hemangioma
Vascular malformation
Granulomatosis with polyangiitis
Sarcoidosis
Malignant
Squamous cell carcinoma
Adenoid cystic carcinoma

Adenocarcinoma
Esthesioneuroblastoma
Chordoma
Lymphoma
Melanoma
Rhabdomyosarcoma
Fibrous histiocytoma

X.B.3. Cost-Effective Work Up of CRSwNP

Because of limited data, CRSsNP and CRSwNP are combined in Section IX.B.3.

X.C. Pathophysiology of CRSwNP

X.C.1. Associated Factors in CRSwNP: Asthma

The association of CRSwNP and asthma has been supported by numerous studies showing similarities between both diseases.[1341-1343] CRSwNP is present in 2%–4% of the adult population,[26,164] often associated with other respiratory diseases such as asthma,[1344] aspirin sensitivity,[1345] and idiopathic bronchiectasis.[1346]

The prevalence of asthma in the general population is around 5% while it scales to 25% in patients with CRS and between 20%–45% in patients with CRSwNP.[196,1347] Two perspectives need to be considered: patients with CRSwNP suffering from asthma and asthmatic patients developing CRSwNP. An England National CRS Epidemiology Study included 221 controls, 553 CRSsNP, 651 CRSwNP, and 45 AFRS patients. The prevalence of asthma was 9.95, 21.16, 46.9 and 73.3%, respectively.[196] Similarly, the GA^{2}LEN RS cohort involved 52,000 subjects demonstrating that almost 50% of CRSwNP patients developed asthma.[195] In non-atopic asthma and late-onset asthma, CRSwNP was found frequently, reaching 15% to 26% depending on the study.[149] Even more, in severe asthmatic patients the prevalence of CRSwNP can reach up to 40.6%.[1348]

The typical patients with CRSwNP and asthma are older, with longer duration of symptoms, higher incidence of allergic rhinitis, bronchial obstruction, higher CT score, total polyp scores (TPS), and higher number of sinonasal surgeries.[195,1349] Similarly, the presence of asthma has been related to worse paranasal sinus disease, significantly higher endoscopy and CT severity scores as well as higher absolute eosinophil counts and total IgE levels.[167] Lin *et al.*[1350] found that patients with moderate-to-severe asthma displayed worse sinus disease than those with mild asthma, with significantly higher mean CT-scores. Subsequently, the association of both asthma and CRSwNP have also been related to an impaired QoL and loss of productivity.[1351-1353] Alobid *et al.*[1354] showed that the QoL in patients with CRSwNP was worse with concomitant asthma mainly on physical functioning, body pain, and vitality. The same group[1344] found that persistent asthma had an accumulative impact on the loss of smell, proposing the loss of smell as a predictive symptom to

identify severe asthma. Other authors have also found lower olfactory outcomes in patients who have associated CRSwNP and asthma[1355] or AERD.[1356]

Considering the strong association between asthma and CRS, the question is raised of whether treatment of one condition may improve outcomes in the other. Some studies have shown that treatment of CRS decreases the severity of asthma.[170,191,1353] Reflecting this, GINA 2019 guidelines recommends the assessment of comorbidities including CRS in every step of the therapeutic approach for asthma.[1357] On the other hand, the American Lung Association–Asthma Clinical Research Centers' Writing Committee study[1358] concluded that no significant improvement in asthma control could be achieved from treatment with nasal corticosteroids.

Evidence suggests that the surgical treatment of CRSwNP with concomitant asthma has a positive impact on asthma clinical and biological parameters (Table X-3). Using objective and subjective sinonasal and asthma outcome measures, studies have demonstrated clinical improvement following ESS.[170,191,1359-1361] In patients with asthma and CRSwNP, ESS showed an improvement in asthma severity scores, reduced need of inhaled corticosteroids and reduced the frequency of asthma-related emergency room visits.[1361] A prospective randomized trial showed that patients with CRSwNP had a significant improvement in nasal and lower airway symptoms after ESS.[1355] The same authors followed a cohort of CRSwNP patients after ESS, showing an improvement in asthma symptoms score, daily peak expiratory flow and nasal inspiratory flow.[1362] Zhang *et al.*[1363] observed a larger QoL improvement measured by SNOT-22 at 1- and 3 months after surgery. In conclusion, data on the impact of surgery for NP on comorbid asthma mostly point towards a beneficial effect of surgery on different parameters of asthma severity.

Given monoclonal antibodies (MAbs) target different inflammatory markers involved in the pathophysiology of CRSwNP the questions arise whether they might have an additional influence on patients suffering from CRSwNP and asthma. A preliminary observational study[1364] conducted on patients suffering from refractory asthma and CRSwNP showed a therapeutic value for both conditions. A recent systematic review concluded that MAbs alone clinically improved CRSwNP. Omalizumab and mepolizumab showed improvements in TPS and symptoms score in patients with CRSwNP when compared with placebo. Reslizumab reduced polyp size in patients with high intranasal interleukin-5 levels. Dupilumab achieved a 70% reduction in TPS compared with 20% in the placebo group ($p < 0.001$).[290]

Although the two most recent randomized controlled studies on dupilumab were designed to assess its efficacy on patients with CRSwNP, those patients also suffering from asthma and who were allocated in the control group had more adverse effects, asthma among them.[60] This finding suggests a potential positive “side-effect” of a monoclonal antibody on asthma in patients with both conditions. In fact, the meta-analysis on the effect of monoclonal antibodies against IL5, anti-IL5R and anti-IL13 showed that all drugs were superior to placebo groups in preventing rates of asthma exacerbation.[1365]

Asthma as a Contributing Factor for CRSwNP

Aggregate Grade of Evidence: B (Level 1: 2 studies; level 2: 7 studies; level 3: 7 studies)
Benefit: Early diagnosis of asthma in patients with CRSwNP.
Harm: Inconvenience of office visit and lab test.
Cost: The lab tests for diagnosis of asthma has associated costs
Benefits-Harm Assessment: Preponderance of benefit over harm
Value Judgments: Asthma in nasal polyposis is highly prevalent
Policy Level: Recommendation for asthma screening in patients with CRSwNP
Intervention: Screen all patients with CRSwNP for asthma symptoms; consider additional testing as needed.

Table X-3. Evidence for the association of CRSwNP and asthma

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoints	Conclusion
Ramonell[1366]	2020	1	Meta-analysis	Patients with severe eosinophilic asthma treated with either benralizumab, dupilumab, mepolizumab or reslizumab	Frequency of acute asthma exacerbations	All mAbs decreased the frequency asthma exacerbations in patients with eosinophilic asthma.
Vashishta[1360]	2013	1	Systematic review and meta-analysis	Studies reporting asthma outcomes among CRS patients undergoing ESS	Overall asthma control (symptoms, FEV1, medication utilization) Frequency of asthma attacks and hospitalizations	ESS is associated with improved asthma control, but not lung function as measured by FEV1.
Bachert[60]	2019	2	Meta-analysis of two RCTs	Sinus 24: dupilumab 300 mg every 2 weeks for 24 weeks Sinus 52: dupilumab 300 mg every 2 weeks for 52 weeks	Changes from baseline to week 24 in NPS, congestion and obstruction	Dupilumab was well tolerated and reduced NPS, sinus opacification, and severity of sinonasal symptoms.
Swierczyńsk	201	2	Pilot RCT	AERD treated	Changes from	Among patients with

a-Krępa[1367]	4			with aspirin desensitization and 624mg daily vs. placebo ATA with nasal polyps under the same protocol	baseline to six months in PROMs (SNOT-22, ACQ) Rescue medication Peak nasal inspiratory flow Inflammatory mediators	AERD, AD improves upper and lower airway patient reported outcomes with decreased corticosteroid utilization and increased peak nasal inspiratory airflow.
Ehnhage[1355]	2009	2	RCT	CRSwNP and asthma treated with ESS and 400 µg fluticasone proprionate nasal drops vs. placebo	Changes from baseline to 21 weeks in: Nasal outcomes (symptoms, polyp score, peak flow, butanol test) Lower airway outcomes (symptoms, incentive spirometry and mean daily peak expiratory flow)	ESS improved mean asthma symptom scores and peak expiratory flow as well as all nasal outcomes No significant difference between fluticasone and placebo cohorts, potentially due to shared impact of ESS.
Ragab[170]	2006	2	Nested analysis of RCT	Asthma and CRS patients treated with ESS or appropriate medical treatment	Changes from baseline to 12 months in: Asthma control and reported symptoms FEV1, FENO and peak flow Medication use Hospitalizatio n	Both medical and surgical treatment of CRS is associated with subjective and objective improvements in asthma.
Dejima[1368]	2005	2	Prospective observation al trial	CRS patients undergoing ESS with or without asthma	Asthma control (peak flow and medication utilization) Sinonasal	Improved surgical outcomes among CRS patients without asthma (vs with). Asthmatics have improved FEV1 and

					symptoms (VAS)	decreased medication utilization following ESS.
Ikeda[1369]	1999	2	Prospective observational trial	Asthma patients with comorbid CRS undergoing ESS under local anesthesia vs. control	Six-month pre and post-operative evaluation of: Peak expiratory flow Corticosteroid utilization Sinonasal VAS	ESS improves asthma control, as measured by increased FEV1. Decreased corticosteroid use noted in a subset of patients with asthma.
Uri[1359]	2002	2	Prospective observational trial	Patients with CRSwNP and asthma undergoing ESS	Asthma and sinonasal questionnaires Spirometry Bronchodilator and corticosteroid utilization	ESS is associated with improved PROMs and decreased utilization of asthma control medications, but not objective measures of pulmonary function.
Zhang[1363]	2014	3	Retrospective review	Adults with CRS and asthma undergoing ESS	QoL (SNOT-22)	Among all CRS patients undergoing ESS, those with nasal polyps and/or asthma experience the largest improvement in QoL (as measured by total SNOT-22 score) at one and three months after surgery
Ehnhage[1362]	2012	3	One-year follow-up of RCT	Patients with CRSwNP and asthma undergoing ESS	PROMs (SF-22, dyspnea/cough VAS, olfaction score) Objective measures (peak nasal and pulmonary expiratory flow, spirometry, NPS, butanol test	Postoperative improvements in asthma symptom scores, peak expiratory flow, sinonasal outcomes including olfaction, and QoL are generally maintained at 12-months.
Batra[1370]	200	3	Retrospecti	Adults with CRS	Subjective	ESS demonstrates a

	3		ve review	and asthma undergoing ESS (~50% AERD)	symptoms Objective measures (CT scores, PFTs, corticosteroid and ED utilization)	beneficial effect on sinonasal and asthma symptoms. Subset of patients with AERD have inferior upper and lower airway uptcomes compared to those without aspirin sensitivity.
Lambli[1371]	2000	3	Prospective observational trial	Patients with CRSwNP and asthma undergoing appropriate medical therapy with or without ESS	Sinonasal symptoms Lower airway symptoms, spirometry and responsiveness	Nonreversible airflow obstruction appears over a 4-yr follow-up period in medically recalcitrant CRSwNP patients requiring ESS.
Dunlop[171]	1999	3	Retrospective	Patients with asthma undergoing ESS for CRS with or without NP	Asthma control (peak flow, rescue medication requirements and hospitalizations)	ESS is associated with improved measures of asthma control among CRS patients with and without nasal polyps.
Senior[1372]	1999	3	Prospective observational trial	Patients with CRS and asthma	Asthma symptom score Asthma exhacerbations Utilization of Asthma control medication	ESS is associated with long-term improvement in asthma control, as measured by patient symptoms, utilization of control medications and frequency of acute exacerbations.
Nishioka[1373]	1994	3	Prospective observational study	Adults with CRS and asthma undergoing ESS	Symptom scores Medication utilization Number of emergency visits	ESS is associated with improved symptom scores and decreased utilization of asthma control medications and ED presentations among patients with comorbid asthma.

X.C.2. Contributing Factors for CRSwNP: Allergy

In order to address the question of what role allergy plays in the pathophysiology of CRSwNP, we must first agree on what we mean by "allergy". Traditionally, this has been defined as systemic IgE-

mediated hypersensitivity in the setting of clinical symptoms attributable to this hypersensitivity. As our understanding of the complexities of the human immune system deepens, our methods of assessing biochemical markers suggestive of allergic disease proliferate, and our characterization of CRS pivots towards endotypes, simple answers to this question elude us.

IgE-mediated allergy has been among the multiple etiologies suggested to cause CRSwNP. Allergy is strongly associated with Th2-mediated response. Multiple studies suggest a prominent role for Th2–mediated inflammation in the pathogenesis of CRSwNP[821,1374,1375] Bachert *et al.* isolated elevated Th2 cytokines IL-5 and IL-13 in nasal polyp tissue.[1374] Similarly, eosinophilic inflammation is commonly identified in both atopy and CRSwNP.[1376,1377] Interpretation of these data are complicated by demonstration that Thymic Stromal Lymphopoetin (TSLP) induces a Th2 inflammatory response in nasal polyp tissue using non-IgE induction methods.[1378] Direct evidence of a causal connection between atopy and CRSwNP presents an equally complex picture.

Inhalants. Some observational population data suggest an association between atopic disease and CRSwNP.[1379] Tan, et. al. found a higher number of inhalant sensitivities in CRSwNP patients as compared to CRSsNP and rhinitis patients, although the overall sensitivity rates were similar.[1380] Several studies have identified associations between systemic hypersensitivity to specific allergens and CRSwNP. These include dust mite,[1381,1382] dust mite and *Olea europaea,*[1383] and dust and cockroach.[1384] Another group found increased rates of *Candida* hypersentivity in CRSwNP patients compared to both allergic controls and CRSsNP patients.[1382] The association of MT polyposis and newly described "central compartment atopic disease" (CCAD) postuates a strong association between allergy and CRSwNP for this specific subtype of CRSwNP. The evidence addressing this specific entity is included in section X.C.2.1.

Other studies have found no significant association between CRSwNP and allergy. Study findings include similar rates of hypersensitivity between CRSwNP and CRSsNP groups;[1385] similar incidence of allergy and endotype profiles between CRSwNP and CRSsNP;[1386] no difference in symptoms among allergic and non-allergic CRSwNP patients during pollen season[1387] no differences in nasal polyp size, CT scores, symptoms, or recurrence of disease between atopic and non-atopic CRSwNP patients[1388] or difference in presenting symptoms or post-operative course of CRSwNP patients based on allergic status[1389,1390] In contrast, one study found increased rates of atopy in CRSwNP patients, though no significant difference in symptoms scores.[1391]

Complicating this picture, rates of systemic atopy vary between eosinophilic and non-eosinophilic CRSwNP populations.[1392] Additionally, local production of specific IgE is seen in the absence of systemic atopy.[1393] Evidence also suggests that circulating IgE is largely mucosally produced.[1394]

Taken together, these data suggest that inhalant allergy may be a disease-modifying factor in CRSwNP.

Food. Collins and colleagues found that CRSwNP patients exhibited positive intradermal testing to wheat, tomato, and potato, but not to inhalants.[1395] Another prospective study demonstrated nearly 8 fold higher incidence of food allergy among polyp patients when compared with healthy

controls.[1396] Lill *et al.* found a strong association between CRSwNP and milk allergy,[1397] though neither wheat nor overall incidence of food sensitivity differed between diseased and healthy populations. Other studies comparing systemic IgE for food sensitivity between CRSsNP and CRSwNP demonstrated no such relationship,[1398] with Al-Quodah finding, "no significant differences in the prevalence, type, number of positive food allergens and class level between the two groups."[1399] These studies present conflicting evidence for the role of food allergy in the pathogenesis of CRSwNP disease.

In conclusion, despite an overlap of immunologic pathways and of symptoms, conflicting data in the literature prevents definitive conclusion about the association between atopy and nasal polyposis. Therefore, allergy can be considered a disease-modifying factor in CRSwNP. As the understanding of CRS and atopy evolve, further study will shed additional light on this relationship.

Inhalant Allergy as a Contributing Factor for CRSwNP

Aggregate Grade of Evidence: C (Level 3: 7 studies; level 4: 8 studies; level 5: 1 study)

Table X-4. Evidence for inhalant allergy as a contributing factor for CRSwNP

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Allergy Testing Method	Association between Allergy and CRSwNP	Conclusion
Xu[1392]	2015	3	Prospective case series	Eosinophilic CRSwNP Non-eosinophilic CRSwNP Controls	Rates of sensitivity to inhalant allergens by *in vitro* methods. Total IgE.			Higher total IgE in eNP compared to nNP and controls. Higher rates of sensitivity among nNP compared to eNP and controls.
Tan[1380]	2011	3	Prosective case control	CRSwNP CRSsNP	Rate of atopy by SPT Number of positive tests		Possible	Higher atopy in CRSwNP than controls, but similar to CRSsNP. CRSwNP had higher number of sensitivities.

Munoz[1383]	2009	3	Prosective case control	CRSwNP Healthy Control	Rate of atopy by SPT	SPT	Yes	Twice as many CRSwNP with sensitivity to dust and *O. europaea* than controls.
Asero[1400]	2001	3	Prosective case control	CRSwNP CRSsNP	Rate of atopy by SPT	SPT	Yes	Higher incidence & more rapid response to *Candida* and increase positivity to at least 1 mold.
Asero[1382]	2000	3	Prosective case control	CRSwNP Patients with known allergy	Rates of sensitivity to specific antigens by SPT	SPT	Yes	Higher prevalence of Candida and dust mite sensitivity in CRSwNP than without polyps.
Pumhirun[1384]	1999	3	Prosective case control	CRSwNP Healthy Control	Rate of atopy by SPT	SPT	Yes	CRSwNP were 6 times more likely to have positive antigen sensitivity than healthy controls.
Keith[1387]	1994	3	Prosective case control	CRSwNP+RW allergy CRSwNP without RW allergy +RW allergic, Non NP	VAS scores during RW season Nasal lavage albumin levels	SPT	No	No difference in allergic symptoms for ragweed positive CRSwNP during ragweed season. Inflammatory markers

								remained elevated year-round.
Ho[1391]	2019	4	Retrospective case control	Surgical CRS patients	Incidence of atopy on *in vitro* methods. SNOT-22.			Atopy associated with CRSwNP and higher SNOT-22 scores.
Bachert[1377]	2018	4	Retrospective case series	CRSwNP	Th2 biomarkers. Patient reported atopic disease			Elevated Th2 biomarkers in patients reporting atopic disease.
Golebski[1378]	2016	4	Retrospective case control	Nasal polyp tissue. Inferior turbinate tissue from healthy controls	mRNA and protein expression level of TSLP, IL-25, and IL-33 on exposure to TLR-specific trigger			Non-allergic, viral induction of Th2 immune response.
Pearlman[1385]	2009	4	Prospective case series	CRS patients	Rate of atopy by SPT Lund-Mackay score	SPT	No	No association between Lund-Mackay score and presence of positive SPT.
Bonfils[1390]	2008	4	Prospective case series	surgical CRSwNP patients	Nasal obstruction Posterior rhinorrhea Loss of smell	*In vitro*	No	No difference in post-operative symptoms or use of steroids in CRSwNP with and without allergy by *in vitro* testing.
Houser[1381]	200	4	Retrospectiv	Surgical	Rate of	*In*	Yes	Increase in

	8		e case control	CRSwNP pts Surgical CRSsNP patients	atopy by *In vitro*/ IDT	*vitro*/ IDT		PAR among CRSwNP. PAR and tobacco associated with NP.
Erbek[1388]	2007	4	Retrospective case series	CRSwNP and allergy CRSwNP without allergy	Polyp size CT score Total eosinophil count Serum total IgE Symptom score Recurrence	SPT	No	Presence of allergy did not affect polyp size, symptoms, CT opacification, or disease recurrence.
Bonfils[1389]	2006	4	Prospective case series	CRSwNP	Nasal obstruction Anterior and posterior rhinorrhea Facial pain Loss of sense of smell	*In vitro*	No	No difference in symptoms at presentation or after 1 year of medical management in CRSwNP regardless of *in vitro* allergy test results.
Mortuaire[1386]	2018	5	Prospective case series	CRSwNP	Rate of atopy by SPT Rate of positive biomarkers (IgE, IgA, IL-5, IL-9, ECP, EDN) in blood and nasal secretions			Concordance of SPT and biomarker analysis (IgE, IgA, IL-5, IL-9, ECP, EDN) in blood and nasal secretions.

Table X-5. Evidence for food allergy as a contributing factor for CRSwNP

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Allergy Testing Method	Association Between Allergy And CRSwNP	Conclusion
Lill[1397]	2011	3	Prosective case control	CRSwNP Control	Incience of food allergy	*In vitro*	Yes	Milk allergy was much more prevalent in CRSwNP, but other foods were not different between study groups.
Collins[1395]	2006	3	Prosective case control	CRSwNP Rhinology clinic patients without NP	Incidence of inhalant allergy Incidence of food allergy	IDT	Yes	Significantly higher rate of food sensitivity in CRSwNP than general population, but similar incidence of inhalant allergy by IDT.
Pang[1396]	2000	3	Prosective case control	CRSwNP (Part 1) CRSwNP and controls (Part 2)	Incidence of known food allergy (Part 1) Incidence of known food allergy using IDT(Part 2)	IDT	Yes	Food allergy was present significantly more often in CRSwNP than controls.
Veloso-Teles[1398]	2019	4	Retrospective case control	CRSwNP non-CRS controls	Levels of IgG antibodies to foods Levels of IgE antibodies to foods	*In vitro*		Levels of IgG to foods lower in CRSwNP patients. Levels of IgE to foods no

								different between CRSwNP and controls.
Al-Qudah[139]	2016	4	Prosective case series	CRSwNP CRSsNP	Prevalence of food hypersensitivities on *in vitro* testing Number of food hypersensitivities Types of food hypersensitivities			No difference in prevalence, type, number of food allergens.

X.C.2.1 Central Compartment Atopic Disease

Central compartment atopic disease (CCAD) was not included in ICAR-RS-2016, as this entity had not yet been described. In 2014, White *et al.* published a case series of patients with middle turbinate (MT) polyps or polypoid edema.[1] In this series 16/16 patients who underwent allergy testing demonstrated sensitivity to at least 1 allergen on testing; this was the first report of an association between allergy and MT polyps/edema. Evidence supporting the strength of this association followed in 2017 in a cross-sectional study by Hamizan *et al.*, which graded the degree of MT edema (normal-focal-multifocal-diffuse-polypoid edema) and compared these findings with allergy testing results in 187 patients determining positive predictive value (PPV). This study reported that multifocal (PPV 85.15%), diffuse (PPV 91.7%) and polypoid edema (PPV 88.9%) – the highest grades of MT edema – had the strongest association with allergy. Using multifocal MT edema as a cutoff, sensitivity (94.7%) and specificity (23.4%) for association with inhalant allergy were determined by receiver-operator (ROC) analysis.

A comparison of traditional paranasal sinus polyposis to MT polyposis was published in 2017 by Brunner *et al.*[3] In this report, the authors describe significant differences between patients with diffuse paranasal sinus polyposis and polyps/polypoid edema originating on the MT. In this analysis, traditional paranasal sinus polyposis patients were more commonly older, male, had CRS, and had higher L-M and NOSE scores. MT polypoid change patients were more commonly younger, female, had AR, and had lower L-M score.

In 2017, DelGaudio *et al.* introduced the term “central compartment atopic disease” to describe an entity associated with MT polypoid edema and atopy that has progressed to involve additional central nasal cavity structures (superior turbinate, posterior nasal septum). CCAD typically also involves the sinus cavities in a medial to lateral progression, sparing the lateral and superior sinus

surfaces such as the ethmoid/sphenoid roof, lamina papyracea, and lateral aspect of the maxillary sinuses. In the introductory multi-institutional case series, CCAD was associated with symptomatic allergy in all patients and allergen sensitivity on testing in 93.3%. It has also been demonstrated that CCAD may coexist with other sinus inflammatory processes and pathologic findings such as AERD[5] and respiratory epithelioid adenomatous hamartoma[6] (REAH). In comparison to other subtypes of CRSwNP, CCAD (whether isolated or associated with diffuse paranasal sinus polyposis) demonstrates significantly higher association with allergy ($p<0.001$) than CRSwNP not-otherwise-specified.

Two studies have evaluated the radiologic characteristics of CCAD with the aim of identifying CT scan findings that point to possible allergic contribution in CRS. Hamizan *et al.* evaluated CT scans of 112 patients (224 sides), noting centrally limited disease was associated with positive allergy testing ($p=0.03$, specificity 90.82%, PPV 73.53%).[8] Roland *et al.* evaluated CT scans from 356 patients, noting certain features – oblique MT orientation, septal involvement and lower L-M score – are associated with CCAD.

Based on literature published in recent years, EPOS2020[10] has included CCAD as a diagnostic category under Type 2 endotypes of diffuse CRS. However, some controversy remains on this topic. In response to a 2020 CCAD editorial by DelGaudio[11], Chandra[12] questions the true presence of polyps emanating from the MT (versus presence of a bulbous MT), points to the low (<5%) prevalence of polyps in AR patients, and notes that local allergic manifestations are features not unique to CCAD.

CCAD is a new concept, largely introduced since ICAR-RS-2016. Early reports, primarily from a few centers, have supported an allergic etiology for CCAD. However additional work should be undertaken to further verify the CCAD concept and treatment responses. This includes evaluation of local allergic responses (antigen-specific IgE, nasal allergen challenge), histologic studies, endotyping of inflammatory processes, and evaluation of clinical outcomes (extent of surgery, pharmacotherapy, allergen immunotherapy).

Inhalant Allergy as a Contributing Factor for Central Compartment Atopic Disease

Aggregate Grade of Evidence: C (Level 3: 1 study; level 4: 8 studies)

Table X-6. Evidence for Central Compartment Atopic Disease

Study	Year	LOE	Study Design	Clinical Endpoints	Conclusions
Hamizan[2]	2017	3	Cross sectional study of graded MT polyps/edema	Allergen sensitivity on testing	Higher grades of MT polypoid edema are associated with

			(n=187)		inhalant allergy. Sensitivity (94.7%) and specificity (23/4%) have been determined using multifocal MT edema as a cutoff on ROC analysis.
Marcus[7]	2020	4	Case-control evaluation of CRSwNP subtypes (n=356)	Allergy and asthma prevalence by subtype	CCAD demonstrates significantly higher association with allergy (p<0.001) than CRSwNP NOS.
Roland[9]	2020	4	Case-control evaluation of CRS patient CT scans (n=356)	CT scan pattern of opacification	Oblique MT orientation, septal involvement and lower LM score are associated with CCAD
Schertzer[6]	2020	4	Case series of REAH patients (n=26)	CCAD involvement in REAH	CCAD was identified in 19.2% of REAH patients. 94.7% of REAH patients had clinical AR.
DelGaudio[5]	2019	4	Case series of AERD patients (n=72)	CCAD involvement in AERD	Central compartment findings in AERD are significantly associated with clinical allergy (p<0.0001)
Hamizan[8]	2018	4	Case series of CRS patients (n=112)	CT scan pattern – diffuse vs. central Allergy test positivity	Centrally located disease was associated with sensitivity on allergy testing (p=0.03, specificity 90.82%, PPV 73.53%).
DelGaudio[4]	2017	4	Case series of CCAD patients (n=15)	Characteristics of CCAD	Introduced the term CCAD. 100% of patients had allergy symptoms. 93.3% were positive on allergy testing.
Brunner[3]	2017	4	Case series Paranasal sinus polyposis (n=23) MT polypoid change (n=44)	Demographics Presence of CRS, AR, asthma SNOT-22, NOSE LM score Eos, total IgE	Paranasal sinus polyposis patients were more commonly older, male, had CRS, and had higher LM and NOSE scores. MT polypoid

					change patients were more commonly younger, female, had AR, and had lower LM score.
White[1]	2014	4	Case series of MT polyps/polypoid edema pts (n=25, 16 had allergy testing)	Allergen sensitivity on testing	There is a strong association between allergen sensitivity and MT polyps/polypoid edema.

X.C.3. Contributing Factors for CRSwNP: Biofilms

With regard to CRSwNP, biofilm presence and polyp status seem to have at most a limited relationship. One study showed no association,[570] while another study showed a trend towards an increased number of bacterial species in CRS with polyps. A more recent study demonstrated an association between biofilms and polyp status.[1401] Interestingly, fungi were only detected in the presence of NPs, although this was a rare finding.[577] In CRSwNP there was no qualitative difference in inflammatory cells between patients with or without biofilms.[1402] Quantitatively, there is an association between biofilms and increased eosinophilic content, in accordance with other evidence that biofilms encourage a Th2 immune response.[729,1403] A possible explanation of this observation is the high prevalence of *S. aureus* as well as *P. aeruginosa* in CRS biofilms.[586,1404] *S. aureus* is associated with production of superantigen thereby driving a Th2 response[729] while pseudomonal quorum sensing molecules have been demonstrated to activate solitary chemosensory cells[609,1405] via canonical taste signaling pathways.[1406] Solitary chemosensory cells (SCCs) are rare (<2%) airway epithelial cells that have demonstrated their ability to regulate epithelial cell antimicrobial peptide secretion via taste receptor transduction.[1407] More recently, SCCs have been shown to be the exclusive epithelial source of the early Th2 cytokine IL-25,[1408-1410] which is elevated in CRSwNPs.[162,1411-1413] Additionally, SCCs have recently been demonstrated to be active producers of leukotrienes[1414] which are elevated in subsets of CRSwNP patients. Thus, pseudomonal biofilms may tonically stimulate SCC function with resultant Th2 cytokine production.

Biofilms as a Contributing Factor for CRSwNP

Aggregate Grade of Evidence: C (Level 3: 2 studies; level 4: 1 study)

Table X-7. Evidence for biofilms as a contributing factor for CRSwNP

Study	Year	LOE	Study Design	Study Groups	Clinical End-point(s)	Conclusion

Danielsen [1401]	2016	3	Cross-sectional study of biofilm presence	27 CRSsNP 34 CRSwNP 25 Control	Biofilm presence from intranasal biospy	97% of CRSwNP subjects, 82% of CRSsNP subjects, and 56% of control subjects had bacterial biofilms present.
Wang[1402]	2014	3	Cross-sectional study of biofilm presence	15 CRSsNP 19 CRSwNP 13 Control	Biofilm presence from intranasal biopsy	73% of CRSsNP subjects, 74% of CRSwNP subjects, and 0% of control subjects had bacterial biofilms present. No significant difference in inflammatory cells in individuals with and without biofilms.
Arjomandi[1403]	2013	4	Eosinophilia versus biofilm presence	20 CRS 9 Control	Eosinophil major basic protein staining	Eosinophil major basic protein staining is significantly higher in biofilm-positive patients.

X.C.4. Contributing Factors for CRSwNP: Fungus

Because of limited data, CRSsNP and CRSwNP are combined in Section IX.C.3.

X.C.5. Contributing Factors for CRSwNP: Neo-osteogenesis

Because of limited data, CRSsNP and CRSwNP are combined in Section IX.C.4.

X.C.6. Contributing Factors for CRSwNP: Gastroesophageal Reflux

Because of limited data, CRSsNP and CRSwNP are combined in Section IX.C.5.

X.C.7. Contributing Factors for CRSwNP: Vitamin D Deficiency

Vitamin D deficiency (VD3) is classically known for its actions in bone and calcium homeostasis. Recently, however, it has also been shown to be a potent immunomodulatory steroid hormone involved in the regulation of epithelial cell, dendritic cell, monocyte, macrophage and T-cell functions.[710,711] The literature on Vitamin D3 in CRSwNP largely consists of case series, case-control and *in vitro* studies.

Several reports have linked CRSwNP and low 25VD3. Adult and pediatric CRSwNP and AFRS patients had significantly lower serum 25VD3 than controls and in adults, low 25VD3 correlated with greater sinus bone erosion as measured on CT scan.[718] A more recent study similarly found that CRSwNP

patients and CF patients with nasal polyps (CFwNP) also demonstrated low serum 25VD3 levels and that 25VD3 inversely correlated with Lund-Kennedy and Lund-Mackay scores in CRS patients and CF patients.[714]

In a retrospective analysis of 70 CRSwNP patients**,** 55% of patients were 25VD3 insufficient (<30 ng/ml) and an additional 30% deficient (<20 ng/ml).[1415] The lowest levels were in African American patients with nearly 80% insufficient. Severity of mucosal disease (defined by Lund Mackay Score on CT) also correlated with low 25VD3 level. In Taiwanese patients with CRSwNP, a study found significantly lower 25VD3 in CRSwNP patients compared to CRSsNP patients.[720] Low 25VD3 also correlated with more severe polyp grade. 25VD3 was inversely related to Lund Mackay score, consistent with US patients.[1415]

With regard to allergic status, a study found that Turkish patients with concurrent CRSwNP and AR had significantly lower serum 1,25VD3 than healthy controls.[1416] This effect was not seen in CRSwNP without AR, implying that allergy is associated with VD3 deficiency. This contrasts with US reports where CRSwNP alone was associated with low 25VD3. The two groups however measured different molecules with the Turkish work measuring the active 1,25VD3 and the US studies measuring 25VD3, conventionally considered the more accurate marker of Vitamin D3 status due to its longer half-life. The Taiwanese study examining interplay of allergic factors in CRSwNP reported an inverse correlation between 25VD3 and total IgE, though this was not statistically significant.[720]

Passive or active cigarette smoke exposure appears to decrease both systemic and local sinus tissue levels of 25VD3. This finding was consistent across CRSwNP and control patients.[719]

In vitro studies also support the role of VD3 in CRSwNP pathogenesis. Studies demonstrate that human sinonasal epithelial cells constitutively express 1α hydroxylase and epithelial cells convert 25VD3 to 1,25VD3 in a dose dependent manner, but that CRSwNP epithelial cells appear to have lower levels of 1α hydroxylase and are less efficient at 25VD3 activation.[719,723] Similarly, when looking at sinonasal CYP27B1 expression (gene encoding 1α hydroxylase), this was lower in CRSwNP patients compared to controls.[724] Additionally, reduction in 1α hydroxylase was shown to be associated with worse subjective disease severity (based on SNOT22 scores).[715] When investigating the effects of exogenous insults with smoke extract, epithelial cell conversion of 25VD3 into active 1,25VD3 became impaired, but addition of 1,25VD3 to smoke exposed cells inhibited their secretion of pro-inflammatory cytokines (IL-6, IL-8, CCL20), alluding to its potential to influence immune tolerance.[719]

CRSwNP patients have 25VD3 deficiencies that correlate with increased numbers of systemic and local dendritic cells, and increased human sinonasal fibroblast (HSNF) proliferation.[717,718,1417] Additionally, low 25VD3 correlates with increases in pro-inflammatory cytokines and *in vitro* studies demonstrate that adding various forms of vitamin D appear to suppress fibroblast proliferation and production of pro-inflammatory cytokines.[1418-1422] There also appears to be a synergistic effect of inhibiting pro-inflammatory cytokines and inhibiting fibroblast proliferation when budoesonide was added to 1,25VD3 or tacalcitol compared to monotherapy.[1423,1424]

Vitamin D Deficiency as a Contributing Factor for CRSwNP

In summary, the following statements can be made about vitamin D in CRSwNP:

(1) Systemic 25VD3 deficiency is common in CRSwNP and correlates with subjective disease severity, and severity of sinus mucosal and sinus bone involvement in CRSwNP
Aggregate Grade of Evidence: C (Level 4: 13 studies)

(2) Local sinonasal VD3 metabolism dysfunction in CRSwNP may contribute to a pro-inflammatory state and appears to be independent of serum 25VD3 levels in CRSwNP
Aggregate Grade of Evidence: C (Level 4: 2 studies)

Table X-8. Evidence for vitamin D3 deficiency as a contributing factor for CRSwNP

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Habibi [725]	2019	4	Case-Control	50 Control 35 CRSsNP 32 CRSwNP	Serum 25VD3 level	Serum 25VD3 significantly lower in CRSwNP compared to controls.
Wang [713]	2019	4	Retrospective Case-Control	21 Control 42 CRSwNP 25 CRSsNP	Serum 25VD3 SNOT22 Lund-Mackay score	Serum 25VD3 lower in CRSwNP. Serum 25VD3 level inversely associated with SNOT22 in CRSwNP.
Christensen [724]	2017	4	Case-control	13 Control 8 CRSsNP 10 CRSwNP	Sinonasal Vitamin D Receptor gene expression level Sinonasal CYP2R1, CYP27B1, CYP24A1 gene expression levels	No difference in VDR expression between CRSwNP and controls. CYP27B1 gene expression lower in CRSwNP compared to controls. CYP24A1 upregulated in CRSwNP compared to controls.
Konstantinidis [714]	2017	4	Case-Control	32 Control 30 CRSsNP 32 CRSwNP 31 CFsNP 27 CFwNP	Serum 25VD3 Lund Kennedy score Lund Mackay score	Lower serum 25VD3 in CRSwNP and CFwNP. 25VD3 inversely correlated with Lund-Kennedy and Lund-Mackay scores in CRS and CF.
Carroll [1417]	2016	4	Case-Control	12 Control (CSF leak/pituitary tumor patients) 15 CRSwNP	HSNF proliferation	VD3 deficiency associated with increased HSNF proliferation in CRSwNP. When treated with 1,25VD3, there was a significant decrease in HNSF proliferation in CRSwNP but not control patients.

Mostafa [716]	2016	4	Case-Control	19 Control 25 AFRS 15 CRSwNP 15 CRSsNP	Serum 25VD3 Calcium Phosphate	25VD3 is lower in CRSwNP and AFRS. No difference in serum calcium between groups. Phosphate is higher in controls and CRSsNP when compared to AFRS and CRSwNP patients.
Schlosser [715]	2016	4	Case-Control	18 Control 13 CRSwNP 13 CRSsNP 6 AFRS	Sinonasal 1α hydroxylase Sinonasal 1,25VD3 SNOT22 Serum 1,25VD3	CRSwNP and AFRS have reduced sinonasal 1α hydroxylase and 1,25VD3. Reduction in 1α hydroxylase associated with subjective disease severity in CRSwNP. No difference in serum 1,25 VD3 between CRSwNP and controls.
Sansoni [726]	2015	4	Case-Control	12 Control 31 CRSsNP 14 CRSwNP	Serum 25VD3 Nasal MCP-1, RANTES, and bFGF levels	Serum 25VD3 is inversely correlated with RANTES and bFGF in CRSwNP. No significant difference in Serum 25VD3 in CRSwNP and controls.
Mulligan [719]	2014	4	Case-Control	21 Control (CSF leak/pituitary tumor patients) 40 CRSsNP 45 CRSwNP	Serum and sinonasal 25VD3 Sinonasal CYP27B1 gene expression Sinonasal 25VD3 to 1,25VD3 conversion	Lower serum and sinonasal 25VD3 in CRSwNP than controls. Cigarette smoke associated with lower 25VD3 level, impairs conversion to 1,25VD3.
Schlosser [1415]	2014	4	Retrospective Case Series	70 CRSwNP	Serum 25VD3 level	Serum 25VD3 insufficiency/ deficiency is common in CRSwNP, especially in African Americans.
Wang [720]	2013	4	Case-Control	25 CRSwNP 20 CRSsNP	Serum $25VD_3$ Polyp grade Lund Mackay Score Serum total IgE	CRSwNP have lower $25VD_3$ than CRSsNP. $25VD_3$ is inversely correlated with polyp grade severity.
Mulligan [717]	2012	4	Retrospective Case-Control	14 control patients) 17 CRSsNP	Serum 25VD3 level Number of CD209+ Dendritic	Serum 25VD3 is lower in pediatric CRSwNP and AFRS. Low serum

				5 CRSwNP 14 AFRS	cells in nasal tissue	25VD3 correlates with increased dendritic cells.
Ozkara [1416]	2012	4	Case-Control	40 Control (healthy volunteers) 30 CRSwNP and AR 30 CRSwNP	Serum $1,25VD_3$ Serum IL-4, IL-10, IFNɣ level	CRSwNP with AR have lower serum 1,25VD3 than control. CRSwNP with AR have Th2 cytokine profile.
Mulligan [718]	2011	4	Retrospective Case-Control	14 Control (CSF Leak) 20 CRSsNP 9 CRSwNP 14 AFRS	Serum 25VD3 level Dendritic cells as percentage of total peripheral blood mononuclear cells	Serum 25VD3 is lower in CRSwNP and AFRS. Low 25VD3 correlates with increased circulating dendritic cells.

X.C.8. Contibuting Factors for CRSwNP: Superantigens

Staphylococcus aureus (SA) has been found colonizing the airways in up to 90% of patients with CRSwNP, with the highest prevalence in patients with comorbid asthma and aspirin sensitivity.[1374] In these patients, SA also grows intramucosally and even intracellularly[1425-1427] and releases over 600 proteins into the mucosa.[1428] Staphylococcal enterotoxins (SEs) are superantigens that stimulate T cells via binding to the T cell receptor Vß chain independent of the antigen-binding site, causing polyclonal activation of T cells with massive cytokine release. In about 60% of CRSwNP, evidence of superantigen effects on the T cell receptor V-beta expansion in both CD4+ and CD8+ lymphocytes was noted.[1429] The presence of Vß skewed T cells in CRSwNP tissue has recently been confirmed, demonstrating that these cells produce type 2 cytokines such as IL-4, IL-5 and IL-13.[1430,1431] The findings of superantigens in CRSwNP and its association with eosinophilic inflammation were independently confirmed by others.[1432-1434] The first description of a possible role of superantigens and IgE-antibodies to superantigen in CRSwNP dates back to 2001.[1374] The presence of IgE specific to SEs was associated with increased levels of total IgE and eosinophilic inflammation in CRSwNP. SEs can function by simultaneously binding as antigens in the conventional manner to CDRs and as superantigens to framework regions of anti-SE IgE in anti-SE IgE-FcεRI complexes.[1435]

Stimulation of mucosal tissue with SEB, the best studied superantigen, over 24 hours induced a significant increase of IL-1ß, TNF-α, IFN-γ, IL-2, IL-4, IL-5, IL-10, and IL-13 in CRSwNP and healthy patients, with this increase significantly greater in NPs compared to controls.[1436] Recently it was shown that SA presence within CRSwNP tissue was associated with a higher spontaneous production of IL-5 by the tissue, which could be reduced by antibiotics and bacteriophages directed against the bacteria,[1428] indicating a direct impact of *S. aureus* on type 2 inflammation. At the same time, *S. aureus,* via components of its cell wall, downregulates IP-10 and other Th1 cell-recruiting chemokines (*e.g.*, CXCL9 and CXCL11), counteracting the SE induced Th1 cell recruitment. This effect translated into inhibition of superantigen-induced Th1 cell recruitment, and favors mucosal type 2 immune responses.[1437]

SEs also down-regulate the anti-inflammatory prostaglandin PGE4 in CRSwNP fibroblasts, and induce growth factors and chemokines in nasal epithelial cells.[1438,1439] In CRSwNP, evidence for local IgE synthesis and class switch recombination was also provided;[1440] recombination activating genes RAG1 and RAG2 mRNA concentrations were increased in polyps and correlated with the magnitude of inflammation and the presence of SE-specific IgE in the NP mucosa, pointing to a very active local Ig production in SE-IgE positive polyps.[1441] The locally formed IgE is polyclonal, with IgE antibodies against several hundred or more allergens, and functional, even in the absence of systemic IgE antibodies or a positive skin prick test.[1442,1443] ISE-IgE were associated with significantly higher concentrations of antagonizing IgG antibodies in NPs.[1444] CRSwNP showed a significantly higher *S. aureus* culture-positivity, a higher detection rate of *S. aureus* superantigens and of specific SE-IgE in a recent meta-analysis[1445] confirming that superantigens may be a risk factor for CRSwNP, and the presence of superantigen also was related to disease severity.

Recent work focused on further SA released serine-protease-like (spl) proteins, which stimulate the release IL-33 from the epithelium, activating ILC2s to produce type 2 cytokines.[1446-1448] This finding could explain how the *S. aureus* bacteria initiate type 2 immune reactions even from the mucosal surface. Once a severe type 2 immune reaction is established, tissue eosinophilia is a typical feature. Activated eosinophils migrate towards the epithelium and, upon stimulation with SA, release extracellular traps containing DNA, MBP and galectin 10 to immobilize and kill the bacteria.[1449] Galectin 10 then forms Charcot-Leyden-Crystals (CLCs) at the epithelial layer, which further damage the epithelium and induce severe neutrophilic inflammation.[1449,1450] As CLCs stay intact for many months, this mechanisms may be relevant for the persistence of CRSwNP disease.

In a cluster analysis, SE-IgE in the NP tissue was the best categorical value to predict comorbid asthma in CRSwNP patients;[178] other positive determinants were total IgE, eosinophilic cationic protein (ECP) and IL-5 in the continuous model, all representing Th2-associated markers. Whereas SE-IgE in CRSwNP patients often is undetectable in serum,[1451] it is associated with asthma in a Europe-wide epidemiological study[1452] and associated with severe, often non-atopic late-onset asthma.[1453] Staphylococcal enterotoxin IgE antibodies, but not IgE against inhalant allergens, were found to be risk factors for severe asthma, hospitalization and oral corticosteroid use as well as limitations in lung function.[1454] Furthermore, serum SE-IgE positivity was recently demonstrated to predict severe asthma and asthma exacerbations prospectively in a nested cohort followed up for 20 years.[1455]

In a study investigating the immune profiles of recurrent vs. non-recurrent polyp disease at the first surgery, SE-IgE was with other factors (total IgE, ECP, IL-5) significantly increased in recurrent polyps, whereas IFN-γ was increased in non-recurrent CRSwNPs.[1456] SA also is frequently found in patients with AFRS (37) and could be demonstrated to coexist with *Aspergillus sp*. in the sinuses, and to modulate the typical IgE immune response in those patients.

In summary, based on a wealth of *in vitro*, ex-vivo and clinical data, *S. aureus* and its products including superantigens appear to have a significant role in the initiation, severity and persistence of CRSwNP as well as in asthma comorbidity and disease recurrence after surgery.

Superantigens as a Contributing Factor for CRSwNP

Aggregate Grade of Evidence: B (Level 1: 1 study, Level 3: 4 studies, Level 4: 3 studies)

Table X-9. Evidence for superantigens as a contributing factor for CRSwNP

Study	Year	LOE	Study Design	Study Groups	Clinical End-point(s)	Conclusion
Ou [1445]	2014	1	Meta-analysis of the relationship of *S. aureus* superantigens and CRSwNP	340 CRSwNP 178 Control	SA-culture positive rate, SA superantigen detection, and SA specific IgE	CRSwNP have an almost 5-fold higher culture positive rate than controls. CRSwNP subjects have a 12-fold higher rate of SE presence and a 17 fold higher rate of specific IgE presence.
Rha [1430]	2020	3	Cross-sectional study of tissue samples from CRSwNP, CRSsNP, and control subjects for SE genes and T-cell phenotypes	20 CRSwNP 20 CRSsNP 23 Control	*S. aureus* enterotoxin superantigen -responsive CD4 T cells, Lund-Mackay score	The fraction of *S. aureus* enterotoxin superantigen-responsive CD4 T cells is increased in CRSwNP, compared to CRSsNP and control subjects. Quanitity of SE-responsive CD4 T cells is predictive of Lund Mackay score.
Van Zele [1456]	2014	3	Cross-sectional study of tissue samples from control, CRSsNP, and CRSwNP subjects for *S. aureus* colonization rates and specific enterotoxin IgE	55 CRSwNP 9 Control	*S. aureus* colonization rate, ECP and IgE present in mucosal tissue	63.6% of CRSwNP subjects were colonized with *S. aureus,* compared to 33.3% of CRS and 27.3% of control subjects. Subjects with NP and asthma formed IgE to SE's at a high rate. ECP and total IgE production significantly upregulated in NPs compared with controls and CRS.
Van Zele [1456]	2014	3	Analysis of tissue from CRSwNP subjects undergoing either primary or revision ESS	21 Primary CRSwNP 15 recurrent CRSwNP	Specific SE IgE	Significantly higher rates of SE specific IgE in recurrent versus non-recurrent CRSwNP
Wang [1432]	2008	3	Cross-sectional study of CRSwNP, CRSsNP, and control tissue for Vß expression	22 CRSwNP 15 CRSsNP 12 control	Tissue reactivity to staphylococc al enterotoxins	55% of CRSwNP subjects' tissue demonstrated reactivity to SE's, while no CRSsNP or control subjects showed reactivity.
Zhang [1442]	2011	4	Cross sectional study of CRSwNP and AR subjects or determination of tissues reactivity in response to SE	14 CRSwNP 12 Allergic Rhinitis	Reactivity of tissue mast cells to SE-B	Specific IgE antibiotics in nasal polyp tissue can be found independently of serum presence. Superantigen-induced polyclonal IgE contributes to chronic inflammation through continuous mast cell activation.

Patou [1436]	2008	4	Cross-sectional study of the effects of SE on nasal polyp and control tissues	12 CRSwNP 13 Control	Cytokine production following SE stimulation	*S. aureus* enterotoxin B stmulation caused increases in several pro-inflammatory cytokines in all tissues, with increases signifincantly higher in CRSwNP tissues compared with control tissues.
Conley [1431]	2006	4	Cross-sectional study of CRSwNP and antrochoanal polyp tissue for Vß expression	20 CRSwNP 3 antrochoanal polyp subjects	Vß expression skewing in domains associated with *S. aureus* SA's	7/20 CRSwNP subjects had skewing in Vß domains associated with *S. aureus* superantigens, while none of the antrochoanal polyps demonstrated similar skew.

X.C.9. Contributing Factors for CRSwNP: Microbiome Disturbance

Because of limited data, CRSsNP and CRSwNP are combined in Section IX.C.8.

X.C.10. Contributing Factors for CRSwNP: Anatomic Variation

The degree to which anatomic variation in the paranasal sinuses might contribute to disease pathophysiology in CRSwNP (*i.e.,* concha bullosae, paradoxical positioning of the middle turbinate, infraorbital ethmoid (Haller) cells, and NSD, among others) is less clear.[338,783-785] CRSwNP patient populations have rarely been independently studied to determine the influence of anatomic variation on disease. The relationship of anatomic variation and disease burden is therefore not well understood in CRSwNP.

Leung *et al.*[1457] investigated obstruction at the OMC in CRSwNP and CRSsNP and noted that OMC obstruction was associated with increasing Lund-Mackay scores in both forms of CRS. In CRSsNP OMC obstruction was associated with adjacent sinus inflammation, while in CRSwNP, this correlation was absent. The authors concluded that paranasal sinus inflammation was not likely to be a post-obstructive phenomenon in the setting of CRSwNP. Jain *et al.*[338] found a significantly higher average number of anatomical anomalies (accessory ostia, conchae bullosae, infraorbital ethmoid cells, lateralized uncinated processes, and paradoxical middle turbinates) in patients with limited disease compared to a cohort with pansinusitis or control group without disease. The authors found 96 anatomic variations in 22 patients in the limited sinus surgery group, while the control group had 68 variants in 27 patients, and the pansinusitis group had 72 variants in 28 patients (p=0.003). In a study by the same group the authors also found a lower rate of anatomic variation in CRSwNP patients undergoing extensive ESS compared with patients with CRSsNP undergoing ESS and patients undergoing limited ESS.[788] Both of these papers suggest that anatomical variants may be related to impairment of the OMC seen in patients with limited disease or undergoing a limited ESS, whereas a primary mucosal abnormality contributes to more diffuse CRSwNP disease.[338] In contrast, a study by Bilge, *et al.*[1458] retrospectively compared CT scans of a cohort of 155 patients with CRSwNP to a

control group of 100 patients without RS. The authors found a statistically higher rate of nasal septal deviation (NSD), concha bullosa, agger nasi cell, frontal sinus hypoplasia, and accessory os in the CRSwNP group and concluded that this may be a contributing factor to the disease process in CRSwNP. This finding contrasts with most other studies, which have found higher rates of anatomic abnormalities in patients with more limited disease.

In conclusion, the relationship between anatomical variants and development of disease in patients with CRSwNP is unclear given the limited amount of literature on the subject. Most of the studies seem to suggest that CRSwNP is a diffuse disease process and, therefore, less influenced by anatomic variation.

Anatomic Variation as a Contributing Factor for CRSwNP

Aggregate Grade of Evidence: Grade C (Level 4: 4 studies). Results of studies are conflicting.

Table X-10. Evidence for anatomic variation as contributing factor for CRSwNP

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Wu [788]	2017	4	Retrospective case control	86 patients undergoing limited ESS or ESS for CRSsNP or CRSwNP	Reduction in symptoms and number of follow up visits needed	Anterior ESS and ESS for CRSsNP was associated with more anatomic variants than CRSwNP.
Bilge [1458]	2016	4	Retrospective case control	155 patients with CRSwNP compared to 100 asymptomatic controls	Anatomical variations seen on CT scan	Anatomical variants including NSD, concha bullosae, agger nasi, frontal sinus hypoplasia and accessory os more prevalent in CRSwNP group.
Jain [338]	2013	4	Retrospective case control	22 patients with limited RS, 28 patients with diffuse disease, 27 controls	Presence of anatomic variants	Frequency of total anatomical variants in the limited group was significantly higher than in the pansinusitis and control groups.
Leung [1457]	2011	4	Retrospective case control	144 patients with CRSsNP and 123 patients with CRSwNP	Association of OMC obstruction with overall LM score	In all patients OMC obstruction correlates with LM score, but only in CRSsNP does OMC obstruction correlate with adjacent sinus involvement.

X.C.11. Contributing Factors for CRSwNP: Septal Deviation

Because of limited data, CRSsNP and CRSwNP are combined in Section IX.C.10.

X.C.12. Contributing Factors for CRSwNP: Innate Immunity

The topic of innate immunity of the sinonasal cavity was introduced in Section IX.C.11. with regard to CRSsNP and there is some degree of overlap between studies particularly with respect to the role of antimicrobial proteins and pattern recognition receptors. This section will highlight the most current data regarding innate immune cell and epithelial derived cytokine contributions in CRSwNP.

Eosinophils. Twelve studies revealed that eosinophil counts in the nasal polyp tissue or nasal secretions of CRSwNP patients were remarkably higher than in controls.[818-821,824,1375,1459-1464] Three studies found that the numbers of peripheral blood eosinophils were significantly increased in CRSwNP or atopic CRSwNP patients compared to healthy controls. [817,1462,1464] However, Zhang, *et al.* [1465] found that tissue eosinophils in NP tissue from China, as measured by ECP and cytokine/chemokine levels (IL-5 and eotaxin), were not significantly different from control tissue and were significantly lower in terms of numbers of eosinophils as compared with polyps from white subjects. Conversely, three studies found that the tissue eosinophils in Asian CRSwNP patients were significantly higher than that of controls. In the past 2 decades, the degree of eosinophilia in NPs appears to have increased in Asian patients. [1466-1468] Taken together, this large body of evidence demonstrated that the majority of patients with CRSwNP demonstrate eosinophillic inflammation. These results suggest that eosinophils play an important role in the pathogenesis of CRSwNP. Regardless of ethnicity and geographic region, eosinophilia in patients with CRSwNP strongly correlates with TH 2 immune response. Eosinophils were found to be express tissue factors that initiate the extrinsic coagulation cascade and subsequent fibrin deposition in the nasal mucosa [1469]. This altered coagulation response may play a role in the formation of nasal polyp stroma.

Neutrophils. Interestingly, six studies also showed that CRSwNP patients had significantly higher tissue neutrophils as compared to healthy controls. However, Zhang *et al.* [1465] found that no significant difference between CRSwNP and controls. Moreover, two studies revealed that the blood neutrophils counts were similar to that in the healthy subjects [1462,1464].

Macrophages. Limited evidence has shed light on the potential role of macrophages in the pathogenesis of CRSwNP. Van Zele *et al.*[821] reported no significant difference between CRSwNP and controls in terms of the number CD68+ macrophages. However, two studies form China showed that macrophages were significantly elevated in the CRSwNP patients.[820,1470] Cao *et al.*[820] found that CRSwNP patients have a significant number of macrophages as compared to healthy subjects. Yao *et al.* [1470] found that the number of CD68+CD163+ alternatively activated (M2) macrophages were increased in eosinophilic CRSwNP. This study showed that TNF-α–induced protein 8–like 2 (TIPE2) was primarily expressed in M2 macrophages.[1470] Furthermore, M2 macrophages are the major FXIII-

A–producing innate cells in NPs[1471] and increased FXIII-A levels by M2 macrophages might contribute to the evident excessive fibrin deposition.

Mast cells. Two studies showed that mast cells are significantly increased in NPs and primarily accumulate in the epithelium.[822,823 1472]. Type 2 cytokines, IL-5, IL-13 and IL-4, are secreted by mast cells, Th2 cells and group 2 ILCs [1473] and therefore mast cells may enhance Th2 inflammation[1469].

Basophils. Two studies[818,1462] revealed that there were no significant differences in the basophils of blood and nasal secretion between CRSwNP and controls however tissue basophils counts were remarkably elevated in the most of non-eosinophilic and some eosinophilic CRSwNP patients. The role of basophils in the pathogenesis of CRSwNP remains unclear.

Fibroblasts. A larger body of evidence showed that the number of fibroblasts was significantly higher in CRSwNP as compared with controls.[825,826,1474,1475] Dobzansk *et al.*[1474] postulated that Wnt signaling by fibroblasts in CRSwNP may contribute to histological features of nasal polyps.

Group 2 Innate Lymphoid Cells (ILCs). ILCs are recombination activating gene (RAG)-independent innate cells and lack lineage markers for T cells or B cells.[1476] ILCs are divided into three genotypes. ILC2s can produce IL-13 and IL-5 when activated by the IL-33, IL-25 and TSLP. The latter cytokines can thereby induce eosinophilic airway inflammation.[1477] Mjösberg *et al.*[1478] reported that ILC2s are highly elevated in nasal polyp tissue of CRSwNP. This study indicated that ILC2s contribute to the process of eosinophilic inflammation in CRSwNP.

Epithelial-Derived Innate Cytokines. Innate responses to aeroallergens and inflammatory stimuli can induce the epithelial-derive innate cytokines IL-33, IL-25 and TSLP, which activate the ILC2s to release Th2 cytokines without antigen presentation.[1469] These cytokines may contribute to the activation of TH 2 inflammation. Furthermore, P-glycoprotein (P-gp) has been shown to be overexpressed in CRSwNP epithelium and directly promotes the secretion of these epithelial derived cytokines.[1479,1480]

In summary, there is significant evidence for altered innate immune responses in CRSwNP relative to control patients. The degree to which this response represents an etiopathologic factor versus a secondary response to other upstream events remains a subject of continued research.

Innate Immunity as a Contributing Factor for CRSwNP

Aggregate Grade of Evidence: not applicable.

Table X-11. Summary of studies on altered innate immunity in CRSwNP.

Study	Year	Study Groups (N=)	Tissue	Technique	Type of Innate Immunity	Findings	Innate Immunity Activity
Key Antimicrobial Proteins and Peptides							
Abigail [816]	2018	CRSsNP (28) CRSwNP (25) Control (17)	Anterior ethmoid tissues	ELISA and IHC	S100A 12	S100A 12 was significantly elevated in CRSwNP compared to normal controls.	Increased
Hirschberg [806]	2016	CRSsNP (19) CRSwNP (24) Control (12)	Ethmoid mucosa (CRSsNP) Polyps (CRSwNP) Sinus tissue (control)	RT-PCR	beta-defensins 1 and 4, cathelicidin and lactoferrin	Beta-defensins 1 and 4, cathelicidin and lactoferrin mRNA level were higher in CRSwNP compared to controls.	Increased
Li[805]	2014	CRSsNP (12) CRSwNP (12) Control (7)	Sinonasal tissue (CRS) Sinonasal tissue (control)	RT-PCR IHC	TFF1, TFF3	Similar TFF1 and TFF3 mRNA and proteins levels in ethmoid tissue of CRSwNP and control.	Normal
Salman[1481]	2012	CRSwNP (21) Control	Nasal polyps Nasal	ELISA	SP-A, SP-D	No difference in SP-A	Normal

		(15)	tissue (control)			and SP-D between two groups.	
Seshadri[870]	2012	CRSsNP (59) CRSwNP (81) Control (48)	Nasal tissue (CRS) Nasal tissue (control)	Microarray RT-PCR ELISA IHC	PLUNC 1, PLUNC 2, Lactoferrin	PLUNC 1, PLUNC 2 and lactoferrin proteins were decreased in CRSwNP tissues compared to that of CRSsNP and controls.	Decreased
Woods[802]	2012	CRSsNP (37) CRSwNP (39) Control (6)	Sinus mucosa (CRS, control)	RT-PCR IHC	Lysozyme	Lysozyme protein, but not the mRNA, was increased in patients with CRSwNP.	Increased
Park[1482]	2011	CRSwNP (202) Control (11).	Nasal polyps IT tissue (control)	Immunofluorescence staining	AMCase, ChT	AMCase was increased in nasal tissue of CRSwNP.	Increased
Wang[1483]	2010	CRSwNP Control	Nasal polyps Nasal tissue (control)	RT-PCR IHC	SP-A	SP-A was increased in sinonasal tissue of CRSwNP.	Increased
Cui[804]	2009	CRSsNP (72) CRSwNP (95) Control	Blood (CRS) Healthy blood	ELISA	C3, C4	Serum C3 level was increased in CRSwNP.	Increased

		(110)					
Ramanathan[1] 484	2008	CRSwNP (32) Control (10)	Epithelial cell isolated from sinus mucosa tissue	RT-PCR ELISA Flow cytometry	TLR9, HBD-2 SP-A	TLR9, HBD-2 and SP-A were decreased in nasal tissue of recalcitrant CRSwNP.	Decreased
Ramanathan[1] 485	2006	CRSwNP (22) Control (11)	Ethmoid mucosa (CRSwNP, control)	RT-PCR	AMCase	AMCase mRNA level was increased in nasal tissue of CRSwNP.	Increased
Claeys[1486]	2005	CF-CRSsNP (14) Non-CF-CRSwNP (15) Control (10)	Sinonasal sample (CRS) IT tissue (control)	RT-PCR ELISA	HBD-2, HBD-3 TLR2, TLR4	HBD-2 was increased in CF-CRSwNP versus Non-CF-CRSsNP and control. No difference in TLR2 and TLR2 was detected between non-CF-CRSwNP and control.	Increased or normal
Chen[1487]	2004	CRSwNP (12) Control (7)	Nasal polyps IT mucosa (control)	RT-PCR IHC	LL-37	LL37 was significantly increased in CRSwNP.	Increased

Schicht[1488]	2004	CRSwNP AR Control	Nasal mucosa (CRSwNP) Nasal mucosa (control)	RT-PCR Western blot IHC	SP-A, SP-B, SP-C, SP-D	SP-B protein level was significantly increased in nasal tissue of CRSwNP.	Increased
Claeys[1489]	2003	Tonsillar disease Hypertrophic adenoids Sinonasal disease	Nasal polyps Turbinate mucosa (control)	RT-PCR IHC	HBD-2, HBD-3 TLR2, TLR4	No difference was seen in nasal tissue among CRSwNP and control groups.	Normal
Pattern Recognition Receptors							
Park [814]	2018	CRSsNP (12) CRSwNP (24) Control (12)	Nasal tissue Nasal polyps	IHC	TLR 9	TLR9 protein level was higher in CRSwNP compared to controls.	Increased
Zhang[812]	2013	CRSsNP (40) CRSwNP (38) Control (23)	Nasal polyps (CRS) Nasal tissue (control)	RT-PCR IHC	TLR2, TLR4, TLR7	TLR2, TLR4, TLR7, and IL-4 were increased in CRSwNP patients when compared with either CRSsNP patients or control subjects.	Increased
Van Crombruggen [811]	2012	CRSsNP (22) CRSwNP	Inflamed sinonasal tissue	qRT-PCR IHC	sRAGE mRAGE esRAGE	sRAGE and mRAGE	Decreased

		(19) Control (17)				levels were decreased in CRSwNP compared to controls.	
Månsson[1490]	2011	CRSwNP (24) Control (10)	Nasal polyps Nasal tissue (control)	RT-PCR IHC	NOD1, NOD2, NALP3	NLR mRNA level was higher in NPs than in normal nasal mucosa.	Increased
Zhao[1491]	2011	CRSwNP (20) Control (15)	Nasal polyps (CRS) Turbinate tissue (control)	DNA microarray RT-PCR Western Blot IHC	125 genes for TLRs signaling pathways	TLR-9 mRNA and protein level were increased in NPs of CRSwNP.	Increased
Xia[1492]	2008	CRSwNP (10) Control (10)	Epithelial cell isolated from nasal tissue	Flow cytometry	TLR9	TLR9 epithelial cell isolated from nasal tissue was remarkably decreased in CRSwNP.	Decreased
Lane[1493]	2006	CRSwNP (30) Control (10)	Nasal polyps Inferior turbinate tissue (control)	RT-PCR	TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, TLR10	TLR2 in nasal tissue was remarkably decreased in CRSwNP.	Decreased or normal

Ramanathan[1] [494]	2006	CRSwNP (10) Control (5)	Epithelial cell isolated from mucosal tissue	RT-PCR Flow cytometry	TLR9	TLR9 in epithelial cells from nasal mucosa was remarkably decreased in CRSwNP.	Decreased
Hirschberg[806]	2016	CRSsNP (19) CRSwNP (24) Control (12)	Ethmoid mucosa (CRSsNP) Polyps (CRSwNP) Sinus tissue (control)	RT-PCR	TLR2, TLR5, TLR6, TLR7, TLR8, TLR9,	TLR2, 5, 6, 7, 8 and 9 mRNA level were higher in CRSwNP compared to controls.	Increased

Table X-12. Summary of studies on altered non-epithelial innate immunity in CRSwNP

Study	Year	Study Groups (size)	Tissue	Technique	Type of Innate Immunity	Findings	Innate Immunity Activity
Eosinophils							
Du [1464]	2020	CRSwNP (30) Control (10)	Blood	CBA	Blood eosinophils	The number of blood eosinophils was significant increased in CRSwNP compared to controls.	Increased
Gion [1472]	2020	CRSsNP (14) CRSwNP (57) Control (13)	Nasal tissue Nasal polyps	H&E staining IHC	Blood eosinophils	The number of blood eosinophils was significantly increased in moderate to severe eosinophilic CRSwNP, but	Increased or normal

						not mild eosinophilic CRSwNP, compared to controls.	
Kim[1463]	2020	Refractory CRSwNP (54) Disease control (76)	Nasal polyps	IHC Immunofluorescence analysis	Tissue eosinophils	Refactory CRSwNP had a significant increased number of neutrophils compared with no refractory disease control.	Increased
Nagata [1461]	2019	ECRS (22) nECRS (11) Control (6)	Sinonasal tissue Nasal polyps	H&E staining IHC	Tissue eosinophils	The number of eosinophils was significantly increased in eosinophilic CRSwNP, but not mild eosinophilic CRSwNP, compared to controls.	Increased or normal
Veloso-Teles [1462]	2019	CRSwNP (37) Control (34)	Serum specimens	Cell counts	Blood eosinophils	The number of blood eosinophils was significant increased in CRSwNP compared to controls.	Increased
Huang[817]	2017	CRSsNP (37) CRSwNP (66) Control (9)	Blood	FACS	Blood eosinophils	The number of blood eosinophils was significantly increased in atopic CRSwNP, but not non-atopic CRSwNP, compared to controls.	Increased or normal

Takahashi [818]	2017	CRSsNP (33) CRSwNP (45) AER (31) Control (24)	Nasal lavage fluids	FACS	Eosinophils of nasal secretion	The eosinophils microparticles were significantly increased in CRSwNP compared to controls.	Increased
Baba [1460]	2015	Eosinophilic CRSwNP (15) Non-Eosinophilic CRSwNP (16) Control (8)	Nasal tissue Nasal polyps	IHC RE-PCR	Tissue eosinophils	The number of eosinophils was significantly increased in CRSwNP (eosinophilic and non-eosinophilic).	Increased
Mahdavinia[824]	2014	CRSsNP (15) CRSwNP (16) NP with AERD (10) NP without AERD (17) Control (15)	Nasal tissue Nasal polyps	IHC H&E staining	Tissue eosinophils	The number of blood eosinophils was significant increased in CRSwNP compared to controls.	Increased
Wen [1459]	2012	CRSwNP (187) Control (45)	Nasal tissue Nasal polyps	ELISA IHC FACS	Tissue eosinophils	CRSwNP had a significant increased number of eosinophils compared to controls.	Increased
Sejima [819]	2012	CRSsNP (9) CRSwNP (19) Control	Nasal tissue Nasal polyps	H&E staining ELISA	Tissue eosinophils	The number of eosinophils was significantly increased in	Increased

		(14)				CRSwNP.	
Cao[820]	2009	CRSsNP (94) CRSwNP (151) Control (50)	Nasal tissue Nasal polyps	H&E staining IHC	Tissue eosinophils	The number of eosinophils was significant increased in CRSwNP compared to controls.	Increased
Zhang[1375]	2008	Belgian CRSwNP (26) Belgian control subjects (21) South Chinese CRSwNP (29) South Chinese control (29)	Nasal tissue Nasal polyps	H&E staining IHC	Tissue eosinophils	Both western and Asian CRSwNP had a significant increased number of eosinophils compared to controls.	Increased
Van Zele [821]	2006	CRSsNP (8) CRSwNP (10) CF-CRSwNP (13) Control (9)	Nasal tissue Nasal polyps	H&E staining ELISA IHC	Tissue eosinophils	The level of eosinophil cationic protein (eosinophils) was significantly higher in CRSwNP compared to controls.	Increased
Zhang [1465]	2006	CRSwNP (27) Control (9)	Nasal tissue Nasal polyps	H&E staining IHC ELISA	Tissue eosinophils	Tissue eosinophils in NP tissue from China, as measured by ECP and cytokine/chemokine levels (IL-5 and eotaxin), was not	Normal

						significantly different from control tissue and was significantly lower in terms of numbers of eosinophils compared with polyps from white subjects.	
Neutrophils							
Du [1464]	2020	CRSwNP (30) Control (10)	Blood	CBA	Blood neutrophils	No significant difference was observed between CRSwNP and controls.	Normal
Kim[1463]	2020	Refractory CRSwNP (54) Disease control (76)	Nasal polyps	IHC Immunofluorescence analysis	Tissue neutrophils	Refractory CRSwNP had a significant increased number of neutrophils compared with no refractory disease control.	Increased
Cao [1495]	2019	CRSwNP (22) Control (15)	Nasal tissue Nasal polyps	RT-PCR IHC ELISA	Tissue neutrophils	CRSwNP had a significant increased number of neutrophils.	Increased
Veloso-Teles [1462]	2019	CRSwNP (37) Control (34)	Serum specimens	Cell counts	Blood neutrophils	No significant difference was observed between CRSwNP and controls.	Normal
Sejima [819]	2012	CRSsNP (9) CRSwNP (19) Control (14)	Nasal tissue Nasal polyps	H&E staining ELISA	Tissue neutrophils	CRSwNP had a significant higher protein level of MPO (neutrophils).	Increased

Wen [1459]	2012	CRSwNP (187) Control (45)	Nasal tissue Nasal polyps	ELISA IHC FACS	Tissue neutrophils	CRSwNP had a significant increased number of neutrophils.	Increased
Zhang[1375]	2008	Belgian CRSwNP (26) Belgian control subjects (21) South Chinese CRSwNP (29) South Chinese control (29)	Nasal tissue Nasal polyps	H&E staining IHC	Tissue neutrophils	Both western and Asian CRSwNP have a significant increased number of neutrophils.	Increased
Van Zele [821]	2006	CRSsNP (8) CRSwNP (10) CF-CRSwNP (13) Control (9)	Nasal tissue Nasal polyps	H&E staining ELISA IHC	Tissue neutrophils	CRSwNP (CF-NP) had a significant higher protein level of MPO (neutrophils).	Increased
Zhang [1465]	2006	CRSwNP (27) Control (9)	Nasal tissue Nasal polyps	H&E staining IHC ELISA	Tissue neutrophils	No significant difference was observed between CRSwNP and controls.	Normal
Macrophages							
Yao[1470]	2017	Eosinophilic CRSwNP (34) non-eosinophilic CRSwNP (41) Control	Nasal tissue Nasal polyps	H&E staining IHC FACS	Tissue macrophages	The number of CD68+CD163+ alternatively activated (M2) macrophages was increased in eosinophilic polyps.	Increased

		(20)					
Cao[820]	2009	CRSsNP (94) CRSwNP (151) Control (50)	Nasal tissue Nasal polyps	H&E staining IHC	Tissue macrophages	CRSwNP have a significant number of macrophages.	Increased
Van Zele [821]	2006	CRSsNP (8) CRSwNP (10) CF-CRSwNP (13) Control (9)	Nasal tissue Nasal polyps	H&E staining ELISA IHC	Tissue macrophages	There was no significant difference between CRSwNP and control in terms of the number CD68 + cells (macrophages).	Normal
Mast Cells							
Gion [1472]	2020	CRSsNP (14) CRSwNP (57) Control (13)	Nasal tissue Nasal polyps	H&E staining IHC	Tissue mast cells	No significant difference was observed between CRSwNP and controls.	Normal
Zhai [1496]	2018	Eos CRSwNP (23) Non-Eos CRSwNP (21) Control (23)	Nasal tissue Nasal polyps	IHC Immunofluorescence FACS	Tissue mast cells (IgD+)	The mast cells were significantly increased in Eos CRSwNP compared to control.	Increased
Baba [1497]	2017	Eos CRSwNP (17) Non-Eos CRSwNP (17) Control (7)	Nasal tissue Nasal polyps	H&E staining IHC Immunofluorescence	Tissue mast cells	The number of mast cells were significantly increased in CRSwNP (Eos and Non-Eos) compared to control.	Increased
Shaw [822]	2012	CRSsNP (6) CRSwNP (9) Control	Nasal tissue Nasal polyps	H&E staining TR-PCR FACS	Tissue mast cells	The mast cells were significantly increased in NP compared to control.	Increased

		(2)					
Takabayashi [823]	2012	CRSsNP (70) CRSwNP (91) Control (42)	Nasal tissue Nasal polyps	TR-PCR ELISA IHC	Tissue mast cells	The mast cells were significantly increased in NP compared to control.	Increased
Basophils							
Veloso-Teles [1462]	2019	CRSwNP (37) Control (34)	Serum specimens	Cell counts	Blood basophils	No significant difference was observed in blood basophils between CRSwNP and controls.	Normal
Takahashi [818]	2017	CRSsNP (33) CRSwNP (45) AER (13) Control (24)	Nasal lavage fluids	FACS	Basophils of nasal secretion	No significant difference was observed in basophils of nasal secretion between CRSwNP and controls.	Normal
Fibroblast							
Dobzanski [1474]	2018	CRSwNP (9) Control (25)	Nasal tissue Nasal polyps	ALI IHC FACS	Human sinonasal fibroblast culture	It showed an increased percentage of Wnt3a+ fibroblasts from patients with CRSwNP.	Increased
Park [825]	2017	CRSsNP (20) CRSwNP (20) Control (10)	Nasal tissue Nasal polyps	Immunofluorescence FACS RT-PCR	Tissue fibroblast (Vimentin + α-SMA+ cells)	It showed an increased percentage of fibroblasts ((Vimentin+ α-SMA+ cells) in NP tissue from patients with CRSwNP.	Increased

Carroll[826]	2016	CRSsNP (22) CRSwNP (13) Control (24)	Nasal tissue Nasal polyps	IHC	Tissue fibroblast	The number of fibroblast was significantly higher in CRSwNP compared with control.	Increased
Carroll[826]	2016	CRSwNP (15) Control (12)	Blood Sinus tissue explants	FACS	Sinonasal explant human sinonasal fibroblast ; proliferation	It showed an increased percentage of fibroblasts ((FSP+ MUC1+ KI67+ cells) in CRSwNP.	Increased
Innate Lymphoid Cells (ILCs)							
Mjösberg[1478]	2011	CRSwNP (4) Control (4)	Nasal tissue Nasal polyps	Flow cytometry analysis	Tissue ILC2s	ILC2s are highly elevated in nasal polyp tissue.	Increased

Table X-13. Epithelial-derived innate cytokines in CRSwNP

Study	Year	Study Groups (size)	Tissue	Technique	Type of Innate Immunity	Findings	Innate Immunity Activity
IL-25							
Dogan[1498]	2019	CRSwNP (33) Control (29)	Sinoasal tissue Nasal polyps	ELISA	Tissue IL-25	IL-25 mRNA level was significantly higher in the CRSwNP group compared to the control.	Increased
Nagata [1461]	2019	ECRS (22) nECRS (11) Control (6)	Sinoasal tissue Nasal polyps	H&E staining IHC	Tissue IL-25	IL-25 protein level was significantly higher in the CRSwNP group compared to the control.	Increased
Ogasawara [1499]	2019	CRSwNP (46) AERD (23) Control (34)	Sinoasal tissue Nasal polyps	H&E staining IHC RT-PCR	Tissue IL-25	IL-25 was not elevated in NPs.	Normal

Hong[162]	2018	CRSsNP (20) CRSwNP (90) Control (16)	Nasal tissue Nasal polyps	RT-PCR IHC	Tissue IL-25	The mRNA and protein levels of IL-25 were significantly elevated in polyp tissues compared to the control uncinate.	Increased
Ozturan [828]	2016	CRSsNP (20) CRSwNP (20) Control (20)	Sinoasal tissue Nasal polyps	ELISA	Tissue IL-25	IL-25 was not elevated in NPs.	Normal
Xu[829]	2016	CRSsNP (12) CRSwNP (35) Control (12)	Sinoasal tissue Nasal polyps	RT-PCR IHC	Tissue IL-25	IL-25 mRNA level was significantly higher in the CRSwNP group compared to the control.	Increased
Lam [1413]	2015	CRSsNP (12) CRSwNP (20) Control (7)	Sinoasal tissue Nasal polyps	H&E staining IHC RT-PCR	Tissue IL-25	IL-25 protein level was significantly higher in the CRSwNP group compared to the control.	Increased
Liao [1500]	2015	Eos CRSwNP (28) Non-Eos CRSwNP (33) Control (28)	Nasal polyps Epithelia cells	RT-PCR IHC	Tissue IL-25	The mRNA level of IL-25 were significantly elevated in CRSwNP (Eos and Non-Eos) as compared to the control.	Increased
Shin[830]	2015	CRSsNP (65) CRSwNP (50) Control (27)	Sinoasal tissue Nasal polyps	IHC RT-PCR ELISA	Tissue IL-25	IL-25 mRNA level was significantly higher in the CRSwNP group compared to the control.	Increased

Miljkovic[1501]	2014	CRSsNP (13) CRSwNP (7) Control (32)	Sinoasal tissue Nasal polyps	RT-PCR FACS	Tissue IL-25	IL-25 mRNA level was significantly lower in the CRSwNP group compared to the control.	Decreased
Lam [831]	2012	CRSsNP (18) CRSwNP (12) Control (7)	Nasal tissue Nasal polyps	RT-PCR	Tissue IL-25	The mRNA level of IL-25 were significantly elevated in polyp tissues as compared to the control.	Increased
IL-33							
Dogan[1498]	2019	CRSwNP (33) Control (29)	Sinoasal tissue Nasal polyps	ELISA	Tissue IL-33	IL-33 mRNA levels was significantly higher in the CRSwNP group compared to the control.	Increased
Nagata [1461]	2019	ECRS (22) Non-ECRS (11) Control (6)	Sinoasal tissue Nasal polyps	H&E staining IHC	Tissue IL-33	IL-33 protein level was significantly higher in the CRSwNP group compared to the control.	Increased
Hong[162]	2018	CRSsNP (20) CRSwNP (90) Control (16)	Nasal tissue Nasal polyps	RT-PCR IHC	Tissue IL-33	The mRNA level, but not protein levels of IL-33 were significantly elevated in polyp tissues as compared to the control uncinate.	Increased
Song[1502]	2017	ECRSwNP (25) nECRSwNP (27) Control (12)	Sinoasal tissue Nasal polyps	RT-PCR IHC	Tissue IL-33	IL-33 expression levels in the CRSwNP group were	Increased

						significantly higher than those in the control group, especially in the ECRSwNP group.	
Kim[832]	2016	CRSsNP (61) CRSwNP (166) Control (19)	Sinoasal tissue Nasal polyps	RT-PCR IHC	Tissue IL-33	IL-33 protein level was significantly higher in the CRSwNP group compared to the control.	Increased
Kouzaki [1503]	2016	ECRS(17) Control (10)	Sinoasal tissue Nasal polyps	ELISA IHC PCR	Tissue IL-33	IL-33 was highly expressed in the polyps of ECRS patients.	Increased
Ozturan [828]	2016	CRSsNP (20) CRSwNP (20) Control (20)	Sinoasal tissue Nasal polyps	ELISA	Tissue IL-33	IL-33 was not elevated in NPs.	Normal
Xu[829]	2016	CRSsNP (12) CRSwNP (35) Control (12)	Sinoasal tissue Nasal polyps	RT-PCR IHC	Tissue IL-33	IL-25 mRNA level was significantly lower in the CRSwNP group compared to the control.	Decreased
Endo[1504]	2015	ECRSwNP Control	Sinoasal tissue Nasal polyps	RT-PCR FACS	Tissue IL-33	IL-33 was highly expressed in the chronic inflammatory polyps of ECRS patients.	Increased
Liao [1500]	2015	Eos CRSwNP (28) Non-Eos CRSwNP (33) Control (28)	Nasal polyps Epithelia cells	RT-PCR IHC	Tissue IL-33	The mRNA level of IL-33 were significantly elevated in NP epithelial cells but not whole tissue as compared to the control.	Increased

Steven [1505]	2015	CRSsNP (27) CRSwNP (15) Control (12)	Sinoasal tissue Nasal polyps	Luminex RT-PCR	Tissue IL-33	The expression level of IL-33 was not elevated in NPs.	Normal
Baba[1506]	2014	ECRS (10) NCRS (10) Control (5)	Sinoasal tissue Nasal polyps	RT-PCR	Tissue IL-33	The expression level of IL-33 mRNA was not significantly different among the three groups.	Normal
Miljkovic[1501]	2014	CRSsNP (13) CRSwNP (7) Control (32)	Sinoasal tissue Nasal polyps	RT-PCR FACS	Tissue IL-33	IL-33 was not elevated in NPs.	Normal
Paris[1507]	2014	CRSwNP (8) Control (9)	Sinoasal tissue	RT-PCR IHC	Tissue IL-33	IL-33 was elevated in CRSwNP.	Increased
Shaw[1508]	2013	CRSsNP (73) CRSwNP (30) Control (8)	Sinoasal tissue Nasal polyps	RT-PCR ELISA	Tissue IL-33	The expression level of IL-33 mRNA was not significantly different among the three groups.	Normal
Lam[831]	2012	CRSsNP (18) CRSwNP (12) Control (7)	Nasal tissue Nasal polyps	RT-PCR	Tissue IL-33	The mRNA level of IL-33 were significantly elevated in polyp tissues as compared to the control.	Increased
TSLP							
Dogan[1498]	2019	CRSwNP (33) Control (29)	Sinoasal tissue Nasal polyps	ELISA	Tissue TLSP	TLSP mRNA levels was significantly higher in the CRSwNP group compared to the control.	Increased

Hong[162]	2018	CRSsNP (20) CRSwNP (90) Control (16)	Nasal tissue Nasal polyps	RT-PCR IHC	Tissue TSLP	The mRNA level, but not protein level of TSLP were significantly elevated in polyp tissues as compared to the control uncinate.	Increased
Liao[1500]	2015	Eos CRSwNP (28) Non-Eos CRSwNP (33) Control (28)	Nasal polyps Epithelia cells	RT-PCR IHC	Tissue TLSP	The mRNA level of IL-TLSP were significantly elevated in Eos CRSwNP but not Non-Eos CRSwNP compared to the control.	Increased
Nagarkar[833]	2013	CRSsNP (60) CRSwNP (86) Control (47)	Nasal tissue Nasal polyps	RT-PCR ELISA	Tissue TSLP	TSLP mRNA levels were significantly increased in NP tissue from patients with CRSwNP compared with control subjects.	Increased
Lam[831]	2012	CRSsNP (18) CRSwNP (12) Control (7)	Nasal tissue Nasal polyps	RT-PCR	Tissue TLSP	There was no difference between CRSwNP and control in terms of the tissue TSLP.	Normal
Boita[834]	2011	CRSsNP (5) CRSwNP (10) Control	Nasal tissue Nasal polyps Epithelia cells	IHC	Tissue TLSP	TSLP protein levels were significantly increased in CRSwNP compared with control.	Increased

X.C.13. Contributing Factors for CRSwNP: Epithelial Barrier Disturbance

Because of limited data, CRSsNP and CRSwNP are combined in Section IX.C.12.

X.C.14. Contributing Factors for CRSwNP: Ciliary Derangements

CRSwNP has more pronounced ciliary dysfunction in some cases compared to CRSsNP, and there are several reasons that it manifests differently. In a recent whole-transcriptomic sequencing study, cilia dysfunction and immune dysregulation are the two main gene ontology categories differentiating between CRSwNP patients and healthy controls.[1509]

The nature of NPs physically disrupts MCC patterns. Additionally, histopathologic studies demonstrate that some regions of NPs do not have ciliated surfaces, which causes a disruption in flow of mucus in the sinonasal tract.[1510] Interestingly, explants from CRSwNP patients demonstrate a faster baseline CBF compared with control explants, suggesting that a local epithelial compensation is occurring to account for "blocked" mucociliary flow. This baseline increase is not observed in CRSsNP explants.[877,1511] Chronically increased CBF has a potential consequence of down-regulating endogenous stimulatory pathways, and the cell loses responsiveness to natural CBF stimulants and cannot be modulated normally.[842] Epithelial damage in CRSwNP has also been associated with squamous metaplasia, and abnormal or absent cilia are often associated with this metaplastic change.[180,181,851,912,913] Scanning electron microscopy confirms the abnormal architecture, with cilia in CRSwNP presenting as overly dense, lengthened, and untidy. Ciliogenesis factors are correspondingly upregulated.[182] Other ciliogenesis-associated markers such as forkhead box j1 (Foxj1) and p73 isoform with an N-terminal transactivation domain (TAp73) are dysregulated in ciliated columnar cells in CRSwNP.[159,1512]

Ciliary Derangements as a Contributing Factor for CRSwNP

Aggregate Grade of Evidence: C (Level 2: 1 study, Level 3: 2 studies)

Table X-14. Evidence for ciliary derangements as contributing factors for CRSwNP

Study	Year	LOE	Study Design	Study Groups	Clinical End-point(s)	Conclusion
Peng[1509]	2019	2	Whole transcriptome RNA sequencing of polyp and non-polyp tissues	42 CRSwNP 28 Control	Differentially expressed genes and gene ontology categories	Ciliary dysfunction is among the most differentially expressed gene pathways in CRSwNP tissues
Li[182]	2014	3	Analysis of cilia architecture, ciliogenesis, and CBF in NP tissue	44 CRSwNP 38 Control	Scanning electron microscopy, proteomic and transcriptomic analysis, CBF	Abnormal ciliary architecture observed in NP significantly more frequently. CBF is decreased in nasal polyp tissue compared to that of controls. Ciliogenesis associated markers are significantly elevated in CRSwNP tissue.

Braverman [1511]	1998	3	Nasal biopsies from control, CRSsNP, and CRSwNP subjects	8 CRSwNP 6 CRSsNP 8 Control	CBF of tissue	An increase in CBF was observed in nasal polyp tissue compared to that of control and CRSsNP tissue.

X.C.15. Contributing Factors for CRSwNP: Immunodeficiency

Little evidence exists examining the role of immunodeficiency in CRSwNP. A systematic review performed by Schwitzguebel *et al.* found that the prevalence of nasal polyposis varies between 13% - 60% of patients with CRS and documented immunoglobulin deficiencies.[1513] Tran Khai Hoan *et al.* examined a prospective case series and concluded that a link between IgG subclass deficiency and CRSwNP seemed unlikely.[1514] Two case-control studies have also examined this subject. Seppanen *et al.* compared CRS (including two thirds with CRSwNP) or RARS to ARS and controls. They demonstrated that low complement C4 levels were more associated with CRS or RARS than ARS and concluded that the isolated low IgG subclass alone had limited value in patient assessment.[937] Cui *et al.* performed a case-control study in Chinese adult patients.[804] They found that increased levels of C3 and mannose-binding lectin (MBL, a pattern-recognition molecule which can activate the lectin pathway of the complement system) might play a modulatory role in CRS development. This finding was especially true for MBL in CRSwNP compared to CRSsNP. The study from Carr *et al.*, in which 42% of CRS subjects were CRSwNP, demonstrated that patients with medically refractory CRS may have a high prevalence of low pre-immunization anti-pneumococcal titer and specific antibody deficiency (SAD). However, no correlation was identified specifically in CRSwNP.[943] Baraniuk and Maibach performed subgroup analysis and found that Ig subclass deficiencies were more prevalent in CRSsNP than CRSwNP although the small numbers of subjects per group precluded statistical significance.[1515] Subgroup analysis of a case-control study of 595 patients with CRS who were evaluated for humoral immunodeficiency with quantitative immunoglobulins and Streptococcus pneumoniae antibody titers found no difference in nasal polyposis when stratifying by SAD severity.[952] Kashani *et al.* report a case series of 239 adults with CRS who were evaluated for SAD, with 27% sub-classified as CRSwNP.[946] In this study, the patients with CRSsNP with asthma had a less robust response to the pneumococcal vaccine compared to CRSsNP patients without asthma, suggesting that CRSsNP asthmatics may have an impaired mucosal response to *S. pneumoniae* exposure as well as an impaired systemic polysaccharide antibody response. In contrast, within the CRSwNP group, there was no significant difference in the number of protective post-immunization titers based on the presence of asthma, suggesting no difference in humoral response.[946] Finally, in their systematic review, Mazza *et al.* appreciated no association between immunodeficiency and the presence of polyps.[1284] They report, however, that the presence of polyps may predict recalcitrant disease in patients with primary immunodeficiency.[1284]

The evidence linking immunodeficiency to CRSwNP is contradictory. In an effort to uncover all possible etiologies, some experts have recommended testing for immunodeficiency in refractory CRSwNP patients. The main reason for this recommendation is that immunodeficiency may alter treatment considerations. In addition, this knowledge of an immune explanation alone may be a relief to the patient with recurrent sinus problems. Further well-designed studies to evaluate the pathophysiology of immunodeficiency and CRSwNP are needed.

Immunodeficiency as a Contributing Factor for CRSwNP

Aggregate Grade of Evidence: C (Level 3: 2 studies; level 4 studies: 7)
Benefit: Identifying patients with PID allows for the opportunity to treat a subset of patients who will respond to Ig replacement therapy.
Harm: Procedural discomfort; Identifying and treating incidental findings or subclinical conditions that might not require independent therapy.
Cost: Procedural and laboratory cost.
Benefits-Harm Assessment: Balance of benefit over harm.
Value Judgments: Evidence for immunodeficiencies in CRSwNP patients is contradictory and low-level.
Policy Level: Option.
Intervention: Patients with CRSwNP may be evaluated for the presence of an underlying PID.

Table X-15. Evidence for immunodeficiency as a contributing factor for CRSwNP

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Mazza[1284]	2016	3	Systematic review	39 studies, predominantly level 4 evidence, of patients with PID and CRS	Data was collected pertaining to immune dysfunction in patients with CRS, the clinical workup for these patients, and the effectiveness of medical and surgical treatments.	No association between the presence of polyps and immunodeficiencies was appreciated; however, some authors concluded that the presence of polyps predicted recalcitrant disease.
Schwitzguebel [1513]	2015	3	Systematic review and meta-analysis	All case series published after 1990 describing patients with CRS, and documented Ig deficiencies (N=1418)	Estimate the prevalence of Ig deficiency in CRS patients	Ig deficiency is a frequent condition in patients with CRS. The prevalence of nasal polyposis in these patients varied from 13% to 60%.
Keswani [952]	2017	4	Case-control	595 patients with CRS who were evaluated for humoral immunodeficiency with quantitative immunoglobulins and Streptococcus pneumoniae antibody titers	Humoral status (Ig levels, antibody titers) Clinical characteristics (Lund-Mackay, endoscopy/CT scores, asthma severity)	Stratification of SAD by severity demonstrates a significant increase in the comorbid severity of asthma and infections in CRS patients. No difference in nasal polyposis when stratifying by SAD severity.
Kashani [946]	2015	4	Case series	239 adults with CRS who were evaluated for SAD Patients were sub-classified as CRSsNP or CRSwNP (n=50, 27%)	Quantitative Ig levels Pre- and post-antibody titers to PPV	Within the CRSwNP group, there was no significant difference in the number of protective post-immunization titers based on the presence of asthma.
Tran Khai Hoan[1514]	2014	4	Prospective case series	Operated (n=118) Not operated (n=43)	Ig and IgG subclass levels, symptom scale, endoscopy	A link between IgG subclass deficiency and CRSwNP seems unlikely.

Carr[943]	2011	4	Retrospective case series	129 CRS (42% with CRSwNP)	Incidence	R-CRS associated with low pre-immunization anti-pneumococcal titer and specific antibody deficiency. No difference with CRSwNP.
Cui[804]	2009	4	Case-control study	CRSwNP (n=95) CRSsNP (n=72) Healthy control (n=110)	Ig and IgG subclass level, plasma C3, C4 level, MBL	Ig, C3, C4, and MBL deficiency is not the main cause of CRS in adult Chinese patients.
Seppanen[937]	2006	4	Case-control study	R-CRS (n=48) ARS (n=50) unselected control (n=150) healthy control (n=48)	Ig and IgG subclass level, plasma C3, C4 level, C4 immune typing	Isolated low IgG subclass had limited value in patient assessment. C4A null alleles are associated with CRS and RARS.
Baraniuk[1515]	2005	4	Retrospective case series	99 CRS (50% with CRSwNP)	Incidence	Ig subclass deficiencies were more prevalent in CRSsNP than CRSwNP.

X.C.16. Contributing Factors for CRSwNP: Genetics and Epigenetics

Because of limited data, CRSsNP and CRSwNP are combined in Section IX.C.15.

X.C.17. Contributing Factors for CRSwNP: Aspirin (Aspirin Exacerbated Respiratory Disease)

Aspirin-exacerbated respiratory disease (AERD), commonly referred to as Samter's triad, and increasingly recognized as nonsteroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (NSAID-ERD) in Europe, is characterized by recurrent CRSwNP, asthma, and distinctive respiratory reactions to aspirin and other non-specific NSAIDs.[1516-1519] Prevalence rates of AERD among the general population have been estimated at 0.6-2.5%, while rates among patients with CRSwNP approach 10%, and are higher in tertiary care populations.[198,1520,1521] The components of AERD do not typically present at once, and the initial presenting condition may vary. Roland, et al. found the most common sequence of presentation, found in 36% of AERD patients, is asthma, followed by nasal polyps, followed by NSAID hypersensitivity.[1522]

Though the clinical presentation of AERD is well-described, the exact pathophysiologic mechanism of AERD is less clear. Nonetheless, it has long been recognized that dysfunction in the arachidonic acid metabolism pathway is fundamental to disease development. NSAIDs affect the arachidonic acid pathway and cause inhibition of the cyclooxygenases (COX), which are necessary for metabolizing arachidonic acid into prostaglandins.[1523] Due to this inhibition, the lipoxygenase pathway is further activated during NSAID-induced reactions, which leads to an imbalance of anti-inflammatory prostaglandins (PG) and proinflammatory LTs. On top of this physiological inhibitory effect, individuals with AERD are thought to have reduced activity of the constitutively expressed COX 1 isoenzyme, as well as increased LT receptor expression. Due to dysregulation in arachidonic acid metabolism, the PG/LT imbalance in these patients is altered to favor a proinflammatory state that fuels the inflammatory cascade characteristically seen in patients with AERD. The activation of eosinophils, mast cells, and basophils likely leads to the release of cysteinyl leukotrienes (cysLTs), prostaglandin D_2, histamine, tryptase, and the stimulation of innate type 2 immune responses.[1518,1519,1524] Pathological evaluation of nasal polyps in patients with AERD demonstrates intense eosinophilic infiltration and activation.[1525] Histopathological analysis reveals that the NP in patients with AERD have the highest levels of tissue eosinophilia when compared to sinus tissue from patients with CRSsNP, inhalant allergies and/or aspirin-tolerant patients with CRSwNP.[1526]

Genetic polymorphisms, or functional epigenetic dysfunction, may potentially play a causative role in the pathogenesis of AERD.[1527,1528] These polymorphisms are thought to alter enzyme kinetics and receptor sensitivity. As a result, the activity of LT-synthase is increased, leading to an overproduction of cysLTs. Sensitivity of LT receptors is upregulated, as is the expression of cysLT receptor 1. Furthermore, the production of prostaglandin E_2 is reduced, in addition to the downregulation of COX-2 and E-prostanoid receptor subtype-2.[1518,1525] All of these effects could add to an aggravation of the eicosanoid imbalance.

The complexity in the interaction of inflammatory mediators in AERD is underlined by the dysregulation of the prostaglandin E_2-dependent control of LT production in peripheral granulocytes. When compared to those from patients with aspirin-tolerant asthma or healthy controls, granulocytes from patients with AERD generate more LTB_4 and cysLTs, and are more resistant to the PGE_2-mediated suppression of LT

generation.[1529] This can be explained in part by an impaired protein kinase A function in AERD, which can lead to the deregulated control of 5-lipoxygenase activity by PGE_2.

Beyond the characteristic type 2 inflammatory signature of AERD, there is has been an increasing emphasis on the role of innate immune responses as a contributing factor to AERD. Type 2 innate lymphoid cells and the associated increased expression of IL-33 and thymic stromal lymphopoietin (TSLP), have been shown to further activate lymphoid and myeloid effector cells, in particular, mast cells.[1518,1519] Both IL-33 and TSLP are strongly expressed in nasal polyp tissue and exhibit a critical role in inflammatory signaling in non-human models.[1524]

Aspirin Intolerance as a Contributing Factor for CRSwNP

Aggregate Grade of Evidence: C (Level 2: 1 study; level 3: 2 studies;level 5: 10 studies)

Table X-16. Evidence for aspirin intolerance as a contributing factor for CRSwNP

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Rajan[1521]	2015	2	Systematic review with meta-analysis	7 groups based on disease (asthma, NP or CRS, or both)	Prevalence study	Prevalence of AERD in patients with CRSwNP is 9.7%.
Stevens[198]	2017	3	Large retrospective prevalence study	AERD CRSwNP and asthma CRSwNP without asthma	Prevalence study and clinical characteristics of CRSwNP	Patients with AERD have more severe CRSwNP phenotype.
Mendelsohn[1530]	2011	3	Large retrospective cohort study	Patients undergoing ESS for NP (n=549)	Recurrence (measured by Kaplan Meier curves)	Revision rates are significantly higher in AERD.
Kowalski[1519]	2019	5	Nonsystematic review/expert opinion			Update on pathophysiology, subtypes and treatment options in AERD.
Cahill[1524]	2017	5	Nonsystematic review/expert opinion			Update on molecular mechanisms of AERD.
Laidlaw[1518]	2016	5	Nonsystematic review/expert opinion			Update on molecular mechanisms and pathophysiology of AERD.

Chang[1532]	2014	5	Bench research			No significant association between the FABP1 polymorphisms and AERD.
Choi[1525]	2014	5	Nonsystematic review/expert opinion			Update on pathophysiology in AERD.
Laidlaw[1529]	2014	5	Bench research			Impaired granulocyte PKA function in AERD may lead to dysregulated control of 5-lipoxygenase activity by PGE(2).
Losol[1528]	2013	5	Bench research			A functional polymorphism in IL5RA may contribute to eosinophil and mast cell activation in AERD patients.
Park[1527]	2013	5	Nonsystematic review			Review on genetic variants responsible for risk of AERD after a genome wide association study.
Szczeklik[1523]	2003	5	Nonsystematic review/expert opinion			Update on pathophysiology in AERD.
Kaldenbach[1526]	1999	5	Bench research	CRSwNP – Inhalant Allergies – AERD	Role of eosinophilic granulocytes	Strongest eosinophilia seen in the group of patients with AERD.

X.C.18. Contributing Factors for CRSwNP: Viruses

Because of limited data, CRSsNP and CRSwNP are combined in Section IX.C.16.

X.C.19. Contributing Factors for CRSwNP: Occupational and Environmental Factors

Because of limited data, CRSsNP and CRSwNP are combined in Section IX.C.17.

X.D. Chronic Rhinosinusitis with Nasal Polyps: Management

X.D.1. Management of CRSwNP: Saline (Spray and Irrigation)

ICAR-RS-2016 found that nasal saline irrigation as an adjunct to other therapies improved symptoms and CRS specific QoL outcomes. High volume (>200ml) was superior to low volume irrigation. Hypertonic and isotonic saline brought similar effects.

An updated search identified three RCTs and two meta-analyses.[442,1048,1049,1051,1058] Of the three RCTs, two were excluded due to mixed ARS/CRS (16% CRSwNP)[442] and mixed CRSsNP/CRSwNP (21% CRSwNP).[1058] One systematic review by Harvey *et al.* was excluded because data were from participants with mixed ARS/CRS (16% CRSwNP).[1051]

As such, data from one randomized trial[1049] and one Cochrane review[1048] were assessed for this review. No published studies compared the effects of saline treatment to non-saline treatment or placebo. We searched for non-randomized controlled trials and observational studies but did not find any additional study.

In an RCT, Cassandro *et al.*[1049] aimed to assess the effects of hyaluronan administered as a nebulizer in CRSwNP patients. They performed an open-label study and randomly assigned eighty patients with CRSwNP who had not undergone sinus surgery to four groups: nebulized saline solution (5ml) bid, nebulized sodium hyaluronate, mometasone furoate nasal sprays 200 µg bid, and both nebulized sodium hyaluronate and mometasone furoate nasal sprays. The nebulized saline solution did not improve nasal symptom scores, endoscopic appearance scores, radiologic scores, rhinomanometry, or saccharine clearance tests at one month, three months, and three months after treatment compared with other treatment groups. It was concluded that nebulized saline was inferior to intranasal steroid spray. This study by Cassandro *et al.*[1049] was one of the two included studies in a Cochrane review in 2016 by Chong *et al.*[1048] The other study assessed a mixed patient population with the majority experiencing ARS. Thus, we did not obtain any additional data from the systematic review by Chong *et al.*[1048] for further assessment.

As such, this updated review included only 1 new randomized controlled trial which used saline as a control arm for assessing the effects of other treatments. Thus data from this study did not directly address the effects of saline as a therapeutic in CRSwNP treatment. In addition, saline in this study was delivered via a nebulizer with a low volume of 5 ml. Various kinds of delivery methods deliver intranasal saline with various volume and pressure of the saline solution, which impact the fluid distribution of topical therapies. The volume of nasal saline can be as low as < 5 ml when using sprays and nebulizers to as large as 250 ml when using squeeze bottles and Neti pots. A positive association between the deeper penetration of topical medications and greater beneficial effects was shown for intranasal corticosteroid treatment.[1077] Systematic reviews and meta-analyses revealed that the therapeutic effects of INCS were greater when corticosteroids were effectively delivered with large-volume and high-pressure devices.[1533] By extension, the same may be true for saline.

For nasal saline treatment, its primary mechanism of action is mechanical clearance of thick mucus and inflammatory mediators.[1534] Thus, effective saline delivery would seem to be beneficial in the treatment of patients with CRSwNP, particularly those with eosinophilic mucin. CRSwNP with eosinonphiic mucin is typically associated with Type 2 sinonasal inflammation, high tissue eosinophilia, and asthma.[1535] A meta-analysis by Hermelingmeier *et al.*[1536] revealed that saline treatment improved MCC time from

2.7% to 31.6%. Improved mucociliary function[1536] is achieved when saline thins mucus[1537] and improves ciliary beat function.[1538] Bonnomet *et al.*[1538] measured CBF of airway epithelial cells obtained from nasal polyps and suggested that saline treatment enhanced ciliary beat frequency and preserved the respiratory mucosa in pathological conditions.

Safety of saline treatment was shown by the study of Cassandro *et al.*[1049] The incidence of throat irritation (0% vs 5%), nasal burning (0% vs 5%), headache (15% vs 10%), upper respiratory infection 15% vs 15%, and treatment-related epistaxis (5% vs 10%) were similar between the saline group and the intranasal steroid group. To date, although there has been no clinical trial to support the use of nasal saline spray for treating CRSwNP, there is evidence showing the benefits of saline treatment on improved mucociliary function. Due to the safety profile of saline treatment and its low cost of around USD$0.24 per day,[1141] there is a greater balance of benefit over harm.

Saline for CRSwNP

Aggregate Grade of Evidence:
Saline sprays: No study
Saline nebulization: B (Level 1: 1 study; level 3: 1 study).
Saline irrigations: No study
Benefit: Mechanical removal of mucus and improved mucociliary function
Harm: Minor adverse effects of throat irritation, nasal burning, and epistaxis (see Table II-1)
Cost: Minimal (US$0.24/day).
Benefits-Harm Assessment: Balance of benefit and harm.
Value Judgments: Patients with CRSwNP usually present with thick nasal and postnasal discharge, which requires topical management. Nebulized saline (5 ml) treatment with effective delivery may be given for mechanical removal of thick mucus.
Policy Level: Option.
Intervention: Nebulized saline (5 ml) treatment is an option for treating CRSwNP, particularly patients with thick mucus.

Table X-17. Evidence for CRSwNP management with nasal saline

Study	Year	LOE	Study design	Study groups (n)	Device	Clinical endpoint	Conclusion
Chong [1048]	2016	1	Systematic review	CRS patients	Nebulizer	Symptom Endoscopy	Referred to Cassandro *et al.*
Cassandro [1049]	2015	3	RCT, NPC, UB	CRSwNP Nebulized saline (20) MFNS (20) NHA (20) MFNS NHA (20)	Nebulizer	Symptom Endoscopy	Nebulized saline was inferior to intranasal corticosteroid for improved nasal symptoms and endoscopic appearances.

X.D.2. Management of CRSwNP: Topical Corticosteroids

X.D.2.a. Topical Corticosteroids: Standard Delivery (Drops and Sprays)

The use of INCS for CRSwNP has been well studied, with ICAR-RS-2016 demonstrating level A aggregate evidence. From 2014 to 2020, a new search on INCS use in CRSwNP resulted in 1213 publications, Medline (154) and Embase (1059). From these citations, an additional 5 RCTS[1539-1543] and 2 systematic reviews with meta-analyses[1544,1545] have been identified. As the prior review of the literature demonstrated 36 RCTs in the setting of CRS which compared topical corticosteroid against placebo,[1064,1068,1355,1546-1578] lower levels of evidence were not considered. A summary of these updated outcomes is provided in Table X-16 with all demonstrating a significant benefit from the use of INCS as sprays or drops over placebo alone.

The updated Cochrane review included 14 studies on CRSwNP alone.[1545] The reported improvement in nasal polyp score was higher in patients on INCS (RR 1.77, 95% CI 1.06 to 2.95; 676 participants; five studies; I2 = 66%). When the absolute proportions of patients improving their polyp score were combined from 8 studies, the overall pooled odds ratio (OR) was 2.07 (95% CI 1.48 to 2.91; 1984 participants; eight studies) favoring the INCS group. For individual symptoms, the corticosteroid group was favored in nasal blockage: MD -0.40 (95% CI -0.52 to -0.29; 1702 participants; six studies; I2 = 47%), rhinorrhea: MD -0.25 (95% CI -0.33 to -0.17; 1702 participants; six studies; I2 = 6%) and loss of sense of smell: MD -0.19 (95% CI -0.28 to -0.11; 1345 participants; four studies; I2 = 0%) but not for facial pain/pressure: MD -0.27 (95% CI -0.56 to 0.02; 243 participants; two studies; I2 = 78%).

Twice daily dosing. Previous reviews and meta-analyses have been published[31,1141,1142,1271,1533,1579,1580] to explain variations in observed clinical effect such as technique, surgical state and agent. Notably, a systematic review on the use of twice daily dosing of INCS in the setting of CRSwNP was performed.[1544] The authors' conclusion was that across 6 RCTs (which include some with exhalation delivery) and 1712 patients, there was a preponderance of evidence favoring twice daily dosing, with 4 RCTs supporting twice daily dosing over once a day. The authors of this study simply assessed the studies in their dose groupings and a formal meta-analysis was not performed. In a separate RCT by Khan *et al.*, 310 adult patients used mometasone 200mcg once or twice daily (and placebo). Over a 4-month period, the authors report a greater improvement in rhinorrhea, post-nasal mucus, nasal peak inspiratory flow (NPIF) and polyp score in the twice daily over once daily group. However, the data reporting in this study is poor[1542]. A small cohort study, assessing post ESS CRSwNP patients that had mild recurrent polyps on once daily mometasone 200mcg were evaluated on twice daily regime, finding reduced polyp score over once daily therapy.[1581]

Higher concentration dosing. Although prior studies have compared low dose to high dose of topical corticosteroid,[1064,1555,1558,1561,1563,1564,1568,1571] recent RCTs from Zhou *et al.*[1543] and Seiberling *et al.*[1541] used higher concentrations of mometasone and dexamethasone, respectively. These studies did not find an observed clinical benefit. Remarkably, only limited clinical improvement is seen by a twice daily mometasone study[1543] and the improved measures of inflammatory changes in NP tissue are also limited.[1582]

The addition of budesonide drops (1mg/day + budesonide spray 256mcg/day) was assessed for a 1 week period, compared to oral methylprednisolone (24mg/day + budesonide spray 256mcg/day), and a

control group (budesonide spray 256mcg/day). Improved endoscopic scores were reported and a change of total nasal symptoms score of 5.71 ± 6.34 in the control group, 9.33 ± 8.78 in nasal drop group and 8.99 ± 7.09 in oral corticosteroid group. These data are not in press but are from conference proceedings.[1540]

Adverse effects. From the Cochrane review, the evidence for the risk of epistaxis was high. Epistaxis is the most common adverse event together with nasal irritation producing itching, sneezing and dryness. The risk of epistaxis was higher in the INCS group compared to placebo (RR 2.74, 95% CI 1.88 to 4.00; 2508 participants; 13 studies; I2 = 0%). No increase in infection or specifically candidiasis has been detected. These minor or moderate adverse events are generally tolerated by patients. None of the studies treated or followed up patients for long enough to report adverse events related to systemic side-effects. Additionally, systemic bioavailability of INCS varies from <1% up to 40-50%, which will influence the risk of systemic adverse effects.[1583]

Long-term administration of INCS to the respiratory mucosa, evaluated by systematic review, does not show any evidence of damage to the nasal mucosa. This review demonstrated that from 34 studies that assessed the nasal mucosa via biopsy, including 11 randomized controlled trials, 5 cohorts, and 20 case series (with a duration of treatment ranging from 5 days to 5.5 years), no atrophic changes were observed. There were two studies that demonstrated the protective effects of INCS against remodeling changes such as squamous metaplasia[1584]. This protection against mucosal remodeling[1584] is relevant as such changes have been implicated in poorer clinical outcomes[1585].

Intranasal Corticosteroids (Standard Delivery) for CRSwNP

Aggregate Grade of Evidence: A (Level 1: 2 studies, Level 2: 5 studies).
Benefit: Improved symptoms, endoscopic appearances, polyp size, and QoL, objective tests of olfaction, airway analysis (NPIF) and polyp recurrence but the magnitude of the clinical effect is small
Harm: Epistaxis, nasal irritation, headache (see Table II-2).
Cost: Moderate depending on preparation
Benefits-Harm Assessment: Benefit outweighs harm.
Value Judgments: Twice daily dosing should be considered if the magnitude of observed clinical benefit is limited.
Policy Level:
INCS: Strong Recommendation.
Twice Daily Dosing: Option.
High concentration/dose: No recommendation due to mixed and insufficient evidence.
Intervention: Topical nasal corticosteroids (sprays or drops) are recommended for CRSwNP before or after sinus surgery. Consideration for twice daily dosing or additional short-term corticosteroid drop if initial treatment effect is small.

Table X-18. Evidence for CRSwNP management with topical corticosteroids (standard delivery with sprays and drops)

Study	Year	LOE	Study Design	Study Groups	Type of Corticosteroid, Dose, Duration, Delivery Method	Clinical Endpoint	Conclusions
Chong[1545]	2016	1	Systematic review of RCTs	RCTs (n=18) RCTs of CRSwNP (n=14)	Analysis including dose, frequency and agent	PROMs Adverse events	The quality of the evidence was moderate for nasal blockage, rhinorrhea and smell disturbance, but low for facial pain/pressure. Increased risk of epistaxis.
Schenkel[1544]	2019	1	Meta-analysis of RCT	6 RCTs (n= 1,712)	Twice daily and Once daily INCS	Polyp score	3 RCTs with twice daily INCS improved NP score. 2 RCTs with once daily INCS with no change in NP score.
Khan[1542]	2019	2	RCT	INCS daily INCS twice daily Placebo (n=310)	Mometasone 200mcg/dose 4months	Polyp score Nasal congestion	Both better than placebo. Twice daily better than once daily.
Seiberling[1541]	2019	2	RCT	INCS high dose (n=8) INCS standard (n=10)	Dexamethasone 0.032% fluticasone propionate 12weeks	SNOT22 Endoscopic Score	No difference at 12 weeks post ESS.

Xu[1540]	2019	2	RCT	Oral corticosteroid +INCS Corticosteroid drop and INCS INCS alone	Methylprednisolone (24mg/d) for 1 week + budesonide spray Budesonide drop (1mg/d) + budesonide spray Budesonide spray 256mcg/day) All one week	Symptoms (VAS) Endoscopic score Serum Eosinophil	Corticosteroid drops and oral were similar. All better than INCS alone.
Zeng[1539]	2019	2	RCT	INCS (n=187) Macrolide(n=187) Post ESS for 3mths	Fluticasone 200mcg daily Clarithyromicin 250mg Daily For 3mths	Symptoms (VAS) Endoscopic score	No difference in symptoms between arms or between subtypes (CRSsNP, CRSwNP (Eos and non-Eos). 1,3,6 and 12mths postop. Non-Eos CRSwNP had less endoscopic inflammation at 6mths.
Zhou[1543]	2016	2	RCT	INCS twice daily (n375) Placebo (n=373)	Mometasone 200mcg twice daily (400mcg) 16weeks	NP score (16 weeks) Symptoms (4 weeks)	Symptoms and NP score favor INCS.

X.D.2.b. Topical Corticosteroids: Nonstandard Delivery

There has been a significant shift in the evidence base for topical corticosteroid delivery via techniques other than standard sprays and drops in the management of CRSwNP. In this summary, interventions that focused on the perioperative management of ESS were not included. Interventions such as implants, stents, mometasone soaked cellulose foam, triamcinolone soaked sponge and other therapies designed to be placed at the time of surgery are reviewed elsewhere in this consensus statement (Section XII.D.7).

X.D.2.b.i. Corticosteroid Irrigations.

There were 5 randomized controlled studies[1077,1078,1586-1588] that assessed the use of corticosteroid irrigations since 2014 and a meta-analysis, which due to publication timing did not include most of these studies[1589] . Previously identified confounding factors such the delivery technique, volume and surgical state of the patients in these trials were addressed since 2014 but continue to produce heterogeneity. There are published comprehensive narrative reviews of corticosteroid irrigations in both the otolaryngology[1089] and allergy literature[1590].

Only one study compared corticosteroid irrigations to standard delivery techniques in a double-blind placebo-controlled trial involving 44 patients which evaluated the use of 240ml corticosteroid irrigations versus simple nasal corticosteroid spray [1077]. All patients underwent similar ESS and post-operatively received 2 mg of mometasone daily via nasal spray or large volume irrigation (240 ml) for 12 months. Every participant in the trial was given both a nasal spray device as well as an irrigation device and were instructed to use the irrigation followed by the spray but were blinded to which device contained the corticosteroid. Patients received post-operative antibiotics and systemic corticosteroids but none of these were given longer than 3 weeks. They were evaluated at 12 months and while both groups improved greatly from either intervention, it was the corticosteroid irrigation group that had larger improvement in nasal blockage (-69.91 ± 29.37 vs -36.12 ± 42.94; p=0.029), Lund-Mackay scores (LMS) (-12.07 ± 4.43 vs -7.39 ± 6.94; p=0.031), and modified Lund-Kennedy scores (mLK) (7.33 ± 11.55 vs 21.78 ± 23.37; p=0.018). Importantly, at the 12-month endpoint, there were several patients that had begun to deteriorate in the nasal spray steroid group and the overall 12-month symptom VAS was better in the nasal irrigation steroid group. One other study compared corticosteroid irrigations in addition to routine care in the management of polypoid AFRS and demonstrated clinically meaningful benefits in symptoms, endoscopic scores and recurrence rate[1587] but was not blinded nor placebo controlled.

In the remaining 3 RCTs, corticosteroid irrigations were compared to saline alone[1078,1586,1588]. Huang *et al.* [1586] performed their study over a 3-month period post complete ESS where patients received 1 mg budesonide or saline. The benefit seen in each group was significant but similar between groups. Tait *et al.* [1078] also performed a double blind placebo controlled trial comparing budesonide irrigations versus saline irrigations in 61 patients. All patients used 240 ml irrigation once daily and were evaluated after 30 days with SNOT-22, LK grading, and a modification of the Clinical Global Impressions scale. The budesonide group had improved scores, but these measures did not reach clinical significance over saline. Rawal *et al.* performed a single blind randomized controlled trial with 50 polyp patients comparing normal saline irrigations (60 ml) to normal saline plus budesonide (0.06 mg/60 ml twice daily for a total daily dose of 0.12 mg/day). All patients underwent ESS and last follow-up was variable between 3 to 6 months after surgery. However, the specifics of the surgical procedures performed were not reported. All patients were given a 12-day corticosteroid taper following surgery. Patient results were evaluated with QoL (SNOT22, RSOM31 [Rhinosinusitis Outcomes Measurement Test], RSDI [Rhinosinusitis Disability Index]) and olfaction (UPSIT [University of Pennsylvania Smell Identification Test] and PEA [Phenyl Ethyl Alcohol]) measures. There were no statistically significant differences between the normal saline arm vs. normal saline plus budesonide at any of the post-operative visits. All of these studies demonstrate a large clinical benefit from the overall intervention, as it includes ESS, with the patient baseline recorded pre-surgery then again at as early as 30 days post the intervention. The influence of ongoing corticosteroid irrigation in the management of patients with CRSwNP is likely to be demonstrated in long term maintenance phase for these patients and a follow-up longer than 3 to 6 months post ESS.

X.D.2.b.ii. Exhalation delivery systems

Two techniques of exhalation delivery mechanisms have been described [1591,1592]. The breath actuated device delivers fluticasone to the nasal cavity via nasal device and the other is exhaled fine particle beclomethasone dipropionate (HFA-BDP) metered-dose inhaler (MDI). The same RCT on corticosteroid via exhalation delivery system was reported multiple times in the literature, Navigate I/II with differing authors, but likely same patient population and has been treated as one study in the aggregate.[1591,1593,1594] All studies show that the use of corticosteroid was better than placebo, but this was the summary finding of the Cochrane review on the use of standard INCS [1545]. While corticosteroid via exhalation delivery system was superior to placebo, the study that is required is against a standard intervention such as corticosteroid spray or irrigation, similar to that performed between corticosteroid irrigations and INCS.[1077]

X.D.2.b.iii. Nebulizer/Atomization/Injection

This group of studies is particularly heterogenous. However, 3 RCTs demonstrated that atomization/nebulization yielded better clinical outcomes over INCS alone.[1595-1597] One study demonstrated that atomization was similar to corticosteroid drops[1597] and another to corticosteroid irrigations.[1086] New evidence for the use of direct injected corticosteroid to polypoid tissue demonstrated an effect similar to a 2 week course of oral corticosteroid but the patients required 5 separate injections over a 4 week period. Although the risk of intravascular injection from particulate material is unlikely in polyp tissue, it was not specifically addressed.

X.D.2.b.iv. Safety and Systemic Absorption

Concerns about safety and the impact of systemic corticosteroid absorption have continued. Studies on betamethasone [1598,1599] and budesonide [1600-1602] irrigations either had no effect or showed clinically negligible changes. However, with direct atomization of budesonide, a first generation corticosteroid that does not undergo first-pass liver metabolism, HPA axis suppression and IOP increases can be seen.[1087]

Patients using 0.5 mg/240 ml of budesonide irrigation either once or twice daily were assessed in a cross-sectional study to evaluate adrenal function in patients on long-term budesonide irrigations over 22 months (mean).[1601] The patients underwent 250 µg cosyntropin stimulation test, of which, 11 (23%) had abnormally low stimulated cortisol levels. None of these patients reported any symptoms. The only risk factor noted to be associated was the concomitant use of corticosteroid inhalers (p=0.024; OR = 30.4, 95% CI [1.57-588]). Patients were evaluated for evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression after using budesonide irrigations, 2 mg total per day, for a minimum of 12 months. None of the patients undergoing cosyntropin stimulation tests had abnormal results, concluding that regular use of budesonide for > 2 years did not lead to HPA axis suppression.[1602]

Intransal Corticosteroids (Nonstandard Delivery) for CRSwNP

Aggregate Grade of Evidence (Versus standard delivery):
- Corticosteroid Irrigation: A (Level 1: 5 studies, level 3: 1 study).
- Exhalation delivery: A (Level 1: 4 studies)
- Atomization/nebulization: A (Level 1: 4 studies)
- Direct injection: N/A (Level 1: 1 study)

Benefit:
- Corticosteroid Irrigation: Benefit over INCS

Exhalation delivery: Benefit only over placebo
Atomization/nebulization: Benefit over INCS
Direct injection: Potential avoidance of oral corticosteroid

Harm: Some evidence of systemic absorption with first generation corticosteroid especially with multiple modalities of therapy (see Table II-2).

Cost: Moderate. Exhalation system costs are significantly higher than standard therapy.

Benefits-Harm Assessment: Negligible side effects compared with oral corticosteroids but caution in patients on multiple topical therapies.

Value Judgments: Corticosteroid irrigations and atomization are likely to be of value in those patients not controlled with standard delivery. Exhalation has not been proven to be better than standard delivery. Direct injection needs more safety data.

Policy Level:

Corticosteroid Irrigation: Strong Recommendation
Exhalation delivery: Option
Atomization/nebulization: Recommendation
Direct injection: No recommendation due to insufficient evidence.

Intervention: Following sinus surgery, those patients with CRSwNP that have moderate-severe disease or are not controlled with simple INCS should be offered corticosteroid irrigation and/or atomized delivery.

1 **Table X-19.** Evidence for CRSwNP management with topical corticosteroids (non-standard delivery)

Study	Year	LOE	Study Design	Study Groups	Type of Corticosteroid, Dose, Duration of Treatment	Delivery Method of Corticosteroid	Clinical Endpoint	Conclusions
Corticosteroid Irrigation								
Huang [1586]	2019	1	RCT	Corticosteroid irrigation (n=30) Saline irrigations (n=30)	Budesonide Isotonic saline Post ESS 3mths	Corticosteroid via nasal irrigation	SNOT22 Endoscopic score SF36 Self Rating Anxiety Scale Self rating Depression Scale	SNOT22 and endoscopic scores improved similarly. SF36, SAS and SDS no changes.
Harvey [1077]	2018	1	RCT	Corticosteroid Irrigation and Placebo spray (n=21) Placebo Irrigation and corticosteroid spray (n=23)	2mg mometasone or placebo 12months (1 year)	Corticosteroid irrigation versus INCS as double placebo	Symptoms SNOT22 SF36 Endoscopic Score Radiology score	Reduced symptoms, lower endoscopic and radiology score when delivered by irrigation compared to delivery by spray.
Tait [1078]	2018	1	RCT	Corticosteroid irrigation (n=37) Saline/Placebo irrigations (n=37)	Budesonide or placebo (30days)	Corticosteroid via nasal irrigation	SNOT22 Endoscopic Score Clinical Global Impressions Scale	Greater change in SNOT22, lower endoscopic scores in corticosteroid irrigation group.
Chaudhary [1587]	2017	1	RCT (AFRS)	Corticosteroid irrigation plus routine care	Budesonide 6weeks	Corticosteroid via nasal irrigation	SNOT22 Endoscopic Score Need for ESS	Lower SNOT22 and endoscopic scores in budesonid

				(n=30) Routine care (n=30)				e irrigation group.
Rawal [1588]	2015	1	RCT	Corticosteroid irrigation (n=25) Saline irrigations (n=25)	Budesonide 0.12mg/daily as divided dose 60ml lavage (each nose) twice daily Variable duration 12-24 weeks	Corticosteroid via nasal irrigation	SNOT-22, RSOM-31, RSDI, UPSIT, PEA test	At the 12 week minimum, no difference between groups.
Yoon [1589]	2018	3	Meta-analysis of controlled studies	Corticosteroid irrigation Saline irrigations	Varying volumes, doses, durations, frequencies, and surgical states	Corticosteroid via nasal irrigation	Symptoms QoL Endoscopic Score	Low quality evidence for additional benefit.
Exhalation Driven Delivery								
Sindwani [1591]	2019	1	RCT	Corticosteroid (exhalation delivery) x3 dose placebo (n=323)	Fluticasone 93 mcg, 186 mcg, 372 mcg twice daily (BID) for 24 weeks	Corticosteroid via exhalation delivery system	NP symptoms SNOT22 MOS Sleep-R SF36 PGIC RSDI NP score	Fluticasone better than placebo.
Leopold [1593]	2019	1	RCT	Corticosteroid (exhalation delivery) x3 dose placebo (n=323)	Fluticasone 93 mcg, 186 mcg, 372 mcg twice daily (BID) for 24 weeks	Corticosteroid via exhalation delivery system	Nasal congestion NP score	Fluticasone better than placebo. 4 week symptom and 16 week NP score
Kobayashi [1592]	2018	1	RCT	Exhaled corticosteroid (n=11) Placebo (n=12)	HFA-134a-beclomethasone dipropionate	Fine-particle inhaled corticosteroid (ICS) exhalation through	NP score Smell QoL Radiologic Score	Corticosteroid better than placebo.

						the nose (ETN)		
Soteres[1594,1603]	2017	1	RCT	Corticosteroid (exhalation delivery) x3 dose placebo (n=323)	Fluticasone 93 mcg, 186 mcg, 372 mcg twice daily (BID) for 24 weeks	Corticosteroid via exhalation delivery system	Anosmia/hyposmia, facial pain/pressure, rhinorrhea, and congestion/ obstruction NP score NPIF	Fluticasone better than placebo. 4 week symptom and 16 week NP score and NPIF.
Atomization/Nebulization								
Velepic[1595]	2019	1	RCT	INCS + saline irrigation Aerosol (combination)	Mometasone (200mcg/daily) and 150ml saline Aerosol (essential oils, saline, glucocorticoids, and antibiotics)	Atomizsed solution v spray	Glasgow Health Status Inventory (GHSI) Endoscopic Score	Aerosol mix did better on GHSI. Endoscopic scores similar.
Dai[1596]	2017	1	RCT	Corticosteroid nebulization (n=15) INCS (n=15)	Budesonide	Corticosteroid via nasal nebulization	Symptoms Endoscopic scores Radiologic scores	Less recurrence in the corticosteroid nebulization group.
Neubauer[1597]	2016	1	RCT	INCS Corticosteroid atomization Corticosteroid drops	Fluticasone spray (100mcg) Budesonide atomizer (0.5mg) Budesonide drops (0.5mg) Twice daily 6months	Corticosteroid via atomizer (cf drops and spray)		Atomizer and drop were better than INCS, but similar to drops, post ESS in SNOT-22 and endoscopic score.
Thamboo[1086]	2014	1	RCT	Corticosteroid atomizatio	1mg budesonide twice daily	Corticosteroid via nasal	SNOT22 ACTH stimulation	Both improved symptoms

				n Corticosteroid Irrigation	either in atomizer of saline irrigation	irrigation	Cortisol levels	but similar. No evidence of HPA suppression.
Local injection								
Kris[1604]	2016	1	RCT	Oral corticosteroid and Corticosteroid drops(n=45) Intra-polyp corticosteroid and Corticosteroid drops (n=45)	Prednisone (1mg/kg/day tapering over 2weeks) Injected triamcinolone (40mg) weekly x5 Then both groups: Fluticasone 400mcg drops twice daily fro 12weeks	Corticosteroid as intrapolyp injection versus oral	Symptoms Endoscopic score Radiology score Cortisol and ACTH	Similar outcomes between oral steroid and intrapolyp injection. No observe systemic effects from injection group.

X.D.3. Management of CRSwNP: Steroid-Eluting Implants (Nonsurgical)

Biodegradeable corticosteroid eluting-implants provide targeted sustained release of medication into the sinus cavity to reduce nasal polyposis (NP) and obstruction.[1605-1608] Currently, the only steroid-eluting implant approved by the US FDA to treat adult patients with NP is the Sinuva implant (Intersect ENT, Palo Alto, CA). The implant contains 1350 mcg of mometasone furoate and is typically inserted in the clinic setting under local anesthesia. It is designed for NP patients who have previously undergone ESS of the ethmoid sinuses. The self-expanding implant softens over time and provides up to 90 days of steroid treatment. A non-US FDA approved steroid eluting implant designed for placement in an unoperated ethmoid cavity has also been reported.[1609,1610]

The Sinuva implant has been investigated in 2 RCTs and a pooled analysis (n=375), which showed significant improvement in endoscopic polyp grade, ethmoid sinus obstruction, and patient-reported symptoms relative to controls at 90 days.[1607,1608,1611] The RCTs utilized bilateral sham procedures as interpatient controls, with both implant and control groups receiving intranasal steroid sprays. At 90 days, 59% of treated patients versus 31% of controls were no longer indicated for revision ESS, although this decreased to 31% of treated patients and 11% of controls at 6 months.[1608,1612] In terms of adverse events, there was no significant increase in intra ocular pressure or cataracts but one episode of epistaxis was reported in the larger Phase 3 trial.[1606,1607]

An economic evaluation estimated cost saving of USD$0.21 per-member per-month or a total of USD$2.56 million per year for a commercial health plan with 1 million members.[292] The evaluation assumed that 50% of eligible patients would undergo implant placement instead of revision ESS and would require two implant placements during a one year period.[292] Limitations of the current data include the relatively short term 90 day follow up of the larger Phase 3 study versus the 6 months available for the prior RCT.[1606,1607] It is not known whether some patients may need the implant more or less frequently.[292] Also, both RCTs removed implants at 60 days despite their ability to elute steroids up to 90 days and both RCTs required the treatment and control groups to continue intranasal mometasone once per day.[292,1605-1607] It is unclear how the implant would perform without the additional benefit of intranasal steroid. Clinical experience with this device is still relatively limited and the evidence, though at a high level, is restricted to short-term outcomes.

Steroid Eluting Implants for CRSwNP

Aggregate Grade of Evidence: A (Level 1: 1 study; level 2: 3 studies)
Benefit: Reduction in ethmoid sinus obstruction and polyp grade leading to decreased need for revision ESS and reduced nasal obstruction patient scores.
Harm: No prior findings of increased risk of elevated intraocular pressure or cataracts
Cost: Cost of implant and risk of nasal discomfort and/or epistaxis
Benefits-Harm Assessment: Benefit outweighs harm
Value Judgments: Corticosteroid eluting implants have been shown to have beneficial impact on ethmoid polyposis and obstruction, and 1 study has shown them to be cost-effective in preventing revision ESS. Experience is early and although evidence is high level, only short-term outcomes are currently available
Policy Level: Option
Intervention: Corticosteroid-eluting implants can be considered as an option in a previously operated ethmoid cavity with recurrent nasal polyposis

Table X-20. Evidence for CRSwNP management with steroid eluting implants

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoints	Conclusion
Stolovitzky [1608]	2019	1	Meta-analysis (n=375)	2 RCTS of CRSwNP patients who were deemed candidates for RESS	Nasal obstruction and congestion (NOSE) score Endoscopically assessed polyp grade and ethmoid obstruction Need for RESS	At 90 days, patients receiving implants and nasal steroid spray had significant improvements in nasal obstruction/congestion score, bilateral polyp grade, and ethmoid sinus obstruction compared to control patients using steroid spray alone. 59% of treated patients were no longer indicated for RESS compared to 31% of controls. Four patients had nasal discomfort and 1 patient had epistaxis.
Kern [1607]	2018	2	Multicenter randomized controlled, single-blinded trial (n=300)	CRSwNP patients who were deemed candidates for RESS	Nasal obstruction, congestion score and NOSE score Endoscopically assessed bilateral polyp grade and ethmoid obstruction by review panel Need for RESS	At 90 days, significant improvement in ethmoid sinus obstruction, nasal obstruction/congestion score, sense of smell, and reduced need for RESS in the implant group versus controls. One patient with epistaxis.
Forwith[1606] (6 month results of Han[1605] 2014)	2016	2	Multicenter randomized controlled, single-blinded trial (n=100)	CRSwNP patients who were deemed candidates for RESS	Nasal obstruction, congestion score and NOSE score Endoscopically assessed bilateral polyp grade and ethmoid obstruction assessed by clinician and review panel Need for RESS	At 6 months, significant improvement in NOSE score, reduction in ethmoid sinus obstruction and bilateral polyp grade in implant group versus controls. Panel review found polyp grade improvement reached significance only in patients with severe polyps. At 6 months, 31% of treated patients were no longer indicated for RESS compared to 11% of controls. No increase in IOP or cataracts
Han [1605]	2014	2	Multicenter randomized controlled, single-blinded (n=100)	CRSwNP patients who were deemed candidates for RESS	Nasal obstruction, congestion score and NOSE score Endoscopically assessed bilateral polyp grade and ethmoid obstruction by clinicians Need for RESS	At 90 days, significant reduction in bilateral polyp grade, ethmoid sinus obstruction in implant group versus controls. Significant improvement in nasal obstruction/congestion score in patients with greater polyp burden in implant group versus controls. At 90 days, 53% of treated patients were no longer indicated for RESS compared to 23% of controls. No increase in IOP or cataracts

X.D.4. Management of CRSwNP: Oral Corticosteroids

Since the publication of ICAR-RS-2016, there have been two Cochrane Reviews analyzing the data on oral corticosteroid use in the management of CRSwNP. Both reviews were from the same group in the United Kingdom and very thoroughly summarize the existing data.

The first review evaluated the data on short courses of oral corticosteroids alone for CRS.[1613] The authors identified seven studies, all of which were randomized controlled trials. Two studies were unblinded while the remaining five blinded both the patients and the health care providers to the treatment group. All patients were adults with the diagnosis of CRSwNP with varying degrees of severity of the disease amongst the studies. Three studies had no minimal grade of nasal polyps for inclusion, two required moderate-to-severe bilateral polyps, and three studies only included severe nasal polyposis.

All studies reported positive results for short course of oral corticosteroids compared to placebo (five studies) or no treatment (two studies). Corticosteroid courses ranged from 14-21 days and included prednisone, prednisolone and methylprednisolone. Total doses ranged from 210 mg to over 1000 mg of prednisone equivalent.

The review reported low quality evidence of an improvement in disease-specific health-related QoL as well as in disease severity after treatment with oral corticosteroids compared to the controls at various time points. After the treatment period had ended, there was no difference in the change from baseline symptom severity between the treatment groups.

There was evidence that immediately after treatment, oral corticosteroids provided improvement in nasal polyp scores. The magnitude of this improvement months after treatment may not be sustained. A high risk of bias existed for both statements.

When analyzing data on the side effects of corticosteroids, there was low quality evidence of increase in insomnia and gastrointestinal disturbances in the steroid group. There was low quality evidence regarding mood disturbances between the two groups and any difference between groups was unclear.

The second review evaluated the data on oral corticosteroids as an adjunct in patients with CRSwNP.[1614] The authors identified two studies, only one of which included adults. This study was an unblinded, quasi-randomized controlled trial in 30 adults with CRSwNP based on endoscopic examination. Patients were treated with a 21 day course of topical INCS alone, oral methylprednisolone alone, or both. The included outcome was the endoscopic nasal polyp score measured on a 4 point scale. The patients receiving the oral corticosteroids plus topical intranasal steroids had an improvement in the nasal polyp score compared to the topical intranasal corticosteroid alone, though there was a high risk of bias in these data.

Providers must also consider the potential risks associated with oral corticosteroid use. A cost analysis compared the risks of corticosteroids with those of sinus surgery in CRSwNP patients. The authors evaluated reported complication rates, QoL changes and Medicare costs between the two treatments. They concluded that the breakeven threshold, favoring surgery over medical therapy, occurred when more than one corticosteroid course was given every two years in CRSwNP patients, once per year in

CRSwNP patients with asthma, and twice per year in AERD patients. Of note, CRSsNP patients were not included in the analysis.[1615]

In summary, evidence exists to support short-term use of oral corticosteroids, either alone or as an adjunct, in symptomatic treatment and polyp size regression in patients with CRSwNP. Variable drugs, dosing and duration were used in the reviewed literature. The beneficial effects last for a short duration only and potential adverse effects of a single burst or multiple short-term bursts must be considered when treating patients.

Oral Corticosteroids for CRSwNP

Aggregate Quality of Evidence: A (Level 2: 7 studies).
Benefit: Significant short-term improvements in subjective and objective measures in CRSwNP patients. Duration of improvement may last 8-12 weeks in conjunction with topical intranasal corticosteroid use.
Harm: More GI symptoms in steroid group, rare severe reactions occur. Transient adrenal suppression, insomnia, and increased bone turnover. All known corticosteroid risks exist, particularly with prolonged treatment. See Table II-2.
Cost: Low.
Benefits-Harm Assessment: Preponderance of benefit to harm with short-term burst with limited, short-term follow-up.
Value Judgments: Significant short-term improvements in subjective and objective measures based on high quality data, low risk and low cost.
Policy Level: Strong recommendation for short-term use.
Intervention: Strong recommendation for the use of oral corticosteroids in the **short-term** management of CRSwNP. Longer term use of steroids for CRSwNP is not supported by the literature and carries and increased risk of harm to the patient.

Table X-21 Evidence for CRSwNP management with oral corticosteroids

Study	Year	LOE	Study Design	Definition of CRSwNP	Study group(s)	Systemic steroid protocol	Clinical Endpoints(s)	Conclusion
Ecevit [1616]	2015	2	RCT	Clinical exam and endoscopic visualization of polyps. N=22	Oral steroids for 17 days	Prednisolone 60 mg for 7 days, then tapering every other day.	Endoscopic polyp score CT scan (Lund-Mackay) Butanol olfactory threshold test Peak nasal inspiratory flow Visual analog scale.	Statistically significant improvements in VAS, Butanol threshold tests, PNIF in study group.
Alobid [1356]	2014	2	RCT	EPOS 2007 N=92	Oral steroids for 2 weeks and intranasal budesonide 400mcg BID for 12 weeks. No corticosteroid treatment for 2 weeks.	Prednisone 30mg daily for 4 days followed by 5mg reductions every two days for a total of 2 weeks.	Smell test (Barcelona Smell Test 24) Nasal congestion (Likert scale) Nasal polyp biopsy at week 0 and week 2. Nasal nitric oxide (chemiluminescence) Polyp size (Lildholdt score) CT scan (Lund-Mackay)	Improvement in smell test, nasal congestion, eosinophil count in polyp tissue, exhaled nasal nitric oxide, and polyp size at week 2 and 12. CT scan showed lower score at week 12 compared to baseline.
Kirtsreesakul [1617]	2012	2	RCT, double blinded	Clinical diagnosis and endoscopic visualization of polyps N=117	Oral steroids for 14 days plus intranasal steroid spray for 10 weeks Placebo plus intranasal steroid spray for 10 weeks	Prednisolone 50mg daily Mometasone furoate nasal spray 200 mcg twice daily	Nasal symptoms (Likert scale) Nasal patency by nasal PEFI Endoscopic grading of polyp size	Improvement of nasal symptoms in steroid arm. At 12 weeks, only hyposmia was significantly different between the two groups, favoring the steroid group. Objective

								measures in steroid arm, polyp size and nasal patency, were improved and maintained throughout the 12 weeks.
Vaidyanathan [1618]	2011	2	RCT, double blind	EPOS 2007 N=60	Oral steroid x 14 days followed by intranasal fluticasone Placebo x 14 days followed by intranasal fluticasone	Prednisolone 25mg/day x 14 days	Endoscopic grading of polyp size Hyposmia VAS Pocket Smell Test Total nasal symptom score RQLQ PNIF EDN CRP Adrenal suppression Bone Turnover	Improvement in most parameters with steroids. Some benefits remained, up to 28 weeks. Transient adrenal suppression seen. Transient decrease in markers of osteoblast activity at 2 weeks, with return to baseline at 10 and 28 weeks.
Van Zele [1619]	2010	2	RCT, double blind, multicenter	Presence recurrent nasal polyps after surgery or "massive" nasal polyps N=47.	Oral steroid for 20 days Oral doxycycline for 20 days Placebo	Methylprednisolone 32mg x 5 days, 16mg x 5 days, 8mg x 10 days	Nasal polyps grade by nasal endoscopy NPIF Nasal symptoms Serum eosinophil count Nasal secretion of IL-5, IgE, MMP-9, ECP	Steroid arm showed improvement in polyp size, NPIF, inflammatory markers, nasal congestion, post-nasal drip, and loss of smell. Return to

								baseline at the end of the study.
Benitez [1620]	2006	2	RCT	Nasal endoscopic examination N=84	Oral prednisone x 14 days plus intranasal budesonide No steroids	Prednisone 30 mg daily for 4 days then decrease dose by 5mg every 2 days. Intranasal budesonide 400 mcg BID for 12 weeks.	Nasal symptoms score Polyp size (Lildholdt score) Nasal patency via anterior rhinomanometry Sinus opacification (Lund-Mackay)	Significant improvement in nasal symptoms, in polyp size and nasal patency at week. Significant improvement maintained for all three endpoints and in CT scores.
Hissaria [1621]	2006	2	RCT, double blind	Visualization of polyps on nasal endoscopy N=41	Oral steroids x 14 days Placebo	Prednisolone 50mg daily	Nasal symptoms (VAS) RSOM-31 MRI Nasal Endoscopy	Greater improvement of nasal symptoms, nasal specific RSOM scores, MRI, and nasal endoscopy in steroid arm.

X.D.5. Management of CRSwNP with Antibiotics

X.D.5.a. Antibiotics for CRSwNP: Oral Non-Macrolide Antibiotics for <3 Weeks

Since ICAR-RS-2016 there has been little change in the literature to support the use of short-term antibiotics for CRSwNP. Most papers are concerned with antibiotic treatment of AECRS.

In an EBRR on antimicrobials in CRS published in 2013, Soler *et al.* found only six studies examining the short-term (<3 weeks) use of antibiotics in CRS.[1119] Only one of these, Van Zele *et al.*, differentiated CRSwNP from CRSsNP patients.[1619] A recent Cochrane review on antibiotic use in CRS, both systemic and topical, also highlighted this paper.[1105] Van Zele *et al.* designed a double-blind prospective RCT of 47 total patients in which one study group took doxycycline 200 mg once followed by 100 mg daily for 20 days. This was compared to two groups, one who received a tapering dose of methylprednisolone and another prescribed a placebo. The authors found that this short course of antibiotics resulted in a small but significant decrease in nasal polyp score as measured on endoscopy. The effect lasted the full 12 weeks of the study but was modest in effect; symptoms were also not significantly affected long-term. The authors point out that the intrinsic anti-inflammatory effects of doxycycline may have been responsible for the reduction in polyp size in addition to or instead of the anti-microbial effect.

Since the Soler *et al.* review there have been only a few trials examining antibiosis in CRSwNP. Sreenath *et al.* prospectively treated CRSwNP patients with a variable duration of antibiotics.[1622] The primary outcome was whether patients were recommended surgery after treatment. The authors randomized nasal polyposis patients to take doxycycline 100 mg twice daily for either 3 or 6 weeks. At follow-up they found no statistical difference in provider recommendation for surgical intervention; at 3 weeks they recommended that 7 out of 7 patients have surgery (100%) whereas in the 6-week cohort they recommended that 5 out of 7 patients have surgery (71%). Between these groups there was no significant difference in symptoms as measured by RSDI nor post-treatment Lund-Mackay CT scores. In fact, the authors noted that symptom scores worsened with longer antibiotic prescriptions. They concluded that in treating CRS with maximal medical therapy the duration of antibiotics may be unimportant and that antibiotics are potentially not indicated. These results are limited by the small sample size, but this is surprisingly the largest cohort study of this kind in the literature.

At the World Allergy Conference in 2015, Schryver *et al.* described a series of RCTs for medical therapy for CRSwNP.[1623] They randomized patients to either 1) a 20-day course of doxycycline, 2) a 20-day steroid taper, 3) 2 injections of mepolizumab, 4) 2-4 injections of omalizumab, or 5) placebo. The patients were then evaluated at 4 and 8 weeks for changes in endoscopic polyp score, symptoms, or inflammatory markers as measured in serum and nasal secretions. They reported significant improvement in polyp score in all groups, including doxycycline. However, these results were only published in abstract form, so no determination was made on the quality of this study.

Most recently, Parasher *et al.* attempted to study doxycycline against placebo in an RCT for CRSwNP with moderate to severe symptoms as measured on a VAS.[1624] Patients were randomized to a 20-day course of doxycycline or placebo; both groups were also prescribed an oral methylprednisolone taper. The primary endpoint was change in SNOT-22 score as measured at 12 weeks. Unfortunately, the authors found this patient population quite difficult to study; 26 of the 49 recruited patients dropped out of the study (53%) and the study was terminated before reaching the expected number needed to properly power their hypothesis. The majority of the dropouts were due to acute exacerbations of asthma or CRS symptoms (58%) and 81% of the dropouts occurred after the treatment period but

before the end of the trial period. There was no difference in dropouts between the treatment arms. The authors found no significant difference in SNOT-22 scores, VAS scores, nor endoscopic nasal polyp score when they performed a mixed-effect model analysis. They concluded that the early end to their trial likely meant that the addition of doxycycline had limited utility in the medical management of moderate to severe CRSwNP.

Despite the widespread use of antibiotics in CRSwNP there is actually little evidence, some of it conflicting, of their efficacy. Given the potential adverse effects of antibiotics, as discussed in previous sections, the use of short courses of oral non-macrolide antibiotics in a non-acute exacerbation of CRSwNP should be discouraged.

Oral Non-Macrolide Antibiotics for <3 Weeks for CRSwNP

Aggregate Grade of Evidence: B (Level 2: 1 study, Level 3: 2 studies).
Benefit: Potential reduction in polyp size with doxycycline without change in symptoms.
Harm: Adverse events in the medication groups included gastrointestinal upset, skin rash, insomnia, and headache; delay of more effective interventions (see Table II-1).
Cost: Variable depending on the antibiotic.
Benefits-Harm Assessment: Preponderance of harm over benefits.
Value Judgments: A lack of evidence and known adverse effects outweigh the possible benefit for routine use.
Policy Level: Recommendation against.
Intervention: Short courses (<3 weeks) of non-macrolide antibiotics should generally not be prescribed for CRSwNP except in acute exacerbations.

Table X-22. Evidence for CRSwNP management with non-macrolide oral antibiotics for <3 weeks

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusion
Van Zele [1619]	2010	2	RCT	Doxycycline Methylprednisolone Placebo	Polyp size Symptoms Inflammatory markers	Reduction in polyp size at week 12. No sustained symptom changes.
Parasher [1624]	2019	3	RCT	Doxycycline + steroid Placebo + steroid	SNOT-22 VAS Nasal polyp scale	Early end to trial due to high drop out rate; no difference between arms.
Sreenath [1622]	2015	3	Prospective, randomized cohort	3 weeks of antibiotics 6 weeks of antibiotics	Recommendation for surgery RSDI score LM CT score	No difference in recommendation for surgery.

X.D.5.b. Antibiotics for CRSwNP: Oral Non-Macrolide Antibiotics for >3 Weeks

There is little in the published literature regarding longer courses (>3 weeks) of oral non-macrolide antibiotic for treatment of CRSwNP. As discussed in the preceding section, there is only one study

specifically addressing the duration of antibiotic therapy in this cohort. Sreenath *et al.* prospectively treated CRSwNP patients with a variable duration of antibiotics to determine any difference in the primary outcome of recommendation for surgery.[1622] The authors found that at follow-up providers recommended surgery independent of whether patients had completed a 3-week or a 6-week course of doxycycline. They found that patients had no difference in Lund-Mackay CT score nor significant change in symptoms as measured by RSDI. The authors actually noted a trend toward worsening symptoms in patients on the longer prescription. They concluded that duration of antibiosis did not affect outcomes and that antibiotics were potentially not indicated in treating CRSwNP.

In contrast, Bezerra *et al.* reported a prospective cohort trial of CRSwNP patients who had failed surgery and were treated with either 1) INCS or 2) INCS plus doxycycline.[1625,1626] The authors treated patients for 12 weeks and evaluated a primary endpoint of SNOT-20 scores. They found a statistically significant improvement in SNOT-20 scores, NOSE scores, and Lund-Kennedy scores for those treated with INCS and doxycycline. The authors noted a benefit, but a decrease in significance, in patients with high levels of serum IgE or the comorbidities of asthma or AERD.

In a proof-of-concept case-series regarding a novel antibiotic for patients with CRSwNP, Hoza *et al.* examined the efficacy of erdosteine, a mucolytic agent with antibacterial, antioxidant, and anti-inflammatory effects.[1627] Oral erdosteine was prescribed alone or in combination with an INCS over the course of 3 months. Significant reduction of symptoms based on SNOT-22 testing was seen in both groups, with significantly better response seen in the group treated without INCS. It is unclear whether the antimicrobial, mucolytic, or some other property of erdosteine was responsible for the improvement seen in this study.

There are only a few studies examining whether greater than 3 weeks of oral non-macrolide antibiotics are indicated in treatment of CRSwNP. The studies available examine several different medications (*e.g.,* doxycycline, erdosteine) and have inconsistent results. On the other hand, the side effects of antibiotics are well known and carry significant risks. Moreover, the authors of these studies are not clear on whether it is the antibiotic or anti-inflammatory effect of these medications that is helpful in certain patients. Therefore, at this time there is insufficient evidence to make a recommendation regarding this therapy.

Oral Non-Macrolide Antibiotics for >3 Weeks for CRSwNP

Aggregate Grade of Evidence: D (Level 3: 1 study, Level 4: 2 studies).
Benefit: Potential symptom relief.
Harm: Adverse effects of antibiotics include skin rash, gastrointestinal upset, and anaphylaxis; delay in more effective therapy (see Table II-2).
Cost: Variable depending on the antibiotic.
Benefits-Harm Assessment: Balance of benefit and harm.
Value Judgments: A lack of evidence and known adverse effects may outweigh the possible benefit.
Policy Level: No recommendation.
Intervention: Practitioners should weight the risks and benefits of extended courses (>3 weeks) of non-macrolide antibiotics for CRSwNP and know that the literature is sparse..

Table X-23. Evidence for CRSwNP management with non-macrolide oral antibiotics for >3 weeks

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusion
Sreenath [1622]	2015	3	Prospective, randomized cohort	3 weeks of antibiotics 6 weeks of antibiotics	Recommendation for surgery RSDI score LM CT score	No difference in recommendation for surgery.
Bezerra [1625,1626]	2014	4	Prospective cohort	INCS INCS + doxycycline	SNOT-20 score NOSE score LK endoscopy score	Statistical improvement in all endpoints with addition of doxycycline.
Hoza [1627]	2013	4	Case-series	Erdosteine Erdosteine with INCS spray	SNOT-22 score	Reduction in symptom score. Better response seen without INCS.

X.D.5.c. Antibiotics for CRSwNP: Macrolide Antibiotics

Macrolide antibiotics have both anti-inflammatory and immunomodulatory properties, in which they demonstrate reduction in pro-inflammatory cytokines, especially interleukin-8, the primary cytokine involved in the recruitment of neutrophils, and TNF-α.[1105,1628] Due to this effect on the primarily neutrophilic rather than eosinophilic component of the inflammatory response, macrolide antibiotics have been found to be most effective specifically in Th1-mediated non-eosinophilic CRS in long durations and low doses.[1,31,1628,1629] Of the two common phenotypes of CRS, CRSsNP and CRSwNP,[1,31,1105,1628] CRSwNP generally responds well to corticosteroids due to its pathophysiology being driven more by excessive T-helper2 inflammation and eosinophilic infiltration.[1,1628,1630] However, there is a subset of CRSwNP characterized by its corticosteroid resistance, which has been found to have a predominantly neutrophilic or mixed histopathology, rather than eosinophilic, and has shown benefit from long-term, low-dose macrolide therapy.[1628]

In 2014, Peric *et al.* evaluated the clinical effects of preoperative long-term, low-dose clarithromycin administration in patients with nasal polyposis. They found preoperative clarithromycin administration delays nasal polyp relapse after ESS.[1631] Varvyanskaya *et al.* assessed the efficacy of long-term macrolide therapy adjunct to the maintenance therapy with nasal corticosteroids in the recurrence-prevention of nasal polyps after ESS. They confirmed that long-term macrolide therapy had significantly improved almost all parameters they had measured, such as SNOT-20, endoscopic and CT scores, with the exception of acoustic rhinometry and VAS.[1632]

In 2014, Korkmaz *et al.* revealed that the combined administration of long-term low-dose oral macrolides with nasal steroids is effective in eradicating biofilm in CRSwNP. However, in terms of CT and symptom scores, such combined therapy was not any better.[1633]

There are several meta-analyses assessing the effect of macrolides on CRS with conflicting conclusions. Pynnonen *et al.* concluded that scientific evidence was not strong enough to support the use of long-term macrolides to treat CRS.[1117] Cervin *et al.* concluded that long-term macrolides were a viable option

in the treatment of CRS on selected patients.[1120] Lasso *et al.* concluded that some positive effects were associated with the use of macrolides for postoperative CRSwNP, but the changes did not reach statistical levels required for a firm conclusion on the use of macrolides for treating CRS patients.[1634] Huang *et al.* concluded that adding oral clarithromycin to intranasal steroid spray likely achieved better results than intranasal steroid spray alone for both CRSsNP and CRSwNP.[1118]

Regarding the characteristics of macrolide responders and factors of success, Oakley *et al.* conducted a case control study of consecutive CRS patients placed on a 3-month low dose macrolide therapy after failing 3 months of corticosteroid irrigation therapy post-ESS. They concluded that the CRS phenotype appearing to respond to macrolide therapy had low tissue and serum eosinophilia, and absence of tissue squamous metaplasia.[1123] Seresirikachorn *et al.* found that low dose macrolides had produced favorable outcomes in patients with CRSsNP compared with CRSwNP, and suggested that a half dose of macrolides should be given for a duration of 24 weeks.[1121]

Although macrolide therapy has been shown to be effective for CRS patients, there are potential adverse effects to consider, such as cardiovascular risks (prolongation of the QT interval resulting in arrhythmia and myocardial infarction), elevated liver enzyme levels, ototoxicity and gastrointestinal side effects.[1635] Bacterial resistance and drug-drug interactions are other potential issues.

CRS is a heterogeneous disorder comprising different phenotypes and endotypes. Most studies assessing the efficacy of macrolides on CRS patients do not separate CRSwNP from CRSsNP, making results harder to interpret.[1111,1114-1116,1539] Only 3 RCTs specifically assessed CRSwNP patients.[1631-1633] Of these, only Varvyanskarya *et al.* found a significant difference in SNOT-20 scores in CRSwNP patients compared to the control group, whereas other subjective measures did not demonstrate a difference.[1631-1633] Regarding endoscopic scores, Peric *et al.* and Varvyanskarya *et al.* both reported better endoscopic scores in the clarithromycin group when given both preoperatively[1631] and postoperatively.[1632] It is also proposed that the efficacy of anti-inflammatory medications may differ among CRS patients with and without surgical interventions due to the varied inflammatory load and sinus anatomy amongst postoperative patients.[1068,1636] More placebo-controlled studies are needed to determine the exact efficacy of macrolides across clearly defined CRS subtypes. These subtypes should be classified based on phenotype as well as endotype.

In summary, there are 5 meta-analyses and 3 RCTs assessing macrolides in CRSwNP. Most RCTs and some cohort studies revealed significant improvement of certain clinical parameters in patients treated with macrolides, while other studies showed no differences. Further RCT studies are needed in the future. Risks of adverse events should be considered so that potential benefits are balanced with potential harms.

Macrolide Antibiotics for CRSwNP

Aggregate Grade of Evidence: B for CRS overall with limited evidence regarding CRSwNP specifically (Level 1: 5 studies; level 2:3 studies; level 3: 5 studies).
Benefit: Macrolides may improve symptom scores and endoscopic scores in CRSwNP patients. But results are mixed among 3 RCTs.
Harm: Significant potential for medication interactions. Rare mild adverse events, such as gastrointestinal side effects, ototoxicity, hepatotoxicity, cardiotoxicity. See Table II-1.
Cost: Low.

Benefits-Harm Assessment: Unclear benefit-to-harm ratio in CRSwNP patients. Benefits of treatment over placebo, and benefits of adding macrolides to other treatment were seen in some studies but not others.
Value Judgments: Optimal drug, dosage, and duration of therapy are not known.
Policy Level: Option.
Intervention: In CRSwNP, macrolides may be beneficial, especially in neutrophil-dominant polyps or in those who are unresponsive to corticosteroids.

Table X-24. Evidence for CRSwNP management with macrolide antibiotics

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Seresirikachorn[1121]	2019	1	Meta-analysis	CRSsNP or CRSwNP. 10 studies	SNOT Symptom score CT score Endoscopy score	Favorable outcomes in patients with CRSsNP, but not in patients with CRSwNP.
Huang[1118]	2019	1	Meta-analysis	CRSsNP or CRSwNP. 7 studies	TNSS VAS Endoscopic score CT score	Adding clarithromycin to intranasal steroid spray may yield better results than intranasal steroid spray alone.
Lasso[1634]	2017	1	Meta-analysis	CRSsNP and CRSwNP. 9 RCT		Positive results were found with macrolide therapy in the postoperative period in patients with nasal polyps.
Cervin[1120]	2014	1	Meta-analysis	CRSsNP and CRSwNP. 2 RCTs, 22 Open/cohort studies		Long-term macrolide is an option for selected CRS patients
Pynnonen[1117]	2013	1	Meta-analysis	CRSsNP and CRSwNP. 3 RCT	SNOT-20 and SNOT-22	Insufficient evidence to support long-term macrolide therapy
Varvyanskaya[1632]	2014	2	RCT	Clarithromycin postoperatively 250mg daily for 24weeks (n=22)	SNOT-20 VAS Olfaction Endoscopy	Significant improvement of all parameters except acoustic

				Clarithromycin postoperatively 250mg daily for 12 weeks (n=22) Control (n=22)	SCT Acoustic rhinometry CT score	rhinometry and VAS in both clarithromycin groups as compared with controls.
Peric[1631]	2014	2	RCT	Clarithromycin preoperatively 500 mg daily for 8 weeks, followed by ESS (n=40) ESS (n=40)	Nasal symptom score Endoscopic score	Preoperative clarithromycin administration postponed nasal polyp relapse after ESS.
Korkmaz[1633]	2014	2	RCT	Clarithromycin 1g daily for 2 weeks, followed by 250 mg daily for 6 weeks (n=15) Mometasone furoate nasal spray 200 µg once daily for 8 weeks (n=19)	CT scan score SNOT-20 SEM for biofilm presence	Adding long-term low-dose oral macrolides to nasal steroids was effective in the eradication of biofilm. There is no statistically difference in SNOT-20 scores between two groups.
Dabirmoghaddam[1637]	2013	3	Cohort study	Clarithromycin 500mg BID for 8 weeks (n=40)	VAS NP size CT score	Improvements found in nasal obstruction, hyposmia, rhinorrhea, NP size, and LM score.
Peric[1638]	2012	3	Cohort study	Clarithromycin 500mg daily (n=40)	NP score	Reduced polyp scores in both non-allergic and allergic patients.
Haruna[1639]	2009	3	Retrospective Cohort study	CRSsNP and CRSwNP: 1. Roxithromycin 150mg daily (n=45) 2. Clarithromycin 200mg daily (n=23)	CT score Symptom score	The efficacy of macrolides was lower in patients with polyposis. Polypectomy resulted in significant improvements in the efficacy of macrolides.
Katsuta[1640]	2002	3	Cohort study	Roxithromycin	Symptom score	Over half of

				500 mg BID	Endoscopy CT scores	patients showed clinical improvement.
Yamada[1641]	2000	3	Cohort study	Clarithromycin 400mg daily for 8 ~ 12 weeks (n=20)	NP size IL-8 level in nasal lavage IL-4, IL-6, IL-10, and MCP-1 levels in nasal lavage	40% of patients showed reduction in polyp size and IL-8 levels.

X.D.5.d. Antibiotics for CRSwNP: Intravenous Antibiotics

Because of limited data, CRSsNP and CRSwNP are combined in Section IX.D.4.d.

X.D.5.e. Antibiotics for CRSwNP: Topical Antibiotics

Because of limited data, CRSsNP and CRSwNP are combined in Section IX.D.4.e.

X.D.6. Management of CRSwNP: Antifungals

Because of limited data, CRSsNP and CRSwNP are combined in Section IX.D.5.

X.D.7. Management of CRSwNP: Biologic Therapy

Biologic therapy has been deployed with encouraging results for asthma and atopic dermatitis. Several monoclonal antibodies that were initially studied for these conditions have now been trialed for CRSwNP. These include dupilumab, omalizumab, mepolizumab, reslizumab and benralizumab. Each of these agents targets pathways in CRS pathogenesis (mechanisms summarized in Table X-23).

For this review, we identified 9 studies that met our criteria of having a biologic intervention with an active comparator group: omalizumab;[58,1174,1642,1643] dupilumab;[56,60] mepolizumab;[57,1644] and reslizumab.[59] No studies were identified for benralizumab. These are summarized in Table X-24.

Dupilumab:
This is the only biologic with US FDA approval for use in CRSwNP. We identified 3 trials with dupilumab as the intervention for CRSwNP. In 2016, an RCT found a reduction in nasal polyp score in participants receiving dupilumab compared to placebo.[56] In 2019, Bachert *et al.* published the phase 3 trial results of dupilumab; the report included results from 2 RCT arms (LIBERTY NP SINUS-24 and -52).[60] Nasal polyp score (NPS) was graded from 0-4 on each side, with eight being the maximum and worst score; a minimum score of 5 was necessary for enrolment into the study.

Subjects in both trials were given 100 mcg mometasone nasal sprays twice daily in addition to dupilumab or control. In the first trial, participants received dupilumab 300 mg subcutaneously every

two weeks (n=143) x 24 weeks or placebo (n=133). In the second trial, participants received dupilumab 300 mg every two weeks for the first 24 weeks (n=295) or placebo (n=153) and then subjects were either given dupilumab 300 mg Q 2 weeks (n=150) or dupilumab 300 mg Q 4 weeks (n=145) for 52 weeks.

In the larger 2019 study, the authors reported a least mean square difference of -2.06 and -1.8 at 24 and 52 weeks in NPS with use of dupilumab versus placebo. The difference in Lund-Mackay CT scores in study vs. placebo group was –7.44 and –5.13 at 24 and 52 weeks, respectively. The magnitude of improvements in patient subgroups with comorbid asthma, NSAID-exacerbated respiratory disease, or previous surgery was similar to that in the overall treatment population. Participants who continued to receive treatment every two weeks during weeks 24 to 52 had overall similar results compared to those who received treatment every 4 weeks during weeks 24 to 52. The most commonly reported adverse events in the study group were nasopharyngitis, injection-site reactions, and headache, all more common than in the placebo group. Conjunctivitis was reported in 7 patients receiving dupilumab and in 1 patient receiving placebo, none severe enough to discontinue therapy. Four patients had eosinophilia with clinical symptoms reported as treatment-emergent adverse events: 1 patient had eosinophilic granulomatosis with polyangiitis (EGPA) during treatment with dupilumab; 1 had eosinophilia associated with arthralgia, asthma exacerbation, and insomnia during dupilumab treatment; 1 had EGPA more than 300 days after a single dupilumab dose; and 1 had EGPA while receiving placebo.

The results from the study should be considered in the context of standard treatments for CRSwNP such as oral corticosteroids, office-based nasal polypectomy and formal revision surgery. Dupilumab had a modest effect on nasal polyp size (average reduction about 25% of total 8-point nasal polyp scale), nasal congestion and smell improvement when considering the overall study group. Dramatic effects in nasal polyp size and smell recovery was reported in some but not all patients, reinforcing the need to better identify factors that most likely predicate response to the therapy. This need to predict response is even more important in light of the high costs of this treatment. The effect of dupilumab on the need for surgery was modest. Based on the data[60] the absolute risk reduction for the study period was 10/143 (dupilumab) vs 25/133 (placebo), an absolute risk reduction estimated to be 10%. In summary, dupilumab is recommended for patients with CRSwNP, especially those who have failed more conventional treatment. Further studies are needed to help decide how to use dupilumab in the context of other medical and surgical treatment options, as well as optimal dose and duration of dupilumab treatment.

Dupilumab for CRSwNP

Aggregate Grade of Evidence: A (Level 2: 3 studies)
Benefit: Dupilumab decreased polyp size, improved nasal congestion, sinus imaging scores, sense of smell and asthma control
Harm: Conjunctivitis and hypereosinophilia are rare
Cost: High cost per injection; total duration of therapy not yet defined
Benefits-Harm Assessment: Likely benefit over harm in patients with CRSwNP not responsive to medical and surgical standard of care
Value Judgments: Cost-effectiveness, optimal dose and duration of therapy not yet clear
Policy Level: Recommendation for dupilumab in patients with severe CRSwNP
Intervention: Dupilumab may be considered for patients with severe CRSwNP who have not improved despite other medical and surgical treatment options

Mepolizumab

Two trials have been conducted for mepolizumab in patients with CRSwNP.[57,1644] The earlier study was performed by Gevaert in 2011, who reported efficacy in reducing polyp size in severe nasal polyposis.[1644] Bachert in 2017 conducted an RCT that showed reduced need for revision sinus surgery following treatment with mepolizumab. Both mepolizumab studies involved an intervention dose of 750mg IV, the formulation and strength available at the time of study, which is not currently available (100 mg for asthma and 300 mg, both subcutaneous, available for asthma and EGPA, respectively). In summary, mepolizumab is an option for patients with CRSwNP who have comorbid eosinophilic asthma.

Mepolizumab for CRSwNP

Aggregate Grade of Evidence: C (Level 3: 2 studies)
Benefit: Mepolizumab decreased polyp size and need for surgery.
Harm: Adverse medication side effects; most common being injection site reaction .
Cost: High cost per injection; total duration of therapy not yet defined.
Benefits-Harm Assessment: Benefit for CRSwNP not clear.
Value Judgments: Consider for CRSwNP in context of asthma or EGPA; dosage used for trial in CRSwNP is higher than available for standard therapy of asthma and EGPA.
Policy Level: Option for patients CRSwNP and asthma.
Intervention: Consider as option for severe CRSwNP with concomitant poorly controlled eosinophilic asthma.

Reslizumab

A single RCT was identified using reslizumab for CRSwNP. There was inconsistency between the outcomes for the 3 mg/kg and 1 mg/kg dosing, and the study included a small number of participants.[59]

Reslizumab for CRSwNP

Aggregate Grade of Evidence: C (Level 3: 1 study)
Benefit: Reslizumab decreased polyp size
Harm: Adverse medication side effects including anaphylaxis (rare)
Cost: High cost per injection; total duration of therapy not yet defined
Benefits-Harm Assessment: Benefit for CRSwNP not clear
Value Judgments: Consider in context of CRSwNP with uncontrolled asthma (indication for which reslizumab is US FDA approved)
Policy Level: Option for patients with CRSwNP and asthma
Intervention: Can be considered as option for severe CRSwNP with concomitant poorly controlled eosinophilic asthma

Omalizumab

We identified 6 studies for omalizumab and nasal polyposis. Gevaert, *et al.* reported results of two identical replicate (POLYP 1 and POLYP 2) DBRCTs studying omalizumab added to mometasone nasal spray versus placebo with mometasone nasal spray for 24 weeks. Inclusion criteria were patients aged 18-75 years with persistent bilateral nasal polyps, nasal congestion, impaired HRQoL, and weight and serum IgE level permitting omalizumab dosing per weight of 30-50 kg and serum IgE level of 30-1500 IU/mL). Co-primary end points included change from baseline to week 24 in Nasal Polyp Score (NPS) and Nasal Congestion Score. Secondary end points included change from baseline to week 24 in Sino-Nasal

Outcome Test-22 (SNOT-22) score, UPSIT, sense of smell, postnasal drip, runny nose, and adverse events. In POLYP 1 and POLYP 2, the mean changes from baseline at week 24 for omalizumab versus placebo were as follows: NPS, –1.08 versus 0.06 (P < .0001) and –0.90 versus –0.31 (P 5 .0140); Nasal Congestion Score, –0.89 versus –0.35 (P 5.0004) and –0.70 versus –0.20 (P 5.0017); and SNOT-22 score, –24.7 versus –8.6 (P < .0001) and –21.6 versus –6.6 (P < .0001). Adverse events were similar between groups.[1645] Pinto, et. al[1174] in 2010 studied CRS in 14 patients (12 CRSwNP) and found no difference on the primary endpoint of sinus CT. The study was limited by a small sample size. Gevaert *et al.*[58] studied 20 subjects with CRSwNP in an RCT and reported benefits in nasal polyp size and symptoms. Bidder *et al.* reported a small case-control study suggesting patients taking omalizumab have improved patient-reported outcome scores.[1642] Mostafa *et al.* performed a single-blinded and small study in patients with CRSwNP (AFRS subtype) and reported that patients taking omalizumab have improved patient-reported outcome scores.[1643] Hayashi, *et al.* used omalizumab in 21 patients with CRSwNP and AERD. They identified reduction in urinary LTE4 and the PGD2 metabolite, suggests a mechanism of action of omalizumab that may work irrespective of "allergy" status.[1646]

Omalizumab for CRSwNP

Aggregate Grade of Evidence: B (Level 2: 1 study; level 3: 2 studies; level 4: 2 studies)
Benefit: Omalizumab improved polyp size in 1 study and patient-reported outcomes in 3 studies
Harm: Risk for anaphylaxis (rare)
Cost: High cost per injection; total duration of therapy not yet defined
Benefits-Harm Assessment: Likely benefit over harm in patients with CRSwNP not responsive to medical and surgical standard therapy.
Value Judgments: Cost-effectiveness, optimal dose, and duration of therapy not yet clear
Consider for CRSwNP in context of allergic asthma uncontrolled with standard therapy
Policy Level: Option to weak recommendation for patients with severe CRSwNP who have not improved despite other medical and surgical treatments. Weaker recommendation is based on limited body of evidence and high costs.
Intervention: Consider for severe CRSwNP with concomitant poorly controlled allergic asthma

Table X-25: Biologic agents trialed for CRSwNP

Drug	Target	Effect on CRS pathogenesis
Dupilumab	Monoclonal antibody that inhibits IL-4Rα (required for IL-4 and IL-13 signaling)	IL-4 and IL-13 are integral to Th2 mediated inflammation.
Omalizumab	Anti IgE monoclonal antibody	Inhibits binding of IgE to IgE receptors on mast cells and basophils; this reduces release of mediators in allergic responses
Mepolizumab Reslizumab Benralizumab	Anti–IL-5 monoclonal antibodies (mepolizumab and reslizumab) or binds to IL-5Ra subunit on eosinophils (benralizumab)	IL-5 is a key mediator in chemotaxis, differentiation, activation and survival of eosinophils, and IL-5Rα is also present on mast cells and some B cells.

Table X-26. Evidence for CRSwNP management with biologic therapy

Study	Year	LOE (1-5)	Study Design	Study Groups	Clinical Endpoints	Conclusion
Gevaert[1645]	**2020**	2	Two replicate randomized, double blind, placebo controlled added to intranasal corticosteroids	Omalizumab or placebo and intranasal mometasone for 24 weeks	Change in nasal polyp score and nasal congestion score	Omalizumab groups with reduced nasal polyp score and reduced nasal congestion score compared to placebo.
Bachert [60a]	2019	2	Randomized, double blind, placebo controlled added to INCS	Dupilumab 300 mg Q 2 weeks x 52 weeks; Dupilumab 300 mg Q 2 weeks x 24 weeks then Q 4 weeks X 28 weeks; Placebo	Change in nasal polyp score; Change in nasal congestion symptom score	Dupilumab groups with reduced nasal polyp score and reduced nasal congestion score compared to placebo.
Bachert [60b]	2019	2	Randomized, double blind, placebo controlled added to INCS	Dupilumab 300 mg Q 2 weeks x 24weeks; Placebo	Change in nasal polyp score Change in nasal congestion symptom score	Dupilumab group with reduced nasal polyp score and reduced nasal congestion score compared to placebo.
Bachert [56]	2016	2	Randomized, double blind, placebo controlled added to INCS	Dupilumab 600 mg loading then 300 mg weekly for total of 16 weeks; Placebo	Change in nasal polyp score	Dupilumab group with reduced nasal polyp score.
Bachert [57]	2017	3	Randomized, double blind, placebo controlled added to INCS	Mepolizumab 750 IV every 4 weeks for 24 weeks; placebo	Number of patients requiring sinus surgery at 25 weeks	Mepolizumab group with higher percentage of people no longer requiring

						surgery.
Gevaert [1644c]	2011	3	Randomized, double blind, placebo controlled (intranasal steroids not allowed)	Mepolizumab 750 IV x 2 doses, 28 days apart; placebo	Change in nasal polyp score	Mepolizumab group with reduced nasal polyp score.
Gevaert [59d]	2006	3	Randomized, double blind, placebo controlled (intranasal steroids not allowed)	Reslizumab 3 mg/kg, 1 mg/kg, placebo single dose	Change in nasal polyp score	No clear differences between 3 mg/kg, 1 mg/kg, placebo.
Pinto [1174e,f]	2010	3	Randomized, double blind, placebo controlled (intranasal steroids unclear)	Omalizumab standard dosing x 6 months, placebo	Sinus imaging	No difference between groups.
Gevaert [58g]	2013	3	Randomized, double blind, placebo controlled (intranasal steroids unclear)	Omalizumab standard dosing x 16 weeks, placebo	Nasal polyp score	Omalizumab group with reduced nasal polyp score.
Bidder [1642]	2018	4	Case/control	Omalizumab for 16 weeks and no omalizumab	SNOT-22	SNOT-22 better in omalizumab compared to controls.
Mostafa [1643h,i]	2019	4	Randomized, single-blind	Omalizumab 150 once mg or no omalizumab	SNOT-20	SNOT-20 better in omalizumab compared to controls.

a. LIBERTY NP SINUS-52
b. LIBERTY NP SINUS-24
c. Rated down for indirectness given that dosing (750 mg IV) used in study is currently not available for use clinically
d. Rated down for imprecision (only 8 patients per group) and for inconsistency (3 mg/kg vs 1 mg/kg dosing)
e. 7/7 in omalizumab CRSwNP; 5/7 in placebo CRSwNP?
f. Rated down for imprecision
g. NP and asthma required to enroll
h. CRSwNP and AFRS diagnosis

i. Rated down for lack of blinding, imprecision, and outcome selection

X.D.8. Management of CRSwNP: Anti-Leukotriene Therapy

Upregulation of the cysLT pathway has been demonstrated in asthma, AR, and CRSwNP. CysLTs are inflammatory mediators synthesized by effector cells, including eosinophils, mast cells, tissue macrophages, and basophils, through the metabolism of arachidonic acid. Both increased cysLT production and upregulation of cysLT receptors have been seen in these conditions, particularly in AERD.[1518] Several studies have examined the effectiveness of anti-LT therapy in CRSwNP and these were recently summarized by Wentzel[1647] and Smith and Sautter.[1648]

Wentzel[1647] performed a systematic review and meta-analysis and found 12 studies that examined the effectiveness of anti-LT therapy in CRSwNP: 5 RCTs and 7 case series. Of the 5 RCTs, which included a total of 179 patients, 2 RCTs compared montelukast, a cysLT receptor 1 (CYSLTR1) antagonist, to placebo;[1649 1650] 2 compared montelukast to INCS;[1651 1652] and 1 compared montelukast and INCS to INCS alone following a course of oral corticosteroids.[1653] Wentzel *et al.*[1647] were able to combine 2 of the RCTs into a meta-analysis. This study found that anti-LT therapy showed improvement in symptoms over placebo, but no difference compared to INCS. They concluded that, although anti-LT therapy showed limited benefit as an adjunctive therapy to INCS, additional study was needed to determine the most beneficial strategy for their use.

The Smith and Sautter review[1648] confined itself to English-language studies that addressed the efficacy of montelukast in CRSwNP. They identified 5 such studies. Three were RCTs,[1649 1652 1653] one nonrandomized, noncontrolled study[1654] and a basic science study.[1655] Overall, they found moderate evidence of efficacy as an adjunctive treatment, used in conjunction with corticosteroids. Interestingly, they noted that the *ex vivo* basic science study showed montelukast combined with zileuton, a selective 5-lipoxygenase enzyme inhibitor, better prevented mast cell activation in CRSwNP tissue than did montelukast alone,[1655] suggesting that blocking the production of cysLTs may be more powerful than blocking a single cysLT receptor.

One double-blinded placebo-controlled study has examined zileuton as an add-on therapy to inhaled and/or oral corticosteroids in patients with AERD[1656] and demonstrated that 6 weeks of zileuton (600 mg QID) not only improved pulmonary function but also resulted in improvement in olfaction, rhinorrhea, and nasal obstruction. The authors reported no adverse drug-related events in the 40 patients studied. Two more recent randomized, postoperative open-label studies (level 1b/2) of patients with CRSwNP[1657] or AERD[1658] showed that the addition of montelukast to INCS did not significantly improve any outcomes post-operatively, when compared to INCS alone, as did a retrospective review of postoperative CRSwNP patients.[1659]

In summary, two reviews and several open-label studies have demonstrated the limited benefit of anti-LT therapy for the treatment of CRSwNP. The risks of LT modifying therapy vary with the specific drug chosen. Montelukast has a relatively limited adverse reaction profile, but zileuton has been associated with reversible hepatic injury.[1660]

Anti-Leukotriene Therapy for CRSwNP

Aggregate Grade of Evidence: A (Level 1: 2 studies; level 2: 3 studies; level 4: 1 study).
Benefit: Improvement in symptoms, comparable to INCS alone. May have limited benefit as an adjunct

to INCS.
Harm: Limited risks. Montelukast has been associated with rare neuropsychiatric events in post-marketing reports. Zileuton is occasionally associated with elevated liver enzymes, requiring monitoring during therapy. See Table II-2.
Cost: Moderate.
Benefits-Harm Assessment: Balance of benefit and harm.
Value Judgments: Montelukast may be beneficial in patients who are intolerant or unresponsive to INCS.
Policy Level: Option.
Intervention: Montelukast is an option for CRSwNP patients either instead of or in addition to INCS.

Table X-27. Evidence for CRSwNP management with anti-leukotriene therapy

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Smith [1648]	2014	1	Systematic review of English-language RCTs	CRSwNP	Symptom improvement; Other clinical parameters	Moderate evidence for montelukast improving symptoms as an adjunct to INCS
Wentzel [1647]	2013	1	Systematic review and meta-analysis of RCTs	CRSwNP	Symptom improvement; Other clinical parameters	Montelukast shows improvement in symptoms over placebo, similar to that seen with INCS
Stryjewska-Makuch [1658]	2019	2	Randomized, postoperative open-label trial of INCS or montelukast or INCS + montelukast	AERD	Postoperative changes in symptom scores Smell tests LK score	All 3 arms showed comparable efficacy, with efficacy of montelukast similar to that seen with INCS.
Van Gerven [1657]	2018	2	Randomized, postoperative open-label trial of INCS or INCS + montelukast	CRSwNP	Postoperative changes in symptoms TPS LMK score	The addition of montelukast to INCS did not significantly improve any outcomes at 3, 6, and 12 months post-operatively.
Dahlen [1656]	1998	2	DBRCT using zileuton 600 mg QID	AERD	PFTs; Symptom scores PNIF	Zileuton resulted in improved PFTs as well as nasal symptoms and PNIF

Yelverton [1659]	2016	4	Retrospective review of all CRS patients who were prescribed montelukast postoperatively and then had a lapse in therapy.	27 eosinopphilic CRSwNP patients, 8 AERD, and 15 AFS	SNOT-20 LK endoscopy scores	Montelukast improved SNOT-20 and endoscopy scores postoperatively in eCRSwNP patients, and endoscopy scores for AFS patients. No significant improvement for AERD patients.

X.D.9. Management of CRSwNP: Probiotics

Because of limited data, CRSsNP and CRSwNP are combined in Section IX.D.8.

X.D.10. Management of CRSwNP: Decongestants

Because of limited data, CRSsNP and CRSwNP are combined in Section IX.D.9.

X.D.11. Management of CRSwNP: Mucolytics

Because of limited data, CRSsNP and CRSwNP are combined in Section IX.D.10.

X.D.12. Management of CRwNPS: Herbal Medication

Because of limited data, CRSsNP and CRSwNP are combined in Section IX.D.11.

X.D.13. Management of CRSwNP: Topical Alternative Therapies

X.D.13.a. Topical Alternative Therapies for CRSwNP: Surfactants

Because of limited data, CRSsNP and CRSwNP are combined in Section IX.D.12.a.

X.D.13.b. Topical Alternative Therapies for CRSwNP: Manuka Honey

Because of limited data, CRSsNP and CRSwNP are combined in Section IX.D.12.b.

X.D.13.c. Topical Alternative Therapies for CRSwNP: Xylitol

Because of limited data, CRSsNP and CRSwNP are combined in Section IX.D.12.c.

X.D.13.d. Topical Alternative Therapies for CRSwNP: Colloidal Silver:

Because of limited data, CRSsNP and CRSwNP are combined in Section IX.D.12.d.

X.D.13.e. Topical Alternative Therapies for CRSwNP Furosemide

The recurrence of edematous nasal polyps after ESS is difficult to control. Investigators have hypothesized that using a topical diuretic, such as furosemide, could reduce recrudescence of this disease by improving edematous infiltrate. To this end, topical furosemide delivered nasally was able to prevent experimentally induced rhinitis within a patient cohort in Italy compared to controls.[1661]

Passali *et al.,* supplemented these findings in two subsequent randomized, non-placebo controlled trials. The authors explored the efficacy of intranasal furosemide in preventing relapse of nasal polyposis for up to 6 years.[1566,1662-1664] In these studies, the experimental group was comprised of patents having undergone recent ESS that were provided furosemide post-operatively for one month. Each patient received 2 sprays in each nostril every day for 30 days; the dose consisted of 50 ug per puff of furosemide diluted in physiological solution. The control group consisted of no treatment while a third group was treated with the intranasal corticosteroid, mometasone. Only 17.5% of patients treated with furosemide had relapses, compared with 24.2% in the mometasone group and 30.0% in the untreated group.[1566,1663] Thus, Passali *et al.* demonstrated that topical nasal furosemide started post-ESS significantly reduced the recurrence of nasal polyps over INCS (mometasone) or no treatment.

Over 13 years later a placebo-controlled clinical trial was carried out in Iran by Hashemian *et al.* The investigators performed a triple blind, randomized-controlled study comparing topical furosemide to a placebo nasal spray in the setting of INCS (fluticasone) use.[1664] Prior to surgery, all patients were treated with 30 mg of prednisolone, 400 mg cefixime, and flucticasone 2 puffs twice a day for 10 days. After surgery, both groups received 400 mg of oral cefixime for 10 days and resumed their INCS. Additionally, the intervention group received 2 puffs twice daily (*i.e.,* 300 µg per day) of topical furosemide for 2 months, while the control group received a placebo spray. The primary endpoint was nasal polyposis as measured by the Meltzer endoscopic grading scale,[1665] CT, SNOT-22 and VAS pain scale. These outcomes were measured six months after the intervention, demonstrating a reduction in polyposis across both groups. This reduction, however, was substantially greater in the furosemide group compared to the placebo group. The grade of polyps was 0 in 79% of the patients in the furosemide group (n = 33) compared with 38% in the placebo group (n = 16). Furthermore, the effects of topical furosemide vs placebo on the severity of polyposis were significantly lower in the furosemide group based on SNOT-22 scoring (difference, 8.05; 95% CI, 3.24-12.85) and VAS (difference, 0.81; 95% CI, 0.22-1.39), but not significantly different based on CT scan scoring (difference, 2.52; 95% CI, −0.35 to 5.39). Finally, adverse events were nearly non-existent in both groups. There was 1 minor complaint of nasal irritation, 2 reports of constipation, and 1 reported headache in the furosemide group, while the placebo group similarly demonstrated 1 complaint of nasal irritation and 2 reported headaches. The

authors suggested that furosemide is a safe and effective topical therapeutic agent in reducing severity of nasal polyposis following ESS.[1666]

There are several important limitations to these studies. Neither Hashemian *et al.* nor Passali *et al.*[1566] reported on the prevalence of asthma or aspirin intolerance in their cohort of patients with CRSwNP. Hashemian *et al.* did not document the type or extent of "sinus surgery,"[1664] whereas Passali *et al.* divided procedure type into endoscopic polypectomy plus anterior ethmoidectomy (n=95), endoscopic polypectomy plus anteroposterior ethmoidectomy (49)[1566,1663] and endoscopic polypectomy (n=26).[1566] Hashemian *et al.* demonstrated no significant difference in the grade of polyposis prior to intervention, whereas Passali *et al.*[1566] stated that "the severity of disease before surgery was similar" in the control and intervention groups.[1566,1663] Nevertheless, post surgical severity of recurrence of polyposis by Passali *et al.* was divided by staging constructed by the authors and compared across groups; interestingly the placebo group, which had the greatest recurrence, had significantly greater amount of stage 3 polyposis.[1566] Hashemian *et al.* reported that after intervention, 79% of the patients in the furosemide group had a polyposis score of 0 compared with 38% in the control group.

Finally, Kroflic *et al.* examined the use of topical furosemide treatment preoperatively to determine surgical outcomes in patients with CRSwNP.[1666] Topical furosemide was given by inhalation (6.6 mmol/l solution) 7 days prior to surgery to 20 patients; this was compared to a separate cohort of 20 patients who received 7 days of oral steroids. Although polyposis grade was not reported, both groups demonstrated significant improvement in nasal symptoms and polyposis on endoscopy. Furosemide did not significantly decrease edema across the entire group. However, on subgroup analysis of previously un-operated patients, the authors found a significant reduction in mucosal edema, which was measured on histopathology as distance from the surface submucous gland.[1666] There was no difference in estimated intraoperative bleeding between the two groups.[1666]

Furosemide for CRSwNP

Aggregate Grade of Evidence: B (Level 2: 3 studies, Level 3: 1 study)
Benefit: Reduced recurrence of nasal polyps following ESS over placebo nasal spray.
Harm: Topical furosemide appears safe. However, no pharmokinetic or pharmodynamic studies have been performed to assess systemic safety with nasal delivery. Systemic absorption is unknown and limited clinical experience and long-term use limits applicability.
Cost: Low.
Benefits-Harm Assessment: Benefits likely balances with harm when used on a rotating basis as studied.
Value Judgments: After ESS in the presence of ineffective polyp control with INCS spray, the addition of topical furosemide to reduce polyp recurrence appears to outweigh the potential risks.
Policy Level: Option.
Intervention: Topical furosemide started after ESS and in combination with an INCS may reduce the recurrence of nasal polyps in patients with CRSwNP.

Table X-28. Evidence for CRSwNP management with furosemide

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Hashemian [1664]	2016	2	Triple Blinded, Placebo Controlled Trial (n=110)	CRSwNP postoperatively treated with INCS + 300ug furosemide vs placebo spray	6 months post ESS Meltzer endoscopic grading scale, CT, SNOT-22, VAS	Furosemide significantly reduces severity of nasal polyps, SNOT-22, & VAS. Furosemide does not reduce CT scores.
Passali [1566]	2003	2	Randomized, non-placebo controlled trial (n=170)	CRSwsNP; furosemide 200 ug (n=97), no treatment (n=40), mometasone INCS (n=33), treatment started 1 month postopertively with 200 ug furosemide for 1 month, off for 2 months for years 1 & 2 years, then on for one month off 4 months for years 3, 4, & 5. Year 6 on for 1 month off for 6 months.	Nasal endoscopy, AcRh	Furosemide reduces recurrence of nasal polyps after ESS.
Passali [1663]	2000	2	Non-blinded, randomized, non-placebo controlled trial (n=104)	CRSwNP underwent ESS started 1 month postopertively with 200 ug furosemide for 1 month, off for 2 months for years 1 & 2 years, then on for one month off 4 months for years 3, 4, & 5. Year 6 on for 1 month off for 6 months.	6 years nasal endoscopy, active AcRh, AcRh to evaluate nasal functionality.	Furosemide reduces recurrence of nasal polyps after ESS.

Kroflic [1666]	2006	3	Prospective cohort (n=40)	CRSwNP treated 7 days prior to ESS with furosemide vs oral steroids	Bleeding, SNOT-22, histology	Furosemide does not reduce inflammatory cell count but does reduce edema in un-operated patients.

X.D.13.f. Topical Alternative Therapies for CRSwNP: Capsaicin

Because of limited data, CRSsNP and CRSwNP are combined in Section IX.D.12.f.

X.D.14. Management of CRSwNP: Influence of Head Position, Device, Surgery, and Nasal Anatomy on Distribution of Topical Medications

Much of the evidence on this topic is evaluated in Section IX.D.13. Topical medication distribution in CRSwNP shares many of the same goals as it does in CRSsNP. Treatment of CRS is primarily focused on reducing mucosal inflammation, removing bacterial infection or pathologic biofilm, and improving sinonasal function.[490] As such, topical therapies play a large role in both CRSwNP and CRSsNP. However, it is in CRSwNP that the advantages of topical drug delivery, with the potential for higher local drug concentration and reduced exposure to systemic medications, has the potential to modify the disease condition. ESS is an important component in managing CRSwNP as it provides anatomical modifications to facilitate topical access, both initially and long term.[1141] Corticosteroids, either topical or oral, are a proven intervention for the primary management of CRSwNP, which is characterized by continual production of inflammatory mediators and polyp formation. Ensuring effective topical delivery within the paranasal sinus cavity is fundamental to the long-term management of CRSwNP.[1077,1667]

Endoscopic sinus surgery plays a significant role in CRSwNP both through direct effects on the mucosa and by facilitating delivery of topical steroids. Indeed, perhaps the greatest benefit of ESS in CRSwNP is improved penetration of topical therapy in post-ESS patients.

Penetration is best accomplished with large volume devices. First generation low-volume devices such as drops, sprays, and nebulizers are an acceptable alternative if nasal cavity or limited sinus delivery is needed, but should not play a significant role in the management of CRSwNP as they do not reliably reach within the sinuses and provide no mechanism for lavage. However, second generation systems using pulsating aerosols or exhalation delivery systems to appear to provide significant deposition of drug to operated sinuses, but do not provide the additional benefit of lavage.[1085,1267-1269,1272-1279,1667]

Enabling effective local pharmacologic management in CRSwNP relies on true sinus distribution of topical therapies. Shifting patients away from reliance on systemic medications and toward consistent local treatment underlies the success of contemporary CRSwNP therapy. Advantages of topical medical therapy include direct drug delivery to diseased tissue, potential for delivery of higher local drug concentrations, and reduced systemic effects. Current evidence suggests that optimal topical sinus delivery occurs after surgery and with high volume irrigation and second generation spray devices.

X.D.15. Management of CRSwNP: Aspirin Desensitization for AERD

ESS today still is the mainstay treatment for NP removal in individuals suffering from AERD. However, in this particular subset of patients, recurrence of inflammatory mucosal changes and ultimately NPs can be seen early on, often within months of surgery, and a high percentage of patients undergo revision surgeries.[1530,1531] Consequently, there is a need for additional treatment options to optimize postoperative results and to minimize the recurrence rate of NPs after sinus surgery. Several researchers have described aspirin desensitization protocols, the respective impact on LT and PG release, and their clinical results.[1668,1669] There is variation in the route of aspirin administration, especially with regard to oral versus intranasal application during the initial desensitization phase.[1670-1672] Where controversy between authors is most prominent is with regard to the best possible maintenance dose, one that is both effective and yet well tolerated. There is agreement between researchers that the best timing to start aspirin desensitization is a few weeks after surgical removal of polyps in an effort to reduce inflammation, mitigate the possibility of polyp relapse, and improve QoL. It is important to perform thorough evaluation of pulmonary function, which should not be worse than 75% of the expected FEV1 for the individual.

In several publications, including a DBRCT in the early 1980s, Stevenson *et al.*[1670,1673] were able to demonstrate the efficacy of aspirin desensitization using a daily aspirin maintenance dose of up to 1300 mg. The authors observed a significant reduction in sinus infections, revision surgeries, and INCS use during this high-dose aspirin desensitization regimen. However, severe aspirin-related side effects including gastric bleeding and gastric pain were observed as well as impaired renal function, nausea and blood-clotting disorders.[1520,1673] These adverse effects led to high dropout rates around 50% after just several months. Unfortunately, aspirin desensitization only offers therapeutic benefit for as long as the daily aspirin is continued. Interruption of the maintenance dose for longer than 48 hours might end the refractory state of tolerance and jeopardize the beneficial effect. Therefore, successful long-term maintenance therapy with aspirin should be continued over years, potentially decades, if benefits are to remain.

Data in the literature with regard to long-term aspirin dosage following desensitization have been as variable as the respective LOE. Rozsasi *et al.*[1674] recommended a maintenance dose of 300 mg daily to reduce NP recurrence and improve sense of smell, whereas several earlier single armed investigations could demonstrate an obvious reduction of NP recurrence, an improvement of the sense of smell, and a reduction of asthma-related complaints with a maintenance aspirin dose of 100 mg daily.[1517,1669] Several cohort studies have been performed with variable maintenance doses ranging from 300mg daily to 650mg BID. These studies assess a wide variety of outcomes including nasal symptom scores, smell scores, revision surgery rates, and polyp scores, and all studies note significant improvement in these outcomes regardless of the maintenance dose utilized.[1675-1680] The optimal protocol to establish efficacious and well tolerable desensitization with the lowest possible maintenance dose of oral aspirin is yet to be determined. Lee *et al.*[1681] recommend an aspirin intake dose of at least 325 mg twice daily for optimal symptom control, but studies have shown that even aspirin doses of 650 mg/day are associated with a considerable risk of gastrointestinal bleeding.[1682,1683]

In 2013, the first DBRCT was published, investigating aspirin desensitization with an initial challenge dose reaching 800 mg aspirin over one day followed by a maintenance dose of just 100 mg daily. This low-dose protocol was noted to be safe, with less than 3% of patients in the treatment group experiencing gastric irritation, all of whom could continue the treatment after adding a PPI.[1684] This study showed that 100 mg as a maintenance dose could significantly reduce the clinical key symptoms

of nasal obstruction, discharge and headache (p=0.001). QoL was also significantly improved over a three-year follow up period in the treatment group (p=0.03), along with a lower polyp score after 36 months. Conclusions drawn from this first study providing high level evidence for a 100mg protocol are that low-dose daily aspirin therapy leads to a significant decrease in respiratory inflammation and helps reduce the need for systemic corticosteroids and surgical revisions in this group of patients.

More recently, additional small randomized, DBRCTs have been performed investigating the efficacy of daily aspirin therapy. In a study of 12 patients who underwent desensitization with oral aspirin (ASA) followed by a maintenance dose of 624mg daily for 6 months compared to 8 patients treated with placebo, patients in the experimental group showed improved nasal symptoms and QoL.[1367] Two additional trials of patients randomized to an aspirin maintenance dose of 650mg BID for 1 month followed by 325mg BID for 5 months versus placebo also showed improved symptoms and QoL.[1685,1686] Two of these studies showed increased rates of adverse events in the ASA-desensitized group compared to placebo.[1367,1685]

In a systematic review, Klimek and coauthors concluded that based on the currently available clinical and pathophysiological data, aspirin desensitization followed by daily aspirin therapy has been proven to be efficacious, safe and suitable to reduce the need for other medications in AERD patients.[1687] Parikh *et al.* have reported on the use of daily topical nasal lysine-aspirin in aspirin-sensitive patients. Interestingly, with only 75 mg applied intranasally, this study provided high level evidence for alterations of cysLT receptors and weaker evidence levels for improved clinical outcomes using this regimen.[1671,1688]

Additional systematic reviews have been performed with aggregate evidence to assess the safety and efficacy of desensitization. A systematic review and meta-analysis by Chu, *et al.* in 2019 included evidence from 5 randomized controlled trials and 233 patients showed moderate certainty evidence that desensitization and daily aspirin therapy improves symptom scores and QoL. However, the evidence from this study also suggested with high certainty that adverse event rates including gastritis were increased with desensitization.[1689] Another very large systematic review of 24 studies reported that 23/24 of these studies recommended desensitization based on improvements in multiple parameters including nasal symptoms, corticosteroid use, revision surgery rate, and polyp scores, although no assessment of adverse events was performed.[1690]

In future trials, potential differences in the clinical benefits of low-dose versus high-dose daily aspirin should be evaluated by randomized double-blind prospective dose-finding trials as the interpretation of the previously reported data in the literature are limited by their open study design. Such trials are needed in an effort to find agreement on the lowest effective and safe dosing.

Aspirin Desensitization for AERD

Aggregate Grade of Evidence: A (Level 1: 2 studies; level 2: 10 studies; level 3: 3 studies; level 4: 12 studies).
Benefit: Reduced polyp re-formation after surgery, increased QoL and reduced CRS-symptoms in AERD. Reduced need for systemic corticosteroids. Reduced number of surgical revisions.
Harm: Gastrointestinal bleeding, increased morbidity in renal disease and blood clotting issues at high maintenance doses. Less than 3% gastrointestinal side effects with low-dose protocols.

Cost: 1) Initial cost of desensitization. 2) Minimal direct costs for daily aspirin doses. 3) Costs potentially reduced if future surgical interventions reduced, less medication use, fewer physician visits for asthma.
Benefits-Harm Assessment: Clear benefit over harm.
Value Judgments: Aspirin desensitization followed by daily aspirin therapy is one of the very few disease-modifying medical treatment options available for patients with AERD.
Policy Level: Recommendation.
Intervention: Aspirin desensitization should be considered in AERD patients after surgical removal of NPs to prevent recurrence.

Table X-29. Evidence for CRSwNP with AERD management with aspirin desensitization.

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Larivee [1690]	2020	1	SR	24 studies (RCTs, case-control, cohort) and 1272 patients undergoing desensitization	SNOT-20/SNOT-22, symptom scores, oral corticosteroid use, revision surgery rates, polyp scores	23/24 studies recommended desensitization based on improved symptoms, decreased steroid use, improved revision surgery rate, improved polyp size and recurrence
Chu [1689]	2019	1	SR with meta-analysis	5 RCTs including 233 patients	Symptom scores, QoL, adverse events	Moderate and high certainty evidence supports improved symptoms and QoL, but increased rates of adverse events
Mortazavi [1686]	2017	2	RCT, placebo controlled	22 patients undergoing desensitization versus 19 in placebo group	SNOT-22, Lund-Mackay score, medication scores, FEV1, IL-4, IL-5	Significant improvement in SNOT-22, medication scores, FEV1 and IL-5 at 6 months. No improvement in Lund-Mackay scores.
Esmaeilzadeh [1685]	2015	2	RCT, placebo controlled	18 patients undergoing desensitization versus 16 in placebo group	Symptom scores (SNOT-22), medication scores, Lund-Mackay scores, FEV1, adverse	Improved symptom scores, medication scores, Lund-Mackay scores, FEV1 at 6 months in

					events	treatment group. 1 patient discontinued therapy due to severe GI bleed, 1 due to skin rash.
Swierczynska-Krepa [1367]	2014	2	RCT, placebo controlled	12 patients undergoing desensitization versus 8 in placebo group	Symptom scores (including ACQ, SNOT-22), inhaled corticosteroid use, adverse events	Significant improvement in symptom scores and inhaled corticosteroid use compared to placebo. 5 patients discontinued therapy due to adverse gastrointestinal events (dyspepsia).
Fruth[1684]	2013	2	RCT, placebo controlled	Patients with AERD after ESS undergoing low dose desensitization with 100 mg ASA over 3 years	Symptom score, medication score, recurrence of polyps over 3 years	Significant improvement in symptoms and medication scores after 3 year long term low dose desensitization
Baker[1520]	2011	2	SR	Patients with AERD undergoing high dose desensitization	GI side effects	GI symptoms are the primary risk in high dose desensitization
Lanas[1682]	2011	2	SR	Patients with AERD and low dose desensitization	GI symptoms and bleeding	Increased risk for GI bleeding in low dose desensitization – decreased by PPI
Lee[1681]	2007	2	RCT	137 AERD patients randomized to different high maintenance doses for desensitization	Symptom and medication scores after one year	Recommendation to start at 650mg twice daily and subsequently decrease to 325 mg twice daily
Pfaar[1672]	2006	2	SR	Patients with AERD undergoing desensitization	Improvement for upper and lower airway and *in vitro*	Desensitization proven effective as the only specific treatment of

						choice
Parikh[1671]	2005	2	Randomized placebo controlled crossover trial	22 Patients with AERD undergoing desensitization with intranasal lysine aspirin	Clinical improvement Improvement of *in vitro* parameters	Improvement only in tissue studies, no clinical benefit after 6 months
Stevenson[1670]	1984	2	DBRCT	Patients with AERD undergoing oral desensitization	Nasal and pulmonary symptom- and medication scores during desensitization	CRS symptoms significantly reduced, asthma symptoms in half of patients
Klimek[1687]	2014	3	Outcome research for aspirin desensitization	Patients with AERD undergoing different regimes of desensitization	Oral, nasal, bronchial and IV application of aspirin for desensitization. Medication score	Aspirin desensitization has been proven efficacious and safe in AERD
Parikh[1688]	2014	3	Outcome research for intranasal lysine aspirin desensitization	Patients with AERD undergoing topical nasal lysine aspirin desensitization	Evidence for the use of intranasal desensitization	Though desensitization has been proven successful, the topical nasal application is still under debate
Gosepath[1669]	2001	3	Prospective cohort study	Patients with AERD undergoing low dose desensitization after surgery	Effectiveness of low-dose desensitization and *in vitro* monitoring after one year	Clinical success after one year with 100mg; correlation between clinical symptoms and *in vitro* monitoring
Adappa [1675]	2018	4	Retrospective cohort study	Patients undergoing desensitization with maintenance dose 650mg BID after ESS (n=34)	SNOT-22, need for revision ESS	Desensitization improved SNOT-22 and revision surgery rates
Cho [1676]	2014	4	Retrospective cohort study	Patients undergoing desensitization with maintenance dose of 650/325mg or	SNOT-22, smell score, endoscopic polyp grade	Desensitization improved all outcomes

				325mg BID after ESS for NP (n=30)		
Ibrahim [1677]	2014	4	Cohort study	Patients undergoing desensitization with maintenance dose of 325mg or 650mg BID (n=111)	Sense of smell or taste, upper respiratory symptoms, lower respiratory symptoms, adverse events	Desensitization improved symptoms in 73%, adverse events in 26% (no severe adverse events)
Havel [1678]	2013	4	Retrospective cohort study	Patients undergoing desensitization with maintenance dose of 500mg daily after ESS for NP (n=146)	Smell score, nasal symptom score, endoscopic polyp grade	Desensitization improved smell score, nasal symptom score, polyp grade
Comert [1679]	2013	4	Cohort study	Patients undergoing desensitization with maintenance dose of 300mg daily (n=40)	Smell score, nasal symptom score, oral corticosteroid use	Desensitization improved smell score, nasal symptom score, and oral corticosteroid use
Mendelsohn[1530]	2011	4	Large retrospective cohort study	Patients undergoing ESS for NP (n=549)	Recurrence (measured by Kaplan Meier curves)	Revision rates significantly higher in AERD
Rozsasi[1674]	2008	4	Comparative cohort study	Patients with AERD undergoing low dose desensitization with 100 vs. 300 mg maintenance dose	Polyp recurrence, symptom and medication scores, asthma control	Low dose is effective in reducing polyp recurrence, less effective for asthma control
Berges-Gimeno [1680]	2003	4	Large, long-term cohort study	172 patients with AERD undergoing desensitization with maintenance dose 650mg BID	Smell score, nasal symptom score, oral corticosteroid use	Improved smell score, nasal symptom score, reduction in oral corticosteroid use
Gosepath[1517]	2002	4	Long term	Patients with	Recurrence of	Long term low

			cohort study	AERD undergoing long term low dose desensitization	NPs and need for surgical revisions	dose desensitization is clinically effective and can be monitored *in vitro*
Amar[1531]	2000	4	Case control study	AERD CRS w/wo asthma	Clinical effect of ESS Recurrent CRS Number of surgical interventions	Surgery is less effective long term in patients with AERD
Stevenson[1673]	1996	4	Large cohort study	65 AERD patients undergoing desensitization up to 3 years	Long term effectiveness	Significant improvement for, CRS symptoms, asthma, olfaction, number of surgical revisions, and corticosteroid use
Lumry[1668]	1983	4	Cohort study	Patients with incomplete AERD	Improvement after aspirin desensitization	77% of patients without asthma showed clinical improvement after desensitization
Moberg[1683]	2011	5	Online questionnaire	Primary cardiovascular (CV) prevention Secondary CV prevention	Adherence to low dose ASA in Patients with GI problems	Poor adherence in patients with GI problems

X.E. Allergic Fungal Rhinosinusitis

X.E.1. AFRS Pathophysiology

AFRS is a noninvasive, eosinophilic subtype of CRSwNP defined by specific characteristics.[1691-1693] The most widely accepted diagnostic criteria for AFRS was proposed by Bent and Kuhn and includes: (1) type I hypersensitivity, (2) nasal polyposis, (3) characteristic CT findings, (4) eosinophilic mucus without fungal invasion, and (5) positive fungal stain.[1694] These criteria help to differentiate AFRS from other subtypes of CRSwNP.

The differences in the clinical presentation of AFRS from other CRSwNP subtypes support likely unique molecular pathways contributing to its pathophysiology. AFRS patients are younger, atopic, and can present with unilateral disease.[1692,1693,1695,1696] Associations with lower socioeconomic status and African American ethnicity have been identified with a male predominance of 1.5 – 2.6:1.[1697-1700] In addition, AFRS almost exclusively presents in geographic regions characterized by warm temperatures and high humidity conducive to fungal growth.[1701] Clinically, AFRS tends to present with severe CT findings and significant polyp burden, yet patients can report minimal sinus symptoms.[1693,1702] Characteristic CT scan findings include expanded paranasal sinus filled with high-density material and often bony erosion of

sinus walls.[1703] Although uncommon in other CRSwNP subtypes, greater than 30% of AFRS patients have skull base or orbital expansion/erosion,[1703-1707] potentially causing visual disturbance or facial deformity.[1691,1693] Vitamin D3 levels are also decreased in CRSwNP and AFRS, with levels inversely correlating with bone erosion. [18] Finally, the prevalence of asthma in AFRS patients has been reported by many groups to be lower than other CRSwNP subtypes (23% vs. 48%-80%).[166,167,1697,1708]

Within the expanded sinuses in AFRS is eosinophilic mucin characterized as thick and tenacious, and consists of necrotic and degranulating eosinophils in a background of mucin, Charcot-Leyden crystals, and fungal hyphae.[1693,1709] Eosinophilic mucin is not present in all forms of CRSwNP.[1709] Dematiaceous fungi and *Aspergillus* are commonly identified in mucin from AFRS, but fungi are diverse and vary based on geographical region.[622,1692,1696,1709,1710] In one Australian study, correlation between fungal species in mucin and systemic fungal allergy was weak.[633] However, mucin collected specifically from the sinuses found a strong correlation between the fungal species and Type 2 T cell memory to the specific fungi in AFRS patients.[622]

Certain biomarkers can distinguish AFRS from other CRSwNP patients. AFRS patients often have extremely elevated serum total and fungal-specific IgE and relatively normal serum eosinophil levels compared to CRSwNP patients.[1692,1693,1695] Serum specific IgE levels (to both fungal and non-fungal allergens) have been shown to correlate with clinical severity and recurrence.[1443,1692,1696,1705] However, controversy exists over the importance of type I hypersensitivity in AFRS pathophysiology, driving additional investigation. Humoral immunity and Ig-independent pathways may contribute. Fungal-specific IgG is typically elevated in AFRS. [1692,1696,1711] Elevated IgG3 levels specific to *Alternaria alternata* and *Aspergillus fumigatus* distinguished eosinophilic RS, including AFRS, from control groups.[633] *S. aureus* is a common organism in CRSwNP and may modify these disease processes as a direct pathogen or via superantigen production.[1697,1712-1714] *S. aureus* colonization is more prevalent in AFRS versus other CRSwNP subtypes.[1697]

Recent microarray data analysis comparing AFRS and CRSwNP highlighted unique activated genes and molecular pathways.[625] AFRS is characterized by upregulated pathways critical in T cell activation and the adaptive immune response, correlating with the elevated serum IgE levels commonly found in AFRS.[625,1715] In terms of specific genes, the most significantly downregulated gene in AFRS as compared to CRSwNP was histatin 1 (HTN1), an antifungal peptide. HTN1 is produced by respiratory epithelial cells, and its limited expression in AFRS may contribute to the accumulation of fungal hyphae within inflamed sinus cavities.[625]

AFRS is a distinct, often more severe, subclass of CRSwNP. Although the precise AFRS pathophysiology remains unclear, limited antifungal activity may allow germination of inhaled fungal spores. In the presence of a breakdown in the epithelial cell barrier, fungal hyphae either alone or synergistically with *S. aureus* upregulate Type 2 immune responses leading to the characteristic type I hypersensitivity, eosinophilic inflammation, and Type 2 cytokine profiles associated with AFRS. Environment, socioeconomic factors, and genetic predisposition also likely contribute.

AFRS Pathophysiology

Aggregate Grade of Evidence: B (Level 2: 7 studies; level 4: 30 studies)

Table X-30. Evidence for pathophysiology differences between CRSwNP and AFRS

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Clinical Description						
Promsopa [1708]	2016	2	Cross-sectional prevalence study	CRSwNP CRSsNP AFRS	Diagnosis of asthma	Significantly higher prevalence of asthma in CRSwNP (48.3%) as compared to AFRS (23.6%) and CRSsNP (16.5%).
Han [1716]	2013	2	Cross-sectional study	AERD AFRS Asthmatic RS with allergy Asthmatic RS without allergy Nonasthmatic RS with allergy Nonasthmatic RS without allergy CF	Clinical data IHC of sinonasal mucosa	AFRS pathophysiology involves fungal-specific allergic reaction whereas AScA is a more undifferentiated allergic response. IL-5 is important in pathogenesis of AFRS, unlike other subclasses of eosinophilic RS.
Rowan [1706]	2019	4	Retrospective case series	AFRS (n=70) CRSwNP (n=70) CRSsNP (n=70)	Clinical data	Concha bullosa more prevalent in AFRS than CRSwNP.
Bakhshaee [1717]	2013	4	Prospective cohort study	Patients with >1 year history of CRSwNP	Clinical and histopathological data	Prevalence of AFRS among Iranian patients with CRSwNP was 9.45%.
Marfani [1707]	2010	4	Retrospective case series	AFRS (n=47)	Clinical data	The majority of AFRS patients with skull base erosion were young, male, and of low socioeconomic status. Unilateral disease present in over 59% of patients.
Ghegan [1704]	2006	4	Retrospective case series	Patients s/p ESS for inflammatory disease AFRS (n=27) Non-AFRS (n=158)	Clinical data	AFRS were 12.6 times more likely to have bony erosion than other CRS. Bony erosion was more common in males and African American patients.
Saravanan [1718]	2006	4	Cross-sectional	CRS patients categorized by	Clinical and pathologic data	AFRS associated with Charcot-Leyden crystals,

			study	presence of eosinophilic mucin with or without fungal elements		bony erosion, type 1 hypersensitivity and heterogenous opacity with sinus cavity expansion.
Ferguson [1719]	2000	4	Literature review and retrospective case series	AFRS (n=431) EMRS (n=69)	Clinical and immunologic data	AFRS associated with younger age of presentation, higher levels of serum IgE levels, and lower prevalence of asthma. AFRS can present with unilateral disease.
Ferguson [1701]	2000	4	National survey; literature review	AFRS	Clinical data	AFRS prevalence varied geographically with higher incidence in the southern more humid regions.
Mukherji [1703]	1998	4	Retrospective review	Patients with AFRS	Clinical data	AFRS was more common in males and in those from southern US states.
deShazo [1720]	1995	4	Retrospective case series	Patients diagnosed with AFRS	Clinical data	Proposal of 5 diagnostic criteria for AFRS.
Bent [1694]	1994	4	Prospective case series	Patients diagnosed with AFRS	Clinical and pathologic data	Defined diagnostic criteria for AFRS.
Histopathologic Evaluation						
Wise [1721]	2008	2	Prospective case control study w blinded analysis	Control group AFRS CRSsNP	IHC of mucosa biopsied from the OMC assessing for IgE	AFRS mucosa had significantly more IgE compared to other groups. IgE was increased more within subepithelial sites when compared to epithelium; Elevated IgE was not fungal-specific.
Laury [1722]	2014	4	Prospective case control study	AFRS CRSsNP Control group	Semiquantitative rtPCR and immunofluorescence of sinus tissue	Periostin was significantly elevated in AFRS compared to CRSsNP and controls; correlated with bone erosion.
Ragab [1723]	2013	4	Prospective case control study	AFRS Mycetoma CRSwNP	Histopathologic and IHC of sinonasal mucosa	$CD8^+$ T cells were the most common cell type in AFRS.

				CRSsNP		$CD20^+$ B cells were most common in CRSwNP and CRSsNP.
Ayers [1724]	2011	4	Prospective case control study	CRSwNP CRSsNP AFRS Control group	IHC of mucosa from the OMC	Dendritic cells and associated chemokines are significantly increased in the mucosa of AFRS and CRSwNP.
Ahn [1725]	2009	4	Prospective case control study	CRSsNP AFRS Control group	IHC of sinonasal mucosa	More fungal and nonfungal IgE is expressed in sinonasal mucosa of AFRS patients, compared with control and CRSsNP patients.
Pant [1726]	2009	4	Prospective case control study	CRS AFRS AFRS-like (fungal allergy, but no fungi in EM) Nonallergic fungal eosinophilic RS 5. Nonallergic nonfungal eosinophilic RS	IHC & flow cytometry of polyp, non-polyp tissue and peripheral blood Clinical characteristics	There is no significant difference between AFRS and other forms of EMCRS with respect to percentage of cell populations and fungal-specific lymphocyte proliferations. A higher percentage of CD8+ T cells were present in AFRS/EMCRS. Fungal-specific lymphocyte proliferation was greater in AFRS/EMCRS regardless of allergy.
Carney [1727]	2006	4	Prospective case control study	Control group AFRS Nonallergic eosinophilic fungal RS (NPs and positive fungal culture or stain, but without fungal allergy) 4. CRSsNP	IHC of infundibular mucosa	AFRS, nonallergic eosinophilic fungal RS and CRSsNP patients have elevated local mast cells, eosinophils and IgE^+ cell numbers compared to controls. No significant difference in eosinophils, mast cells or IgE^+ cell numbers between AFRS and nonallergic eosinophilic fungal RS, suggesting local IgE production in all CRS subsets.

Systemic Immunologic Response						
Porter [622]	2014	4	Prospective case control study	AFRS CRSsNP CRSwNP Controls	Fungal culture, Flow cytometry, Elispot and ELISA	T cell memory for fungal antigen was specific to fungi cultured from sinus cavities and noted in only patients with Type 2 immune response.
Rai [1728]	2018	4	Prospective case control study	AFRS Non-atopic controls	Flow cytometry, quantitative RT-PCR	Increase in Th17 cells and activity relative to Treg in AFRS vs controls.
Matsuwaki [1443]	2013	4	Prospective case control study	AFRS CRSwNP Control	IHC of sinonasal mucosa Serum and local IgE	Serum and local total IgE were significantly increased in AFRS compared to other groups. Local total IgE was increased in both CRSwNP and AFRS. Local IgE correlated with local ECP in all subjects, and more so with fungal-specific IgEs.
Hutcheson [1705]	2010	4	Prospective case control study	AFRS CRS	Serum total IgE and IgG anti-*Alternaria*-specific antibodies Serum antifungal IgE by Western immunoblotting	Mean serum total IgE was significantly higher in AFRS vs CRS. Mean serum IgG anti-*Alternaria* antibodies were significantly elevated in AFRS vs CRS. Statistically significant increase in mean number of IgE antifungal bands from AFRS vs CRS.
Pant [633 22]	2005	4	Prospective case control study	Eosinophilic mucin CRS CRS w/o mucin Fungal allergy only Non-atopic Control	ELISA for serum Ig levels	Fungal-specific IgG3 levels were elevated in all eosinophilic mucin CRS patients, irrespective of the presence of fungal allergy or fungi within eosinophilic mucin.
Other Immune Mechanisms						
Patel [1729]	2019	4	Prospective case control	AFRS Fungal ball	Immunofluorescent, flow cytometry,	Fungal antigens stimulated expansion

			study	CRSsNP	ELISA	of solitary chemosensory cells and increase IL-25 production in AFRS and patients with fungal balls.
Seiberling [1712]	2005	4	Prospective case control	CRSwNP CRSsNP Control group Antrochoanal polyp	Presence of SEA, SEB, SEC, SED and TSST-1 by ELISA IHC of sinus tissue	Association between toxin detection and CRSwNP with positive correlation to eosinophil counts.
Clark [1697]	2013	4	Retrospective case series	CRSwNP AFRS	Sinus culture	There is a higher prevalence of *S. aureus* in patients with AFRS versus patients with other types of CRSwNP.
Mulligan [718]	2011	4	Retrospective case series	AFRS CRSwNP CRSsNP Control group	VD_3 deficiency Circulating levels of immune cells Degree of bone erosion on sinus CT	CRSwNP and AFRS have insufficient vitamin D_3 levels. Vitamin D_3 levels inversely correlate with circulating dendritic cells and bone erosion.
Den Beste[847]	2013	4	Cross-sectional	AFRS Healthy control	Transepithelial resistance Tight junction protein levels Immunofluo-rescence	AFRS cells had increased epithelial cell permeability and altered expression of tight junction proteins.
Gene Expression						
Tyler [625]	2018	2	Prospective case control – blinded analysis	AFRS CRSwNP	mRNA levels Pathway analysis	Although AFRS and CRSwNP share many common pathways, AFRS significantly upregulates pathways important in adaptive immune response. An antimicrobial peptide is one of the most downregulated genes in AFRS as compared to CRSwNP.
Tyler [1715]	2017	2	Prospective case control-blinded analysis	AFRS CRSwNP CRSsNP AERD Healthy control	mRNA levels	Several genes are significantly differentially expressed between CRSwNP and AFRS, supporting AFRS as a separate endotype

						from other CRSwNP
Ebert [629]	2014	2	Prospective case control study – blinded analysis	AFRS CRSwNP Control group	Gene expression profiles in mucosal tissue assessed by microarray analysis	Protease-activated receptor 3 gene expression was elevated compared to controls but not if compared to CRSwNP.
Orlandi [1730]	2007	2	Prospective case control	AFRS EMRS control	Gene expression profiles in NP tissue using microarray analysis	38 genes were differentially expressed in AFRS vs controls.
Schubert [993]	2004	4	Prospective case control	AFRS Hypertrophic sinus disease	HLA DNA genotyping	66% of AFRS patients carried at least one HLA-DQB*03 allele. Allelic variants differed between the 2 groups.
Demographic and Socioeconomic Factors						
Miller [1700]	2014	4	Retrospective case series	Patients who met 3 of 5 AFRS Bent-Kuhn diagnostic criteria	Demographic and socioeconomic factors Measures of disease severity	Majority of patients were African American with higher prevalence of bone erosion in males. Lower socioeconomic status was associated with more severe disease.
Wise [1699]	2008	4	Retrospective chart review	AFRS CRSwNP CRSsNP	Demographic and socioeconomic factors	Age of presentation was lower for AFRS compared to CRSwNP and CRSsNP. AFRS patients resided in counties with higher poverty level vs CRSsNP.
Ghegan [1698]	2007	4	Retrospective chart review	AFRS	Demographic and socioeconomic factors	Majority of patients were African American. Males had higher prevalence of bone erosion. Socioeconomic factors did not significantly correlate with bone erosion.

X.E.2. AFRS Management

As a subtype of CRSwNP, there are significant similarities in the management of AFRS and CRSwNP. Several reviews on the management of AFRS often advocate the primary role of sinus surgery to remove fungal laden eosinophilic mucin and extended courses of postoperative oral corticosteroids in AFRS.[1693,1714,1731] Despite the widespread acceptance of these treatment modalities, there are no studies that have specifically addressed surgery as the recommended initial step in the management of AFRS as compared to medical therapy or the optimal duration of postoperative oral corticosteroids.

X.E.2.a. AFRS Management: Anti-Fungal Therapy (Oral and Topical)

Although several clinical trials have addressed the role of oral antifungals in CRS, only a handful of studies have specifically included AFRS. Consequently, ICAR-RS-2016 concluded that there were insufficient studies to either recommend for or against the use of antifungals in AFRS. Since then, 4 additional studies in this area have been published.

Patro *et al.*[1732] performed a prospective randomized study on 52 AFRS patients to either 4 weeks of preoperative itraconazole or not. Both groups experienced a significant improvement in SNOT-20 and Lund Mackay scores at 24 weeks postoperatively.

Rojita *et al.*,[1733] in a prospective trial of 60 patients with AFRS undergoing ESS, compared the postoperative use of topical nasal steroids to itraconazole (100mg BID) for 6 months. Hepatic enzyme abnormalities occurred in 6.6% of patients while taking itraconazole. Both groups experienced a significant decrease in SNOT scores, IgE levels and similar recurrence rates.

Verma *et al.*[1732] performed an unblinded RCT on 175 patients examining the use of itraconazole (100mg BID) given either pre- or post-operatively. All patients received 6 weeks post-operative oral steroid taper. SNOT-20, LM and endoscopy scores improved with itraconazole as compared to oral steroids alone; with better scores in the preoperative itraconazole group.

Finally, a Cochrane systematic review[1734] examining topical and oral antifungals in AFRS patients was unable to make a recommendation due to the low quality of evidence.

Overall, there continues to be few studies examining oral or topical antifungal therapy for AFRS and most are either low-level, have few subjects, and/or contain methodologic weaknesses. At this point, there is insufficient evidence to recommend for or against antifungal therapy in AFRS.

Antifungal Therapy for AFRS

Aggregate Grade of Evidence: C (Level 1: 1 study; level 2: 2 studies; level 3: 3 studies; level 4: 5 studies).
Benefit: May decrease time to recurrence and improve endoscopic scores
Harm: Potential elevation in liver enzymes associated with medication side effect. Some antifungals are metabolized by the CYP system and can affect steroid metabolism
Cost: Low
Benefits-Harm Assessment: Benefit appears modest at best.
Value Judgements: Itraconazole appears to only mildly improve the recurrence and postoperative symptoms of AFRS with potential risk of adverse events
Policy Level: Option
Intervention: Can consider topical or oral antifungals in AFRS patients recalcitrant to maximal topical steroid therapy and immunotherapy

Table X-31. Evidence for AFRS management with oral antifungal therapy

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Head [618]	2018	1	Systematic review	CRS patients	N/A	Studies including AFRS is lacking
Verma [1732]	2017	2	Non blinded Prospective T	AFRS patients undergoing ESS: 4wk itraconazole preop then surgery (n=25) 4wk itraconazole postop (N=100) No itraconazole (N=50)	SNOT 20 Lund Mackay Nasal endoscopy score	Preop and postop itraconazole showed significant improvement in SNOT, LM and endoscopy scores. Preop itraconazole showed better results compared to postop but similar recurrence rate.
Khalil [1735]	2011	2	Non-blinded prospective RCT (not placebo controlled)	AFRS patients: 1. Oral itraconazole 2. Fluconazole nasal spray 3. Combined (1) and (2) 4. Fluconazole irrigation 5. Conventional medical therapy only	Recurrence rate (not clearly defined)	Recurrence rates in the 5 groups were 66.7, 10.0, 14.3, 28.6, and 75.0%, respectively (no stastical analysis was done)
Rojita [1733]	2017	3	Prospective non-randomized control	AFRS patients recruited preoperatively and meds started immediately post ESS: 1. Prednisolone 30 mg QD 1 mo followed by topical steroid 2. Oral itraconazole 6 mos	Eosinophil count Serum IgE SNOT 22	Itraconazole can be considered an effective treatment alternative to steroids.
Patro [1734]	2015	3	Randomized Prospective case control	AFRS patients undergoing sinus surgery	SNOT-20 Nasal endoscopy score	Preoperative itraconazole reduced

				1. Oral itraconazole 1 mth pre-op 2. No pre-op treatment	Lund Mackay	hyperdensity in postop CT, improved polyp size and nasal endoscopy score. Reduction in postop fungal culture in itraconazole arm.
Gan [1736]	2014	3	SR of level 3 and 4 studies	AFRS patients	N/A	With quality of evidence rated as C, oral antifungals recommended as option in postsurgical refractory AFRS
Seiberling [1737]	2009	4	Case Series	Polyp recurrence treated with itraconazole: 1. AFRS (n=9) 2. AFRS-like (n=1) 3. Nonallergic fungal eosinophilic RS (n=13)	RS symptoms; Endoscopy	83% had improved symptoms and endoscopy (7/9 with AFRS); 3/19 who responded had to stop due to elevated liver enzymes
Chan [1738]	2008	4	Case series	AFRS (n=32) patients who had failed other medical therapies	RSOM-31	56% had significant or moderate improvement and 44% had little or no change
Jen [1739]	2004	4	Pilot study	Patients with "a history of AFRS" with progression of symptoms treated with fluconazole spray (n=16)	Nasal endoscopy Symptoms	75% had stabilization or decrease in mucosal edema and symptoms.
Rains [1740]	2003	4	Case Series	AFRS (n=137)	Recurrence	50.4% recurrence and reoperation in 20.5%
Kupferberg [1741]	1997	4	Case Series	Postoperative AFRS patients receiving:	Symptoms	1 of 3 patients receiving only oral antifungals

				1. No treatment (n=9) 2. Oral corticosteroids (n=100) 3. Oral corticosteroids and oral antifungals (n=2) 4. Oral antifungals only (n=3)		reported improvement in symptoms

X.E.2.a. AFRS Management: Immunotherapy

Type I hypersensitivity to fungi is a criterion for AFRS diagnosis and may represent a significant component of the pathophysiology of AFRS; however no new study has been published since ICAR-RS-2016. As such, Gan *et al.* remains the only evidence-based review with recommendations regarding IT for AFRS.[1101] They identified two level 3b studies and 3 level 4 studies which showed some value in treating AFRS with IT. Unfortunately, there were significant drawbacks in all of the studies including small sample sizes, mixture of IT with other medical treatments, and the absence of standardized control groups. Given the limited current evidence, additional clinical trials are needed to examine this question.

Immunotherapy for AFRS

Aggregate Grade of Evidence: N/A (Level 3: 1 study).
Benefit: May reduce inflammation and reduce other allergic symptoms
Harm: Risk of local and systemic reactions, including anaphylaxis (rare).
Cost: Moderate
Benefits-Harm Assessment: Equal
Value Judgements: Immunotherapy may be an option for patients with AFRS if they also have other allergic symptoms
Policy Level: Option
Intervention: immunotherapy remains a reasonable treatment option

Table X-32. Evidence for AFRS management with Immunotherapy

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Gan [1736]	2014	3	SR of level 3 and 4 studies	AFRS patients	N/A	IT may reduce mucosal inflammation; harm is similar to other IT treatments; cost is high

X.E.2.b. AFRS Management: Anti-IgE

Given the Type I fungal hypersensitivity and typical extremely elevated serum IgE levels, anti-IgE may represent a treatment option for AFRS patients. ICAR-RS-2016 found minimal evidence in this area and made no recommendations. Since then, two studies have been published. Gan *et al.*[1742] performed a retrospective review on AFRS patients receiving omalizumab. They reported decrease in the use of corticosteroids and antifungals as well as good SNOT22 and endoscopic scores. However, they did not have a comparison arm and results compared to the pre-surgical state. Therefore, it is difficult to make any treatment conclusions. Mostafa *et al.*[1643] performed a prospective single-blind RCT examining 20 patients with AFRS. Patients received one dose of omalizumab 150mg 2 weeks postoperatively or twice daily topical nasal steroids for 6 months. The study revealed significantly lower IgE levels at 12 weeks in the omalizumab arm. Moreover, there was a decrease in SNOT and TNSS score favoring the omalizumab arm at 24 wks. However, as this study only included a 6-month treatment period, it is difficult to determine the long-term benefit of using anti-IgE therapy.

Anti-IgE for AFRS

Aggregate Grade of Evidence: B (Level 2: 1 study; level 4: 1 study).
Benefit: Reduce the level of circulating IgE
Harm: Unknown risks of prolonged use of biologics
Cost: High
Benefits-Harm Assessment: At this time benefit outweighs harm
Value Judgements: Anti-IgE therapy will reduce the circulating levels and improve subjective symptoms in the short term
Policy Level: Option
Intervention: Consider use in difficult to treat AFRS patients with persistent thick mucoid and inflammatory discharge despite topical steroid therapy.

Table X-33. Evidence for AFRS management with anti-IgE

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Mostafa [1643]	2019	2	RCT	AFRS patients within 2 weeks of ESS: Single SC omalizumab	SNOT 22 scores TNSS scores Total IgE levels Endoscopic score	Significantly lower IgE level for omalizumab arm @ 12 weeks but none at 24wks; no

				(150mg) Topical steroids twice daily		difference in endoscopic score; Significant improvement in SNOT and TNSS favoring omalizumab.
Gan [1742]	2015	4	Retrospective review	AFRS patients with moderate to severe asthma receiving omalizumab	Use of corticosteroids or antifungals SNOT 22 score Endoscopic score	Decrease in SNOT-22, IgE and endoscopic score after surgery; all patients weaned off oral corticosteroid; no comparison arm.

X.F. Chronic Rhinosinusitis with Nasal Polyps: Complications

Complications from CRSwNP can be broadly classified into: (1) erosion and compression of the orbit and skull base, and (2) outflow obstruction with mucocele formation. Alternatively, these can also be categorized in anatomic terms: (1) orbital complications resulting in loss of vision, proptosis, diplopia, and epiphora and (2) intracranial complications such as meningitis, altered mental status, and other neurologic deficits, including olfactory loss.

Although erosion of the lamina papyracea and skull base can occur with longstanding polyp growth, direct compression of the orbit and brain is rare. In a series of 82 patients with AERD, two patients developed encroachment and subsequent infections of the lacrimal apparatus, and two patients had erosion of the medial orbital wall, leading to orbital cellulitis in one and proptosis in the other.[1743] Reports of intracranial invasion or involvement in the setting of NPs are rare. Typically, orbital and skull base involvement is characterized by smooth expansion without dural or periorbital invasion.

In AFRS substantial involvement of the skull base and lamina papyracea occurs in up to 50% of cases.[1704,1744] The role of gender and ethnicity is unclear, but African-American males have been reported to have a higher incidence of erosion.[1745] Compressive non-infective optic neuropathy with visual loss is less common (about 4%) but can also occur.[1746]

NPs can also cause sinus outflow obstruction, leading to mucocele formation. In one study of NP patients, the incidence of mucocele in unoperated CRSwNP cases was 0.6%, while the incidence in surgically treated patients was 2.5/100 patients per year.[1747] The frontoethmoid region was the most commonly affected. Furthermore, patients with AERD were at increased risk. In the aforementioned series of 82 patients with AERD, three of the seven orbital complications involved mucoceles encroaching the orbit. Of these three, two developed blindness as a result of optic nerve ischemia. A control group of aspirin-tolerant patients did not have any orbital complications.[1743] Overall, mucocele formation in CRSwNP is rare, but prior surgery and aspirin-sensitivity may be risk factors.

XI. Acute Exaccerbation of Chronic Rhinosinusitis (AECRS)

XI.A. AECRS: Incidence and Prevalence

Acute exacerbations of CRS (AECRS) are described as a worsening of sinonasal symptom intensity with a return to baseline symptoms often after intervention with corticosteroids and/or antibiotics.[1,26-29,1748] The frequency of these CRS-related systemic medication treatments is a valid metric of QoL in CRS[1749] and may be considered as an exacerbation-defining event.[1748,1750] CRS patient-identified "flares" or sinus infections, which may also be considered exacerbation-defining events, have previously been associated with decreased QoL[27] and changes in inflammatory mediators detected in nasal mucus.[1010,1751] Yamasaki *et al.* have previously shown that CRS patients frequently report the use of antibiotics and oral corticosteroids in the previous 3 months (34.4% and 17.8%, respectively) and 12 months (54.8% and 27.4%).[28] In a subsequent study, Phillips *et al.* considered patients reporting greater than 3 episodes of oral corticosteroids or antibiotics in the previous 12 months to represent the exacerbation prone phenotype of CRS,[1748] which constituted 17.8% of CRS patients in Yamasaki *et al.*[28] The prevalence of AECRS may vary with the patient cohort being studied, season, and how the exacerbation was defined. These estimates for AECRS incidence are inherently limited as indirect measures of AECRS, as they may not be inclusive of all AECRS or may simply reflect poor disease control rather than a discrete AECRS.

IX.B. Pathophysiology of AECRS

Although there are many contributing factors, CRS is characterized by a dysfunctional host-environment interaction.[31] AECRS pathophysiology is still early in its characterization, and challenging to study given heterogeneous definitions, but early investigations hypothesized mechanisms underlying CRS and ARS. Substantial study has focused on the identification of risk factors leading to an AECRS with rare emphasis on the pathophysiology of the development of AECRS. Associations of risk factors with AECRS, despite differing definitions of AECRS, include body mass index, asthma, hay fever, sinus surgery history, and winter season consistently predicting increased AECRS.[212] AECRS also occurs less frequently when asthma is well controlled in asthmatic CRS patients, independent of CRS symptom severity.[29] These risk factors taken together with the first principles underlying ARS and CRS pathophysiology suggest that AECRS is due to an imbalance of host defense and environmental factors similar to the pathophysiology of ARS and some of the same pathophysiological processes associated with CRS.

Bacterial overgrowth and infection contribute to acute exacerbations and acute purulent episodes in the scenario of underlying chronic inflammatory changes associated with CRS. The frequent presence of biofilm-forming organisms represents a large reservoir for opportunistic infections.[1752] However, the low number of studies, the diversity of the different study cohorts, and the lack of a universal definition of AECRS make it difficult to draw any conclusion concerning the role of bacteria in AECRS. Clinical experience suggests antibiotics that cover the most common organisms associated with both ARS and CRS are likely effective in reducing the symptoms of the AECRS. This again points to some role for bacteria in AECRS, though the antibiotic effects may be altering the immune response in addition to their antimicrobial properties. However, one randomized, controlled trial failed to show a difference in outcomes in patients receiving antibiotics versus placebo. Patients with AECRS received amoxicillin-clavulanate or placebo for two weeks. There was no difference in the clinical course between the treatment and control groups. Both groups exhibited overall improvement of symptoms on day 14 compared to day 0.[211]

Brook *et al.* compared organisms isolated from the maxillary sinus of patients with CRS with those suffering from an AECRS.[1753] The identified organisms were predominantly anaerobic and similar to those generally identified in CRS (*Prevotella, Porhyromonas, Peptostreptococcus*, and *Fusobacterium* subspecies). However, in addition to the predominance of the anaerobic organisms, aerobic bacteria that are usually found in acute infections were also cultured. *Streptococcus pneumoniae* and *Haemophilus influenzae* were found more frequently in patients with AECRS compared to those with CRS without frequent acute exacerbations. It is known that bacterial infection further leads to Th1 and Th2 responses resulting in activation of neutrophils and secondarily eosinophils in many cases.[1754]

Disturbance of the host mucosal immune system may also play an important role in AECRS. Immunologic changes at the level of receptors, cytokines, interleukins and other mediators, including MCC, is considered crucial for the basic "first line of defense" of the respiratory mucosa. Rank *et al.* performed a pilot study which investigated immunological changes in nasal secretion of CRSwNP patients during clinical worsening of their CRS symptoms. IL-6, major basic protein, myeloperoxidase, eosinophil-derived neurotoxin (EDN) and uric acid were significantly elevated during AECRS.[1751] In the subset of AERD CRS, salicylates are known to trigger respiratory exacerbations. Philpott *et al.* suggested that there is an association between symptom exacerbation in response to food products with higher potential salicylate content, specifically wine, in both CRSsNP and CRSwNP patients.[1755] It has also been described that MCC is impaired in a subgroup of patients with chronic inflammatory mucosal changes. This appears not a result of impaired beat frequency of the cilia themselves, but rather to a lack of coordination of the motor arrays as well as altered viscosity of the mucus blanket caused by the elevated levels of mediators and cellular proteins within.[1756] The prolonged contact time of microorganisms to mucosal surfaces and antigen presenting cells appears to be another factor in the individual susceptibility to acute exacerbations of CRS. Similarly, some of the changes seen in atrophic rhinitis in combination with CRS has been hypothesized to be another predisposing factor for AECRS.[1757]

The seasonal variation observed in AECRS has also been investigated. Rank *et al.* performed a retrospective cohort study of 800 patients, finding that AECRS is more likely to occur during winter months, suggesting a pattern similar to ARS. The authors discussed different hypotheses, including a potential relationship between CRS disease activity and viral infection, air quality, air temperature, air humidity, or indoor allergen/irritant exposure as potential contributing factors. However, Talat *et al.* argued that seasonal variations in CRS symptoms may be explained by changes in mood, in the winter, which is associated with increased depressed mood, potentially causing people to feel that CRS has worsened.[1758]

XI.C. Management of AECRS

No evidence-based treatment recommendations for AECRS currently exist. Following the initial ICAR-RS publication,[1] advances have been made towards understanding the etiology, immunological features, and possible risk factors of AECRS. [29,212,1010,1751,1759]. Consensus guidelines and expert opinion recommend short-term antibiotics for AECRS, in the setting of a positive culture to provide symptomatic relief.[1,31] The treatment for ARS with the implementation of antibiotics has been extrapolated and applied to AECRS, despite AECRS being recognized as a distinct entity from ARS[210,1760] Antibiotics and treatment of the pre-existing CRS are often implemented.

There is only one RCT to date that investigated patients with AECRS. Patients were randomized to amoxicillin-clavulanic acid for 14 days compared to placebo. The patients were evaluated using the Visual Analogue Scale-Severity Scoring Assessment (SSA), and the absolute score difference between day 0 and 14 was calculated. Next, the Lund-Kennedy nasal endoscopy scores were obtained on day 0 and 14, and endoscopy directed middle meatus swabs were collected on day 0 and 14. The SNOT-22 was used to evaluate the QoL after treatment at 12 weeks. The results showed that antibiotics did not change the short-term evolution of symptoms or nasal endoscopy findings. Despite the amoxicillin-clavulanate providing high coverage (82% of the bacteria cultured), only 29% demonstrated eradication of the original organism on day 14. The QoL scores in the antibiotic group when compared to the placebo cohort were similar at 12 weeks. The addition of an antibiotic to intranasal steroid spray did not provide additional benefit. A fundamental limitation of this study was the small sample size.[211] Several non-randomized studies have been reported in the literature. However, it is difficult to draw meaningful conclusions due to the heterogeneous nature of the studies, the adoption of varying criteria for an AECRS diagnosis, diverse clinical endpoints documented, and small sample sizes. Recently, a retrospective chart review of patients with AECRS compared outcomes of culture-directed and non-culture directed (empiric) antibiotic use. Culture-directed therapy for AECRS showed an improvement in Lund-Kennedy endoscopy scores long term, but not in the short term. Furthermore, culture directed antibiotics does not improve short or long-term QoL in CRS.[1761] This is in contrast to an earlier study that showed a decreased short-term QoL improvement in the post ESS patients treated with culture inappropriate antibiotics, which is defined as at least one cultured organism resistant to or not covered by the prescribed post-operative antibiotics. In these cases, the antibiotics were not adjusted after culture results were available. However, the decreased QoL was no longer apparent at 6 months in this study.[1762] Overall, it is difficult to draw any comparisons, as this cohort represented patients treated with antibiotics post ESS, who may not meet ICAR-RS definition of AECRS.[1]

In summary, clinical studies for the management AECRS are still lacking and further high-quality studies are needed in this area. Because of the paucity of evidence, no recommendation is currently possible.

Table XI-1. Evidence for management of AECRS

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoints	Conclusion
Sabino[211]	2017	2	RCT	Amoxicillin-clavulanate for 14 days (21) Placebo (11)	SSA Lund-Kennedy score Nasal endoscopy Culture results SNOT-22	Amoxicillin-clavulanate did not change short term evolution of symptoms or QoL scores compared to placebo.
Yan[1761]	2018	4	Retrospective review	Culture-directed antibiotic (61) Empiric antibiotics (61)	Lund-Kennedy score short term (<1 month) and long term (1-6 months); SNOT-22 short term (<1 month) and long term (1-6	Culture directed therapy improved long term endoscopy scores compared to empiric therapy but not short-term endoscopy scores or short and long term QoL scores.

					months)	
Zhang[1762]	2014	4	Retrospective review	Post ESS 14 days of antibiotics 1. Culture inappropriate antibiotics (27) 2. Culture appropriate after adjustment (19) 3. Culture appropriate antibiotics (66) 4. Undetermined (264)	SNOT-22	Culture inappropriate antibiotics results in a decrease QoL at 3 month follow up.

XI.D. Complications of AECRS

Data on orbital, osseous, and intracranial complications related to AECRS are scarce, but are usually related to refractory, untreated, or misdiagnosed CRS.[31] The most common complication of CRS involves orbital infections. In two large retrospective reviews of orbital complications, 43%-58% of cases were associated with CRS,[464,1763] mostly seen in patients with CRSsNP [66% (19/30)] or those who underwent sinus surgery [61% (18/30)].[464] Interestingly, the most severe orbital complications (pre-septal vs. post-septal) occurred in CRS patients with a history of prior sinus surgery.[464,1763] Mucoceles are relatively rare and grow slowly unless AECRS produces a mucopyocele. They occur most often in the frontoethmoidal region and the symptoms presented in AECRS are those related to an orbital complication of ARS.[31,1764-1769]

The most common osseous complication in adults is osteomyelitis of the frontal sinus. It may present as a Pott's puffy tumor or frontal sinus cutaneous fistula. Eyelid and/or periorbital edema is the most common finding in patients with orbital involvement, and preseptal cellulitis is by far the most prevalent orbital complication in Pott's puffy tumor.[468] Intracranial complications of AECRS are rare but potentially severe. Bayonne *et al.* did not find any cases with CRS among 25 patients identified in a retrospective study of 13 years.[1770]

XII. Surgery for Chronic Rhinosinusitis

XII.A. General Concepts

XII.A.1. Goals of Sinus Surgery

In recent years, CRS has been increasingly recognized as a diffuse inflammatory disorder with a spectrum of endotypes rather than an obstructive or infectious disease.[61] As a result, treatment regimens have evolved to focus on decreasing mucosal inflammation and not merely improving sinus patency or ventilation. Hence, ESS has become the standard for surgical treatment of CRSsNP and CRSwNP in patients who meet the appropriate indications.[283] In CRS, the primary surgical aims are: (1) relief of symptoms with improvement in QoL; (2) reduction in the amount of mucosal disease as well as enlargement of sinus drainage pathways for topical drug delivery; (3) avoidance of surgical complications; (4) prevention of complications related to untreated sinus disease[1771] While the magnitude of the change in QoL before and after surgery is an important surgical outcome for ESS[1772], patients are also more likely to undergo ESS if they report more severe symptoms.[1773] Therefore, the decision to recommend surgery for CRS should always take into consideration the severity of associated symptoms.

In performing ESS, a stepwise systematic approach should be employed to avoid possible surgical complications such as injury to the orbit or skull base.[1774] The goal of opening the natural drainage pathway via the surgical removal of diseased mucosa and bony partitions during ESS has been advocated for decades.[1775] By restoring an aerated sinus, previously dysfunctional sinuses may be returned back to a normal state.[1776,1777] Importantly, while enlarging the drainage pathways of the sinuses, attention should be paid to meticulous surgical technique.[1778] A well-performed ESS is not immune to revision; however, there are a number of factors that have been shown to be associated with revision sinus surgery that are potentially preventable. These factors include the extent of ostial enlargement and sinonasal tissue removal continue to be a matter of significant debate. While some studies have demonstrated a lack of strong evidence for the superiority of ESS over simple polypectomy, others have suggested polyp recurrence rates are lower with a more complete sinus surgery.[1779,1780] In a recent multi-institutional study, a more complete sinus surgery was an independent predictor of greater postoperative improvement in a patient's SNOT-22 score.[1781] A 2014 Cochrane systematic review[14] concluded that ESS did not appear to be superior to medical treatment; however, postoperative medical regimens were not standardized, steroid irrigations were not utilized, and surgeries ranged from simple polypectomy to full ESS. Therefore, it is difficult to draw conclusions from this Cochrane review given the heterogeneity of the included studies. Several other studies suggest that the goals of ESS for CRS are broader than simply removing areas of obstruction, [1777,1778,1782] and establishing postoperative access for topical therapies, which directly deliver medication to the disease site, has increasingly become a goal of surgery.[1089]

Unoperated sinuses or those with ostial obstruction cannot be reliably penetrated by nasal irrigation compared to those in patients who have undergone ESS.[1134] Several cadaveric and computational model studies have also demonstrated that ESS enhances the delivery of topical irrigations to all paranasal sinuses, particularly the frontal and sphenoid sinuses.[1076,1783] Studies comparing the effects of topical therapy with or without ESS have reported greater symptom improvement, decreased polyp recurrence,

and decreased polyp size in patients with ESS.[1533,1784] Therefore, the treatment paradigm for CRS has evolved to performing a wide and complete ESS for adequate delivery of topical therapy in patients that meet surgical criteria.[1089,1778,1785,1786]

In evaluating CRS patients for ESS, surgeons should carefully consider the potential improvement in QoL and the surgical approach to establishing patent drainage pathways for the delivery of topical medications while safely avoiding complications.

XII.A.2. Surgical Venue: Office versus Operating Room

With development of new surgical technologies and heightened awareness towards delivering cost-effective healthcare, office-based sinonasal procedures have become a common part of the rhinology practice.[1787] One example is the rise of balloon catheter dilation (BCD); an analysis of Medicare reimbursements found that in the six years after the introduction of CPT codes specific to BCD (in 2011), the frequency of BCD (both in-office and operating room) increased from 7,496 to 43,936 procedures per year.[1788] Office-based procedures offer several potential patient benefits, including avoidance of general anesthesia, reduced recovery time, and lower costs compared to procedures in the operating room.[1789]

Patient selection is crucial in achieving successful outcomes in office-based procedures. Patients with anxiety or difficulty tolerating nasal endoscopy are unlikely to comfortably undergo office-based procedures.[1790] Patients on anticoagulation or antiplatelet therapy may also be poor candidates, as aspirin 325mg and warfarin have been associated with worse procedural bleeding during BCD.[1791] However, in properly selected patients, office-based procedures can be performed safely with relatively few complications. The largest study to date of 315 patients undergoing office procedures (166 turbinoplasty, 118 ESS, 35 septoplasty, 34 rhinoplasty, 4 septorhinoplasty) reported a 2.5% complication rate overall (5.9% among ESS), with the most common complications being pain, vasovagal response, and epistaxis.[1792] While office procedures can also be offered to patients whose comorbidities make them poor candidates for general anesthesia, clinicians should be aware that patients may still experience wide, asymptomatic fluctuations in blood pressure and pulse during office procedures.[1793]

For CRSsNP, in-office BCD can be used to dilate the paranasal sinuses.[1794-1802] A randomized multicenter trial demonstrated equivalent improvement in SNOT-20 scores and comparable revision rates at 2 years when comparing in-office BCD to ESS under general anesthesia.[1802] Importantly, studies on BCD have been limited to cohorts with milder disease based on radiographic scores.[1803] While traditional ESS can be performed in the office under local anesthesia with a low complication rate,[1792] there remains a lack of robust sinonasal outcomes data for these procedures.

For CRSwNP, microdebrider-assisted polypectomy can be utilized in patients with recurrent polyposis after ESS.[1804,1805] Steroid-eluting stent placement in the ethmoid cavity is another effective in-office treatment option for recurrent polyposis after ESS.[1606,1608,1806] In-office primary ESS and BCD have not been validated in patients with CRSwNP.

Adjunctive procedures can also be offered in the office setting to patients undergoing treatment for either CRSsNP and CRSwNP. Office-based image-guided navigation is available, offering similar user interfaces to units designed for the operating room.[1807] Inferior turbinoplasty can successfully

performed in patients with concomitant nasal obstruction from turbinate hypertrophy,[1808,1809] and cryotherapy can improve rhinorrhea and congestion in selected patients.[1810,1811]

When selecting the best setting for sinonasal procedures, clinicians should consider patient goals, comorbidities, and disease severity, as well as provider expertise and equipment availability. While the data suggest that office-based sinus procedures can be performed safely, there remain significant gaps in evidence. Robust long-term outcomes data is necessary, especially for emerging in-office technologies. Improving the levels of evidence for office-based procedures can facilitate matching patients to the best approach based on disease severity or appropriateness criteria.

XII.A.3. Primary vs. Revision Surgery: How Do Decision-Making Approach and Goals Differ?

The common goals of both primary and revision ESS for CRS are to relieve subjective symptoms and improve QoL, reduce objective disease burden, and prevent complications of untreated disease, all while minimizing surgical risks.[1782] However, these two scenarios present distinct challenges, and proper patient management requires a thorough understanding of their respective unique clinical goals to inform the clinician's decision-making approach.

Primary ESS potentially offers the greatest opportunity for long-term success.[1812,1813] While some studies have demonstrated comparable improvements in both primary and revision ESS groups,[1814] others have shown that outcomes are significantly better after primary surgery.[1815,1816] This highlights the potential risk for iatrogenic damage to healthy sinus mucosa, which must be avoided through meticulous mucosal preservation. One study comparing directed ESS to full ESS found similar outcomes on both endoscopy and symptom assessments, supporting a more conservative approach to avoid collateral damage to previously uninvolved sinuses while fully dissecting involved sinuses.[1817] However, in cases of more extensive polyposis, more extensive surgery may be required up front. Studies that examined CRSwNP patients in both the primary and revision setting found that those who underwent complete ESS had better sinus-specific outcomes compared with targeted ESS.[1780,1781,1818] Image guidance during primary surgery has been associated with a reduced rate of revision surgeries, although has not been shown to reduce the risk of complications.[1819]

Revision surgery may be required in cases of persistent inflammatory disease or recurrent nasal polyposis and can be an effective tool to produce symptomatic relief.[1820,1821] This may be due to inadequate primary surgical extirpation, postoperative scarring and neo-osteogenesis, or inadequate postoperative medical management.[1822] One study identified a revision rate of nearly 20%.[287] An understanding of both patient and iatrogenic factors as the etiology for persistent disease is critical to determine candidacy and approach for revision surgery.[1822] The technical aim is to remove residual bony partitions of all previously addressed and unaddressed sinuses, address scarring, and remove diseased tissue, with additional interventions such as drilling only used after this has been accomplished.[1812,1822,1823] If revision sinus surgery is required, long-term topical therapy is likely necessary, and so the creation of a sinus cavity amenable to this intervention should be a primary goal. To achieve this goal when revising an otherwise well-done primary surgery, it may be necessary to perform a medial maxillectomy, endoscopic modified Lothrop, or a sphenoid drill-out depending on the patient's individual sinonasal anatomy.[1822,1824]. The potential benefits of revision surgery must be weighed against the incidence of CSF and orbital injuries, which have been reported higher in some series.[98,102] Image guidance may be particularly useful in this context to navigate the altered anatomy.[1782,1822,1825]

XII.A.4. Anesthesia Technique in Sinus Surgery

XII.A.4.a. Total Intravenous Anesthesia (TIVA) vs. Inhalational Anesthesia

As ESS has advanced over the last four decades, the agents used to anesthetize patients undergoing these procedures has similarly evolved. From the early years of ESS, there has been recognition that anesthetic type impacts the amount of blood lost during the procedure.[1826] As bleeding during ESS limits visualization, increases operative time, and risk of complications, appropriate anesthetic selection is imperative.[1827] Today there are two anesthetic paradigms in ESS: total intravenous anesthesia (TIVA) and inhalation anesthesia (IA). Both can be used to lower patients' blood pressure, a technique called controlled or deliberate hypotension, to reduce bleeding.[1827]

Initially described by Blackwell *et al.*, the maintenance phase of TIVA typically consists of a propofol infusion alone or in combination with a short acting opioid such as remifentanil or fentanyl.[1828] IA relies on inhalation of a halogenated ether such as isoflurane, sevoflurane, or desflurane. Similar to TIVA, IA may be administered alone or in combination with an opioid, as above.[1829] Unlike in IA, TIVA utilizes a central mechanism to reduce peripheral pressures and associated potential for venous bleeding. Propofol leads to deceased cerebral metabolic rate and lower cerebral blood flow.[1830] This decreased blood flow to the internal carotid artery decreases blood flow to the ethmoidal and supraorbital arteries, potentially decreasing bleeding in areas supplied by these vessels: the sphenoid, ethmoid, and frontal sinuses. IA, on the other hand, leads to hypotension through peripheral vasodilation. This can lead to increased capillary bleeding.[1831] While initially more costly, TIVA now has a lower cost than IA.[1832] The use of TIVA is also associated with a decreased incidence of early postoperative nausea and vomiting compared with sevoflurane or desflurane in patients undergoing ambulatory surgery.[1833]

A total of 17 prospective studies have been undertaken to determine if bleeding is reduced during ESS in patients anesthetized with TIVA compared to IA. Four systematic reviews, three with meta-analyses, have been completed. All three meta-analysis found that surgical visualization was improved with TIVA. Only Kolia *et al.* found that estimated blood loss (EBL) and operative time were also reduced.[1834] While many of the recent studies were randomized and blinded, the quality of these studies is low. Particularly problematic is the confounder posed by remifentanil which results in decreased heart rate, cardiac output, and blood pressure without peripheral vasodilation, all of which may confound study findings.[1829] Additional study controlling for the impact of intraoperative opioid should be undertaken.

Total Intravenous Anesthesia for ESS

Aggregate Grade of Evidence: C (Level 1: 4 studies; level 2: 16 studies; level 3: 1 study)
Benefit: TIVA may improve surgical visualization and reduce blood loss anda decreased incidence of early postoperative nausea and vomiting compared to IA with sevoflurane or desflurane.
Harm: No evidence of increased risk with TIVA.
Cost: TIVA may have a lower cost than IA in some health systems and a higher cost in others.
Benefits-Harm Assessment: Preponderance of benefit over harm.
Value Judgments: TIVA appears to display several advantages over IA, however local practice patterns, drug supplies, individual patient situations, and anesthesiologist comfort play a large role. Intraoperative opiates may also impact blood loss and is an uncontrolled confounder in many studies. The use of remifentanil infusion should be considered. Surgeons and anesthesiologists should jointly agree on the

optimal plan foreach patient.
Policy Level: Recommendation
Intervention: The use of TIVA in functional ESS is recommended where possible in conjunction with anethesiologist preference. Value judgements and costs should also be taken into consideration.

Table XII-1. Evidence for anesthesia technique in sinus surgery.

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoints	Conclusion
Kolia [1834]	2019	1	Systematic review of RCTs	IA (n = 267) TIVA (n = 263):	Surgical visualization EBL Operative time	TIVA improves visualization as well as reduces EBL and operative time
Boonmak [1829]	2016	1	Systematic review of RCTs	1) Visualization (n = 277): a) IA (n = 140) b) TIVA (n = 137) 2) Operative Time (n = 214): a) IA (n = 111) b) TIVA (n = 103)	EBL Surgical visualization Operative time Failure of deliberate hypotension Mortality within 24 hours	Deliberate hypotension with TIVA may improve visualization. Operative time and EBL was not different. All low quality evidence.
DeConde [1835]	2013	1	Systematic review of RCTs	IA (n = 269) TIVA (n = 249)	Heart rate Mean arterial pressure Anesthesia time Operative time EBL Surgical visualization	TIVA may improve surgical field, but this is based on low quality studies
Kelly [1836]	2012	1	Systematic review of RCTs	7 studies qualitatively reviewed	No meta-analysis	Mixed results with severe limitations in studies
Little [1837]	2018	2	RCT, double-blind	IA (n = 15) TIVA (n = 15)	Surgical visualization (Wormald) Surgical visualization (Boezaart) EBL Operative time Time to extubation	TIVA improves visualization

Brunner [1838]	2018	2	RCT, double-blind	IA (n = 33) TIVA (n = 37)	Surgical visualization (Wormald) EBL Operative time Time in PACU Time to discharge	TIVA improves visualization and reduces EBL
Chaaban [1839]	2013	2	RCT, double-blind	IA (n = 15) TIVA (n = 18)	EBL Surgeon rating Anesthesiologist rating Operative time	No significant difference in operative time, EBL or surgeon rating. IA had higher anesthesiologist scores indicating easier management
Marzban [1840]	2013	2	RCT, single-blind	IA (n = 22) TIVA (n = 22)	EBL Surgical visualization (VAS)	TIVA improves surgeons' ratings of visualization and reduces EBL
Cho [1841]	2012	2	RCT, single-blind	IA (n = 32) TIVA (n = 36)	Operative time Mean arterial pressure Heart rate Change in hemoglobin Surgical visualization	TIVA improved surgical visualization, particularly in patients with more extensive disease
Gomez-Rivera [1842]	2012	2	RCT, double-blind	IA (n = 12) TIVA (n = 11)	Sinonasal blood flow EBL Surgical visualization (Boezaart) Operative time Anesthesia time	No difference in visualization or EBL. TIVA increased blood flow after 1 hour of surgery.
Ankichetty [1843]	2011	2	RCT, double-blind	IA (n = 40) TIVA (n = 40)	Time to optimal MAP EBL Operative time Surgical visualization (Boezaart) Complication rate	No difference in surgical visualization or EBL. Hypotension can be obtained with either IA or TIVA.

Ragab [1844]	2010	2	RCT	IA (n = 35) TIVA (n = 35)	Heart rate Blood pressure Operative time EBL Surgical visualization (VAS and Boezaart)	TIVA improves surgical field (VAS and Boezaart scores). Hypotension can be obtained with either IA or TIVA.
Yoo [1831]	2010	2	RCT, double-blind	TIVA (n = 20) IA w/ sevoflurane (n = 20) IA w/ desflurane (n = 20)	Surgical visualization (Boezaart) Heart rate MAP	No significant differences in surgical visualization were noted between TIVA and IA
Ahn [1845]	2008	2	RCT, double-blind	TIVA (n = 20) IA (n = 20)	Heart rate MAP Operative time Anesthesia time Surgical visualization (Likert Scale) EBL	TIVA results in less bleeding and better surgical visualization, especially in patients with a extensive disease
Beule [1846]	2007	2	RCT, double-blind	TIVA (n = 24) IA (n = 22)	Operative time MAP Heart rate EBL Surgical visualization (VAS) Impact of bleeding (VAS)	No significant differences in surgical visualization or EBL were noted between TIVA and IA
Wormald [1847]	2005	2	RCT	TIVA (n = 28) IA (n = 28)	MAP Heart rate EBL Surgical visualization	TIVA results in a better surgical visualization than IA.
Sivaci[1848]	2004	2	RCT	TIVA (n = 32) IA (n = 33)	Operative time MAP EBL	TIVA may decrease bleeding compared with conventional IA
Tirelli[1849]	2004	2	RCT	TIVA (n = 27) IA (n = 37)	MAP Heart rate EBL Surgical visualization	TIVA reduced EBL. Controlled hypotension obtained with either IA or TIVA
Eberhart[1850]	2003	2	RCT, double-blind	TIVA (n = 45) IA (n = 43)	MAP Heart rate EBL Surgical visualization	TIVA improved surgical visualization. Controlled hypotension was

					(Fromme) Surgical visualization (VAS)	obtained with either IA or TIVA
Pavlin[1851]	1999	2	RCT, double-blind	TIVA (n = 30) IA (n = 26)	MAP Heart rate EBL Surgical visualization Length of stay	No significant difference in EBL; visualization and time to discharge improved with TIVA
Milonski[1852]	2013	3*	RCT	IA w/ fentanyl (n = 30) IA w/ remifentanil (n = 30) TIVA (n = 30)	Anesthesia time Operative time EBL Blood loss rate	TIVA provides better control of hypotension, leading to lower EBL and shorter operating time

* Level of evidence downgraded due to opaque reporting of randomization strategy and baseline measures of disease severity

XII.A.4.b. Hypotensive Anesthesia

Obtaining an excellent surgical field improves operative technique and surgical outcome with a shorter operating time. A significant amount of research has been conducted into determining which anesthetic technique is best to achieve this and whether total intravenous anesthesia (TIVA) or inhalational anesthesia (IA) is preferable.[1827,1829,1831,1835,1836,1838,1841,1843,1844,1847] In many of these articles the authors state that controlled hypotension (defined as a MAP between 50 and 70mmHg) is an important element in achieving the best operative field[1829,1831,1843,1844,1847,1850,1853-1856] but there is little known about what mean arterial pressure (MAP) is best for ESS,[1853,1854] what considerations need to be taken into account when choosing which drugs to use to achieve this MAP, and what MAP is safe. [1853,1854] It is well described that prolonged hypotension can result in patients having post-operative cerebral ischemic effects such as memory loss, neurological deficits and even death.[1853,1854] The brain has a built-in protective mechanism to help prevent cerebral ischemia by been able to adjusting the blood flow when variations in blood pressure occur. This is termed cerebral autoregulation and allows the brain to adjust the blood flow to match the cerebral metabolic needs. It is generally accepted that the ischemic threshold for the anesthetized brain is about 50% of those of the awake patient due to the lower metabolic requirements of the anesthetized brain. In the systemic reviews on TIVA versus IA[1829,1835,1836] there was significant variation in the studies as to what MAP was aimed for with some studies having a MAP above 70mmHg so although these patients had TIVA there was no attempt to induce controlled hypotension.

One of the factors that contribute to significant bleeding in the surgical field is disease load.[1838,1847] Patients with extensive sinus disease and polyps have a greater degree of vascularity and will usually bleed more than patients with minimal disease. [1838,1847] Even though interventions in this patient group are more likely to result in a difference in surgical field than interventions in low disease load patients, this is seldom addressed in any of the published studies. In an RCT Brunner *et al.*[1] compared TIVA and IA in nasal polyp patients with a high Lund and Mackay score (high disease load) and showed that TIVA was significantly better than IA in controlling the surgical field. Even though TIVA was shown to give a better surgical field, the MAP that they aimed for in both patient groups was 70-80mmHg. In a study by Ha *et al.*[1854] the patients served as their own control so the bleeding for a specific disease load was studied at both a high and a low MAP. In this study the bleeding scores did track the MAP emphasizing the need to address the MAP in patients with a poor surgical field.

There have been a number of studies comparing TIVA with IA where the target MAP was 50 to 60 mmHg[1855,1856] but it is unclear from these studies what MAP is most effective in ESS and what MAP is safe. Ha *et al.* in 2 studies[1853,1854] correlated MAP with cerebral perfusion by placing a Doppler probe on the temporal region over the middle cerebral artery and measuring flow through the artery. At the same time the MAP and cardiac output were measured by an arterial line. In the first study[1853] there was a strong correlation between the MAP and the cerebral blood flow through the middle cerebral artery (V_{MCA}) with a correlation between the MAP and the bleeding scores. In the second study[1854] the MAP was intentionally varied throughout the ESS procedure with the bleeding score observations blinded to the MAP. The V_{MCA} was measured at the same time point. The correlation between MAP and V_{MCA} was again demonstrated, with both the MAP and the cardiac output tracking the bleeding score. It was also demonstrated that to maintain the V_{MCA} at above 50% of the baseline for 90% of the anesthetic time the MAP needed to be kept above 60mmHg. This was confirmed by a study by Farzangan *et al.*[11] who used Near Infra-Red Spectrometry (NIRS) to measure cerebral oxygenation and confirmed that cerebral oxygenation was maintained with a MAP > 55 mmHg.

In summary, controlled hypotension is an important part of optimizing the surgical field[1855,1856] but a safe MAP of between 60 and 70 mmHg needs to be part of the anesthetic protocol. The target MAP is best achieved with a combination of TIVA,[1827,1829,1836,1847,1850,1853-1856]alpha-receptor agonists (clonidine or dexmedetomidine)[1841] and B-blockers.[1844,1850,1853-1856].

Hypotensive Anesthesia for ESS

Aggregate Grade of Evidence: B (Level 1: 3 studies; level 2: 10 studies; level 3: 1 study)
Benefit: Controlled hypotension with MAP of between 60 and 70 mmHg improves the surgical field.
Harm: MAP < 60mmHg may result in cerebral ischemia.
Cost: Minimal additional cost to achieve target MAP.
Benefits-Harm Assessment: Preponderance of benefit over harm.
Value Judgments: A MAP of between 60 and 70 mmHg preserves cerebral blood flow in healthy patients and improves the surgical field especially in high disease load patients.
Policy Level: Recommendation
Intervention: Controlled hypotension (MAP between 60 and 70 mmHg) is safe and improves the surgical field.

Table XII-2. Evidence for hypotensive anesthesia in sinus surgery.

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoints	Conclusion
Boonmak[1829]	2016	1	Systematic review of RCTs	1) Visualization (n = 277): a) IA (n = 140) b) TIVA (n = 137) 2) Operative Time (n = 214): a) IA (n = 111) b) TIVA (n = 103)	EBL Surgical visualization Operative time Failure of deliberate hypotension Mortality within 24 hours	Controlled hypotension with TIVA may improve visualization.
DeConde[1835]	2013	1	Systematic review of RCTs	IA (n = 269) TIVA (n = 249)	Heart rate Mean arterial pressure Anesthesia time Operative time EBL Surgical visualization	TIVA may improve surgical field, but this is based on low quality studies
Kelly[1836]	2013	1	Systematic review of RCTs	7 studies qualitatively reviewed	No meta-analysis	Mixed results with severe limitations in studies

Brunner[1838]	2018	2	RCT, double-blind	IA (n = 33) TIVA (n = 37)	1) Surgical visualization (Wormald) 2) EBL 3) Operative time 4) Time in PACU 5) Time to discharge	Higher disease load decreased visualization
El-Shmaa[1856]	2017	2	RCT, blinded	B-blocker Nitroglycerin Both groups IA	MAP Heart rate EBL Surgeon satisfaction scale 1-4	Controlled hypotension MAP 60 B-blockers less EBL and higher surgeon satisfaction
Ha[1854]	2016	2	RCT	n=36 (356 time point observations)	MAP Heart rate Middle cerebral artery blood flow Surgical visualization (Wormald)	Controlled hypotension MAP correlated with surgical visualization and cerebral blood flow MAP > 60 safe
Ha[1853]	2014	2	RCT	N=8 (105 time point observations)	MAP Heart rate Middle cerebral artery blood flow Surgical visualization (Wormald)	Controlled hypotension MAP correlated with surgical visualization and cerebral blood flow MAP > 60 safe
Cho[1841]	2012	2	RCT, single-blind	IA (n = 32) TIVA (n = 36)	Operative time Mean arterial pressure Heart rate Change in hemoglobin Surgical visualization	TIVA improved surgical visualization, particularly in patients with high LMS
Ankichetty[1843]	2011	2	RCT, double-blind	IA (n = 40) TIVA (n = 40)	Time to optimal MAP EBL Operative time Surgical visualization (Boezaart)	Controlled hypotension in higher LMS improved visualization

					5) Complication rate	
Ragab[1844]	2010	2	RCT	IA (n = 35) TIVA (n = 35)	Heart rate Blood pressure Operative time EBL Surgical visualization (VAS and Boezaart)	Controlled hypotension improved visualization with TIVA.
Yoo[1831]	2010	2	RCT, double-blind	TIVA (n = 20) IA w/ sevoflurane (n = 20) IA w/ desflurane (n = 20)	Surgical visualization (Boezaart) Heart rate MAP	No significant differences in surgical visualization with controlled hypotension MAP 65
Wormald[1847]	2005	2	RCT	TIVA (n = 28) IA (n = 28)	MAP Heart rate EBL Surgical visualization (Boezaart)	Controlled hypotension improved visualization with TIVA
Eberhart[1850]	2003	2	RCT, double-blind	TIVA (n = 45) IA (n = 43)	MAP Heart rate EBL Surgical visualization (Fromme) Surgical visualization (VAS)	Controlled hypotension MAP 50-60 TIVA better visualization
Farzanegan[1855]	2018	3	Prospective observational trial	n=41	MAP Heart rate EBL Cerebral oxygenation	Controlled hypotension MAP >55 maintained cerebral oxygenation

XII.A.5. Perioperative Pain Management and Opioid Reduction

According to a recent national survey, post-operative opioid analgesics are prescribed by up to 95% of providers following sinonasal surgery. However, increasing evidence suggests that patients only require a small portion of the prescription for adequate pain control, and the majority of the medication remains unused.[1857-1859] Therefore, the judicious prescribing of opioids after rhinologic surgery coupled with adjunctive non-opioid use represents a practical opportunity for otolaryngologists to reduce the

amount of opioid medication prescribed. This section will review studies of postoperative analgesia regimens as well as several reports of non-opioid adjuncts to reduce immediate postoperative pain.[1860,1861]

Pain-relieveing efficacy in scheduled post-operative dosing of oral acetaminophen for analgesia after sinonasal surgery has been reported.[1862] In addition to the use of oral acetaminophen, several recent RCTs have also demonstrated effectiveness in pre-operative intravenous dosing of acetaminophen.[1863-1865] Both of these interventions have demonstrated reduction in immediate postoperative pain and decreased opioid requirements.[1863-1865] Acetaminophen's effectiveness at controlling post-operative pain, excellent safety profile, and ability to be used safely in most NSAID intolerant patients makes its use as first line analgesia strongly recommended.

Several RCTs utilizing NSAIDs for perioperative pain control in sinonasal surgery have demonstrated reduced opioid consumption.[1861,1866-1870] Moeller *et al.*[1868] demonstrated that IV ketorolac is an effective analgesic in the setting of sinonasal surgery with similar effects to IV fentanyl, without increasing the risk of hemorrhage. Turan *et al.*,[1866] meanwhile, showed that the use of pre-operative rofecoxib, a COX-2 inhibitor, resulted in decreased pain scores, reduced the use of rescue analgesia, and prolonged times to first analgesic requirement. More recently, Wu *et al.*[1871] performed a multicenter cohort study comparing two groups of patients undergoing sinonasal surgery, one treated with acetaminophen/hydrocodone as the primary post-operative pain control regimen and one treated with ibuprofen and acetaminophen as the primary regimen with acetaminophen/hydrocodone for breakthrough pain. Total opioid use and patient reported pain scores were decreased in the group treated with Ibuprofen when compared to the cohort treated with opioids.

Several studies reported that the administration of local anesthetics in sinonasal surgery, including lidocaine and bupivacaine, as either injection or infused in post-operative nasal packing led to decreased VAS scores and lower analgesic requirements.[1861,1872] Other studies have reported the use of sphenopalatine ganglion block or infraorbital nerve block to provide analgesia by targeting the sensory innervation of the nasal mucosa.[1873,1874]

Dexmedetomidine, a highly selective α2 adrenergic receptor agonist, is often utilized in the practice of anesthesia as it produces sedation, anxiolysis, and analgesia without causing respiratory depression. Administration prior to sinonasal surgery was found to result in significant reductions in VAS pain scores compared with placebo-saline solutions.[1875]

Pregabalin and gabapentin are new generation anticonvulsants with anti-hyperalgesic and anti-nociceptive properties. Although these medications are US FDA approved for the treatment of seizures and neuropathic pain, they are frequently used off-label for the treatment of other types of acute and chronic pain, including in peri-operative pain management. The use of pre-emptive gabapentinoids in nasal surgery has been well documented in several RCTs, with the majority reporting significantly lower VAS pain scores compared to placebo.[1876-1881]

In summary, there is growing evidence that opioid use after sinus surgery is decreasing and non-opioid alternatives are gaining acceptance. Future studies that continue to validate the use of alternative medications will hopefully lead to a reduction in opioid prescription and use.

Table XII-3. Summary of evidence for perioperative pain management

Analgesic Type	Aggregate Grade	Benefit	Harm	Cost	Benefit-Harm Assessment	Value Judgments	Policy Level	Intervention
Acetaminophen	B (Level 2: 3 studies, Level 3: 1 study)	Safe analgesic, effectively controls postoperative pain and reduces need for opioids.	GI upset, toxicity (>3000 mg)	Low for PO, High for IV	Preponderance of benefit over harm	Safe, effective, low cost analgesic for PO formulation.	Recommend PO formulation	First line PO analgesia in post-operative patients.
NSAIDs	A (Level 2: 7 studies, Level 3: 1 study)	Safe, analgesic, effectively controls postoperative pain and reduces need for opioids.	Interferes with platelet function and bleeding time. NSAID intolerance in patients with AERD. May exacerbate kidney dysfunction.	Low	Balance of benefit and harm	Effective, low cost analgesic, but should not be used in intolerant patients.	Option	Analgesia option in patients who do not have intolerance, kidney dysfunction.
Local anesthetics	B (Level 2: 9 studies, Level 3: 3 studies)	As a peripheral nerve block-reduces need for opioid analgesia. When soaked in a topical nasal pack-effectively	Minimal risk – local irritation, edema, toxicity (4.5m/kg)	Low	Preponderance of benefit over harm	Intraoperative nerve blocks are effective, safe, reliable method to control postoperative pain.	Recommend	Easy, quick, and effective in providing analgesia when performed intraoperatively.

		reduces pain and enhances comfort.						
Alpha-2 Agonists	B (Level 2: 5 studies, Level 3: 3 studies)	Provides sedation, anxiolysis, and analgesia without causing respiratory depression	Minimal risk-hypotension bradycardia, dry mouth.	High	Balance of benefit and harm	Value is limited relative to the cost; pain benefit is short lived.	Option	Can be a consideration to use intraoperatively.
Gabapentinoids	A (Level 2: 4 studies)	Effective in chronic pain, can help reduce opioid analgesic use postoperatively.	Dizziness, drowsiness, headache, nausea, vomiting,	Moderate	Balance of benefit and harm	Off label indication; Reduces pain scores and need for other analgesics, but there is potential for drowsiness.	Option	Can be a consideration in multi-modality pain control.

Table XII-4. Evidence for non-opioid analgesics following sinus surgery

Study	Year	LOE	Design	Study Groups	Clinical Endpoints	Conclusion
Acetaminophen						
Tyler[1865]	2017	2	Prospective, DB RCT	Acetaminophen 1g IV (31) Saline IV (29)	VAS at 15, 30, 45, and 60 minutes, and 2, 12, and 24 hours Rescue morphine consumption in first 6 hours Adverse effects Patient satisfaction	Inconclusive results. The data suggest that perioperative IV acetaminophen may reduce immediate post-op pain and opioid requirements compared to placebo.

Koteswara[1864]	2014	2	Prospective, DB RCT	Acetaminophen 1g IV, 15 minutes before induction (20) Acetaminophen 1g IV at the end of surgery (19)	VAS Time to first analgesic requirement Total analgesic consumed in 24 hours	Pre-emptive IV acetaminophen provided effective and reliable postoperative analgesia after ESS compared to intraoperative paracetamol.
Kemppainen[1863]	2006	2	Prospective, DB RCT	Acetaminophen 1g IV (36) Saline IV (38)	NRS Time to oxycodone use Total oxycodone use Need for rescue analgesia	Acetaminophen provides adequate pain relief in most patients, but may be insufficient by itself.
Kemppainen[1862]	2007	3[a]	Prospective, DB RCT	Scheduled acetaminophen 2 tablets 665mg, 3 times daily (38) As needed (PRN) acetaminophen 665mg (40)	Return to normal daily activities	Scheduled acetaminophen for 5 days after surgery leads to effective pain control without the need for opioid analgesics.
NSAIDs						
Moeller[1868]	2012	2	Prospective, DB RCT	Ketorolac 30mg IV (16) Fentanyl 25μg IV (18)	Postoperative VAS 0, 30, 60 minutes Supplemental analgesia POD 1, and POD 7 questionnaire Hemoglobin levels; bleeding	Ketorolac IV is a safe analgesic in the setting of primary ESS without increased risk of hemorrhage or acute blood-loss anemia. It provided similar analgesia to fentanyl IV.
Keles[1882]	2010	2	Prospective, DB RCT	Piroxicam-β-cyclodextrin 20 mg PO (25) Piroxicam-β-cyclodextrin 40 mg PO (25) Placebo PO (25)	Postoperative VAS at 30 minutes, and 1, 2, 4, 6, and 24 hours Morphine consumption	Preemptive administration of piroxicam-β-cyclodextrin effectively reduces analgesic consumption, with 40 mg of the drug more effective

						than the 20-mg dose, without side effects.
Leykin[1883]	2008	2	Prospective, DB RCT	Parecoxib 40mg IV (25) Ketorolac 30mg IV (25) dosed intraoperatively and q8 hours post-op.	Postoperative VAS at 10, 20, and 30 minutes, and 1, 2, 3, 4, 5, 6, 12, 24 hours Morphine consumption	When given with intraoperative local infiltration with 1% mepivacaine, parecoxib is as effective in treating early postoperative pain as ketorolac.
Leykin[1884]	2008	2	Prospective, DB RCT	Parecoxib 40mg IV (25) Proparacetamol 2g IV (25)	Postoperative VAS at 10, 20, and 30 minutes, and 1, 2, 3, 4, 5, 6, 12, 24 hours Morphine consumption.	When given with intraoperative local infiltration with 1% mepivacaine, parecoxib is not superior to proparacetamol
Church[1885]	2006	2	Prospective, DB RCT	Hydrocodone/ acetaminophen 7.5/750mg PO (14) Rofecoxib 50mg PO (14)	Postoperative VAS at PODs 1, 2, 3, and 4 Requirement for rescue analgesia Adverse events Patient satisfaction	The use of nonopioid analgesics after ESS may provide similar pain control to oral opioids.
Turan[1866]	2002	2	Prospective, DB RCT	Rofecoxib 50mg PO (30) Placebo PO (30)	Postoperative VAS at 30 minutes and 2, 4, 6, 12, and 24 hours Intraoperative VRS at 5, 15, 30, 45, and 60 minutes Total fentanyl consumption Time to first analgesic need	Preoperative administration of rofecoxib provides a significant analgesic benefit for intraoperative and postoperative pain relief and decreased the need for opioids after nasal surgery.
Elhakim[1886]	1991	2	Prospective, DB RCT	Ketoprophen IV (30) Pethidine IV (30)	Postoperative VAS at 1, 2, and 4 hours	A single IV dose of ketoprofen during anesthesia is an

					Opioid consumption Adverse events	effective alternative to pethidine and provides lower pain scores and faster recovery.
Wu[1871]	2019	3	Prospective cohort study	NSAID group – ibuprofen 200mg, acetaminophen 325mg, hydrocodone-acetaminophen 5/325mg rescue PO (101) Non-NSAID group - acetaminophen 325mg, hydrocodone-acetaminophen 5/325mg PO (65)	Postoperative VAS scores Mean opioid pills taken Bleeding rate	The introduction of NSAIDs to acetaminophen and opioid pain regimen results in reduced pain and overall opioid use.
Local Anesthetic						
Al- Qudah[1873]	2013	2	Prospective, DB RCT	Saline injection (30) Lidocaine injection (30)	Postoperative VAS immediately after surgery, 6, and 24 hours after surgery	SPG injection of 2% lidocaine with epinephrine effectively reduces pain and need for analgesia after ESS.
Cekic[1874]	2013	2	Prospective, DB RCT	Levobupivicaine injection (15) Levobupivicaine + tramadol injection (15) Saline injection (15)	Postoperative NRS at 1, 2, 4, 6, and 12 hours Time to first analgesic dose Total meperidine requirement	Bilateral infraorbital nerve block with 0.25% levobupivacaine is an effective technique in the treatment of postoperative pain in nasal surgery and can be used safely with adjuncts.
Mo[1887]	2013	2	Prospective, DB RCT	Lidocaine-soaked polyurethane foam pack (31) Saline-soaked	Postoperative VAS at 1, 4, 8, 16, 20 and 24 hours after	Lidocaine-soaked packs significantly reduced postoperative pain

				polyurethane foam pack (32)	surgery Blood soaked guaze Vital signs	without significant changes to vital signs.
DeMaria[1888]	2012	2	Prospective, DB RCT	Lidocaine injection (35) Saline injection (35)	Recovery time Postoperative NRS every 15 minutes until discharge Adverse events Opioid consumption	Regional anesthesia using SPG blockade appears to shorten hospital stay and reduce narcotic requirements immediately post-operatively, but loses these effects after 24 hour in ESS patients.
Kesimci[1889]	2012	2	Prospective, DB RCT	Bupivacaine injection (15) Levobupivacaine injection (15) Saline injection (15)	Postoperative VAS at 2, 6, and 24 hours after surgery Additional analgesics required	SPG block with bupivacaine or levobupivacaine improved postoperative analgesia compared to saline control with good patient and surgeon satisfaction.
Cho[1890]	2011	2	Prospective, DB RCT	Bupivacaine injection (29) Saline injection (27)	Postoperative VAS POD 0, 7, 30. SNOT-20 CT/ Endoscopy scores	There was a trend towards reduced postoperative pain with bupivacaine compared to saline after ESS.
Mariano[1891]	2009	2	Prospective, Triple-Blinded RCT	Bupivacaine injection (20) Saline injection (20)	Duration of post anesthesia recovery Pain scores	Bilateral infraorbital bupivacaine does not decrease actual time to discharge after outpatient nasal surgery despite a beneficial effect on postoperative pain following GA in ESS patients.

Higasahawa[1892]	2001	2	Prospective, DB RCT	Bupivacaine injection (15) Saline injection (25)	Isoflurane consumption Postoperative pain intensity at 15 minutes	Infraorbital nerve block with general anesthesia is effective in reducing the consumption of isoflurane and postoperative pain intensity in ESS.
Friedman[1893]	1996	2	Prospective, DB RCT	Lidocaine injection (39) Bupivacaine injection (44)	Postoperative NRS at 2, 6, and 24 hours Analgesic requirement	Long acting anesthetic agent bupivacaine provided similar analgesia to shorter acting anesthetic agent lidocaine.
Rezaeian[1894]	2019	3[c]	Prospective, RCT	Bupivacaine injection (20) Saline injection (20)	VAS at immediately post-op, 6, 12, 24, 48 hours and 7 and 21 days after surgery	SPG block with bupivacaine was a simple, safe, and effective method to manage post-operative pain afer ESS.
Haytoglu[1895]	2016	3[b]	Prospective, RCT	Lidocaine sinus pack (30) Bupivacaine sinus pack (30) Ropivacaine sinus pack (30) Prilocaine sinus pack (30) Saline sinus pack (30)	Postoperative VAS at 1, 2, 4, 8, 12 and 24 hours Requirement for rescue analgesia Presence of synechia	Bupivacaine nasal packs resulted in lower pain values, less additional analgesia, and less nasal discharge and bleeding after ESS.
Yilmaz[1872]	2013	3[d]	Prospective, DB RCT	Levobupivavaine hydrochloride sinus pack (20) Saline sinus pack (21)	Postoperative VAS at 30 minutes and 1, 2, 8, 12, 24 hours Rescue analgesia consumption	Use of levobupivavaine packs after ESS is an effective method to control postoperative pain and improves patient comfort/ tolerability compared to saline control.
Alpha $_2$ – Agonists						

Karabayirli[1896]	2017	2	Prospective, DB RCT	Dexmedetomidine IV (25) Remifentanil IV (25)	Postoperative VAS Surgical field/ bleeding Adverse effects Rescue analgesia demand Sedation score	Compared with remifentanil, DEX during ESS showed limited hemodynamic benefits, but it is associated with faster recovery.
Tang[1860]	2015	2	Prospective, DB RCT	Dexmedetomidine nasal (30) Placebo nasal drops (30)	Postoperative VAS at 2, 4, 8, 12, 24, and 48 hours Hemodynamics Stress hormones Inflammatory marker levels	Intranasal DEX with local anesthesia used in ESS resulted in decreased perioperative stress and inflammatory response improved analgesia, and better hemodynamic variables as well as satisfaction scores.
Lee[1897]	2013	2	Prospective, DB RCT	Dexmedetomidine IV (32) Remifentanil IV (34)	Surgical field conditions Hemodynamic parameters Sedation score Pain in PACU	There was no difference in the operative field, or post-operative pain scores for remifentanil and DEX in ESS.
Guven[1875]	2011	2	Prospective, DB RCT	Dexmedetomidine IV (20) Saline solution IV (20)	Hemodynamics Postoperative VAS at 30 minutes and 24 hours Side effects	Using DEX resulted in improved intraoperative bleeding, hemodynamic stability and postoperative VAS scores.
Karaaslan[1898]	2007	2	Prospective, DB RCT	Dexmedetomidine IV (35) Midazolam IV (35)	Postoperative VRS Consumption of tramadol Patient	Both DEX and midazolam provided adequate analgesia and sedation in those

					satisfaction scores Adverse Events	undergoing nasal surgeries, with higher amounts of rescue tramadol used in the midazolam group
Kim[1899]	2015	3	Prospective, Cohort Study	Dexmedetomidine IV (18) Remifentanil IV (21)	Surgical field visualization Hemodynamic parameters Postoperative VAS	Both remifentanil and DEX provided similar surgical field visualization, hemodynamic stability, and post-operative pain scores.
Wawrzyniak[1900]	2014	3[e]	Prospective DB RCT	Clonidine IV (20) Midazolam IV (20)	Anesthetic requirement Hemodynamic profile Pre-operative anxiety/ sedation Postoperative VAS	Premedication with clonidine provided more favorable hemodynamic parameters and better pain control compared to midazolam.
Gabapentinoids						
Rezaeian[1901]	2017	2	Prospective, DB RCT	Scheduled Pregabalin 50mg 3 times daily PO (35) Scheduled Acetaminophen 500mg, 4 times daily PO	VAS at immediately post-op, 12, 24, 48, and 72 hours Adverse events	Pregabalin is more effective and with lower adverse events compared to acetaminophen for patients undergoing ESS
Mohammed[1902]	2012	2	RCT	Gabapentin 1.2g PO (40) Placebo PO (40)	Hemodynamics Postoperative VAS at 1hour Opioid usage Adverse events	Gabapentin decreased dose requirements of intraoperative hypotensive agent and postoperative morphine, without signifcant side effects.
Kazak[1879]	2010	2	Prospective, DB RCT	Gabapentin 600mg PO (30)	Intraoperative VAS at 5, 15,	Monitored anesthesia care

				Placebo PO (30) given 1 h prior to surgery	30, 45, and 60 minutes Postoperative VAS at 30 minutes and 2, 4, 6, 12, and 24 hours Total consumption of remifentanil and propofol Time to first analgesic need	combined with preoperative analgesia with a low dose of (600 mg) oral gabapentin is an efficient option with tolerable side effects.
Turan[1880]	2004	2	Prospective, DB RCT	Gabapentin 1200mg PO (25) Placebo PO (25) given 1h prior to surgery	Intraoperative VRS at 5, 15, 30, 45, and 60 minutes Postoperative VAS at 30 minutes and 2, 4, 6, 12, and 24 hours Total fentanyl consumption Time to first analgesic need	Gabapentin provides a significant analgesic benefit for intraoperative and postoperative pain relief in patients undergoing nasal surgery, but is associated with increased risk of dizziness.

[a] Downgraded due to outcome measures used.
[b] Downgraded due to no randomization
[c] Downgraded due to no blinding
[d] Downgraded due to randomization not described
[e] Downgraded due to VAS only assessed at one time point

XII.A.6. Sinus Surgery Utilization Trends and Variation

Recent studies estimate the utilization of ESS in the United States as between 0.94[1903] to 1.17[1904] cases per 1000 persons, or about 320,000 cases per year. This is somewhat higher than rates of surgery published in Europe, with around 0.71 cases per 1000 persons.[1905] Evidence suggests that population-adjusted rates of ESS may be decreasing, with one study showing a 24% reduction between 2005-2011 in California.[1906] Concurrently, balloon catheter dilation (BCD) has become increasingly adopted by some otolaryngologists as a procedural management option for CRSsNP,[1907-1910] with one analysis of a Medicare database demonstrating a 486% increase in utilization from 2011 to 2017.[1788] While one hypothesis for the decrease in population ESS rates may be that balloon catheter dilation (BCD) techniques are supplanting traditional ESS procedures, it appears that the overall number of ESS procedures over this timeframe has remained relatively stable,[1907,1908] and providers who performed more BCDs did not reduce their volume of other sinus procedures.[1911] Interestingly, when comparing diagnosis codes between ESS and BCD patients, a significantly higher prevalence of headache disorder, facial pain, allergic rhinitis was noted in patients undergoing BCD,[1912] suggesting that balloon sinus dilation may be used in a different patient population than the traditional ESS cohort. Utilization of balloon sinus dilation also appears to be significantly associated with financial support from industry in two studies,[1911,1913] although the authors note evidence for a causative effect is limited.

There is substantial geographic variation of ESS utilization, as noted by a recent study by Rudmik *et al.*[1] that found a 5-fold difference between U.S. regions with the highest rates of ESS utilization compared to those with the lowest, in agreement with prior studies.[1914] A similar finding was noted in a study of state ambulatory surgery databases, which also found variations based on surgeon volume and payer type for CRSwNP patients.[1915] This problem is not unique to the U.S. healthcare system, as studies in Canada[1903] have also found similar regional variations. Significant differences in utilization based on ethnicity and payer are also present, as demonstrated by Woodard *et al.*, who showed the rate of ESS in a Medicaid population was only 0.40 per 1000 persons, substantially lower than the average.[1916] Sex-adjusted rates of ESS for Hispanic and African American patients were also significantly lower than Caucasians in this study across all age groups. The primary drivers of these discrepancies remain an area of active investigation.

XII.B: Indications for Sinus Surgery

XII.B.1. Appropriate Medical Management

Statements regarding indications for sinus surgery invariably cite “failure of maximal medical therapy” (MMT) as a requirement before proceeding. Surgery without a prior trial of medical treatment is, and should be, uncommon. While there is great consistency between guidelines regarding the need for such a trial, there remains significantly less consensus on what MMT entails. Additional factors to consider include definitions of failure of MMT, the economics of continued medical therapy, and comparative clinical outcomes between MMT and surgery. There has been limited additional published evidence on this topic since the ICAR-RS-2016 publication.[1] Thus this version will serve as an update, where appropriate, of the work the previous authors presented.

It has now been established that prolonging the time between diagnosis and surgery for CRS may negatively impact outcomes.[95,1917,1918] The term “maximal “ medical therapy has thus fallen out of favor, inasmuch as it implies surgery should be delayed until all available options have been exhausted.

Therefore, instead of using the term "maximal medical therapy", the term "appropriate" medical therapy (AMT) will continue to be used in this updated document. AMT is used in order to suggest striking a balance between proceeding to surgery before appropriate nonsurgical options have been tried and delaying too long so that outcomes are negatively impacted. (In referring to past work regarding "maximal" medical therapy in this review, the MMT term will be retained.)

XII.B.1.a. What is appropriate medical therapy (AMT)?

The development of a sturdy definition of AMT remains elusive, likely due in part to the significant heterogeneity inherent in RS.[278] While there are numerous studies evaluating the efficacy of individual drug classes in the treatment of CRS, discussed elsewhere in this ICAR-RS-2021 document, there are no clinical trials evaluating the optimal combination of drugs. There are several guidelines where recommendations are made, and these generally demonstrate consistency with regard to inclusion of INCS and saline irrigation, with more selective use of oral corticosteroids and antibiotics (Table XII-5).[26,526,1919] A systematic review from 2015 demonstrated that INCS, oral antibiotics, and oral corticosteroids were used in 91%, 88%, and 62% of all MMT protocols for a mean of 8 weeks, 23 days, and 18 days, respectively.[1920]

While incorporating the best available evidence into a recommendation for AMT, including evidence from this ICAR-RS-2021 document, a few key points should be remembered. First, addition of surgery into the benefit-harm assessment, with its own potential benefits, harms, and costs, alters this balance. Second, AMT is typically given as a combination of therapies, and traditional recommendations for therapy in CRS address them as single modalities. Third, as a result of the lack of trials of optimal therapy combinations, the best we can provide at this point are consensus recommendations extrapolated from available evidence. Current recommendations here do not differ from those provided in ICAR-RS-2016.

Intranasal Corticosteroid Sprays. Given the favorable balance of benefit to harm for INCS use, there is little debate to include this treatment in AMT protocols.

Saline Irrigations. The same is true of saline irrigations. They should be included in AMT protocols.

Oral Corticosteroids. The inclusion of a short course of oral corticosteroids should be considered separately for CRSwNP and CRSsNP, based on differing amounts of evidence and recommendations for each condition.

For CRSwNP, the best available evidence and balance of benefits and harm appear to favor a single short course of oral corticosteroids. Section X.D.3 summarizes this evidence and recommends their use. It should be noted however, that repeated or prolonged trials may not be beneficial. Leung *et al.*'s economic analysis of potential complications demonstrated that a breakeven threshold favors surgery over medical therapy when CRSwNP patients required oral corticosteroids more than once every 2 years.[1615]

For CRSsNP, given the generalized lack of evidence and risk of significant adverse events, it is challenging to provide a recommendation to include oral corticosteroids in an AMT protocol. The efficacy of oral corticosteroids in CRSsNP is unknown (see Section IX.D.3).

Oral Antibiotics. As in the case of oral corticosteroids, it is helpful to differentiate recommendations for CRSwNP and CRSsNP.

Antibiotic use in CRSsNP is reviewed in Section IX.D.4, where insufficient evidence is found to recommend for or against their use in the case of nonmacrolide antibiotics. Macrolide antibiotics are found to be an option in CRSsNP. As part of possible AMT, the benefit-harm assessment for antibiotics changes once surgery is in the balance. Antibiotics are therefore recommended for AMT in CRSsNP.

Section X.D.4 reviews antibiotic use in CRSwNP and recommends against courses <3 weeks for non-AECRS. No evidence was found regarding nonmacrolide courses longer than 3 weeks and, as in CRSsNP, macrolides are considered to be an option in CRSwNP. In balancing these potential harms and benefits against those of surgery, antibiotics should be considered an option for AMT in CRSwNP.

There is divergence regarding the choice of antibiotics. North American guidelines advocate the use of culture-directed antibiotics, or in the absence of culture data, a broad-spectrum antibiotic such as amoxicillin-clavulanate. In contrast, EPOS bases their recommendations on antibiotic-associated anti-inflammatory effects; thus, long-term macrolides are considered optional for patients with CRSsNP. The prior 2012 edition of EPOS included doxycycline as a management option for CRSwNP, however the updated 2020 version no longer recommends this as an option. The ICAR-RS-2016 statement found insufficient evidence to recommend one class of antibiotics over another in an AMT protocol.

Surveys of otolaryngologists from around the world (Table XII-6) reveal broad adherence to combination treatment recommendations. This does not confirm the effectiveness of such regimens, but does suggest acceptance of published guidelines. Newer surveys are needed that investigate “appropriate” medical therapy specifically, and combination therapies.

In summary, the evidence for what should constitute AMT prior to surgical intervention is lacking. Recommendations are given based on available evidence, but the grade of evidence is D, leading to weak strength of recommendation.

Appropriate Medical Therapy Prior to Surgery

Aggregate Grade of Evidence: D.
Benefit: Symptomatic improvement; avoidance of risks and costs of surgical intervention.
Harm: Risk of medication adverse events, potential for increasing antibiotic resistance (see Table II-2).
Cost: Direct cost of medications and management of adverse events.
Benefits-Harm Assessment: Differ for particular therapy and clinical scenario.
Value Judgements: Perceived lower risk of antibiotic treatment versus risks of surgery, although evidence has shown a low breakeven threshold for surgery versus oral corticosteroids. Additional evidence is needed in assessing antibiotic vs. surgery benefit-harm balance. Clearly, patient preference plays a large role in the decision to continue medical therapy or to proceed with surgery.
Policy level: Recommendation, though weak based on strength of evidence
Intervention: *For CRSsNP:* Appropriate medical therapy prior to surgical intervention should include INCS, saline irrigations, and antibiotics. Oral corticosteroids are an option. *For CRSwNP*: Appropriate medical therapy prior to surgical intervention should include a trial of INCS, saline irrigations, and a single short course of oral corticosteroids. Oral antibiotics are an option.

Table XII-5. Evidence for appropriate medical therapy prior to surgery

Guideline	Antibiotics	INCS	Systemic corticosteroids	Saline Irrigation	Other
AAOA Guidelines 2009[526]	Yes	Yes	Yes for CRSwNP or CRSsNP if initial 2 week treatment fails	Not specified	Oral or topical decongestants
AAO-HNS Guidelines 2015[88]	Yes – culture directed	Optional	Optional	Optional	Treatment of AR
BSACI 2008[1921]	macrolide antibiotics	Yes	Yes in mod/severe CRSwNP; No for CRSsNP	Yes	Leukotrienes optional in AERD patients; Antihistamines for AR
Canadian Guidelines 2011[151]	Yes – culture directed	Yes	Yes in CRSwNP; Optional in CRSsNP	Optional	Leukotrienes optional in AERD patients
EPOS 2020[26]	Optional long term macrolides for CRSsNP	Yes	Optional	Yes	

Table XII-6. Results of surveys to establish medical therapy trial prescribing habits prior to surgery

Survey	Antibiotics	INCS	Systemic corticosteroids	Saline Irrigation	Other
AAOHNS Survey 2006, n=80[1197]	94%	94%	34%		47% oral decongestants 47% mucolytics
ARS Survey, 2007 n=308[1922]	51% always, 30% almost always		10% always, 20% almost always		
Chinese Oto-HNS Alliance Survey, 2020 n=134[1923]	19% always, 34% often	51% always, 40% often	3% always, 12% often	35% always, 45% often	
ENTUK Survey, 2013, n=159[1924]	92%	61% always, 27% sometimes	4% always, 30% sometimes	23% always, 42% sometimes	3% antihistamines 4% topical decongestants

XII.B.1.b. How long should appropriate medical management last?

There are no published RCTs addressing the optimal duration of AMT, or its individual components when specifically used in this setting. A recent meta-analysis demonstrated benefit with half-dose macrolide

therapy when used for a duration of 24 weeks in patients with CRSsNP, although this effect was seen in a diverse population (presurgical, concurrent ESS, and postsurgical).[1121]

Recommendations diverge with respect to guidelines, with European groups allowing for a prolonged course of low-dose macrolides in CRSsNP, while North American groups recommend a longer course than would be prescribed in ABRS, but up to a maximum of 4 weeks (Table XII-7). This is reflected in clinical practice with 1 in 4 specialists using a course of 6 weeks or more in the UK, compared with less than 1 in 30 amongst US rhinologists (Table XII-8).

Duration of Medical Therapy Prior to Surgery

Aggregate Grade of Evidence: D.
Benefit: Symptomatic improvement; avoidance of risks and costs of surgical intervention.
Harm: Risks of medication adverse events, potential of increasing antibiotic resistance.
Cost: Direct cost of medications and management of adverse events.
Value Judgements: Low risk of treatment and delay of surgery versus risks of surgery considered in recommending a 3-4 week trial.
Policy Level: Recommendation, though weak based on strength of evidence.
Intervention: A trial of 3-4 weeks of AMT should be considered as the minimum.

Table XII-7. Duration of medical therapy trials prior to surgery recommended by major guidelines

Guideline	Antibiotics	INCS	Systemic corticosteroids	Saline Irrigation
AAOA Guidelines 2009[526]	3-4 weeks	At least one month	8-12 days	Not specified
AAO-HNS Guidelines 2015[88]	2-4 weeks	Not specified	Not specified	Not specified
Canadian Guidelines 2011[151]	'Slightly longer than for ABRS'	Not specified	2 weeks in CRSwNP; Optional in CRSsNP	Not specified
EPOS 2020[26]	Not explicitly stated	6-12 weeks	1-3 weeks	6-12 weeks
BSACI 2007[1921]	12 weeks of macrolide antibiotics	Not specified	5-10 days	Yes

Table XII-8. Results of surveys to establish duration of prescribed medical therapy trials prior to surgery

Survey	Antibiotics	INCS	Systemic corticosteroids
ENT UK Survey, 2013, n=159[1924]	<2 weeks: 29% 2-4 weeks: 26% >6 weeks 26%	3-6 months: 67%	0-5 days: 42%, 6-10 days: 29% 11-15 days: 29%

ARS Survey, 2007 n=308[1922]	0-2 weeks: 12% 2.1-3 weeks: 37% >6 weeks: 3%	Not specified	0-5 days: 7% 6-14 days: 67%
AAOHNS Survey 2006, n=80[1197]	Mean duration >5 weeks	Mean duration 6 weeks	Mean duration 1 week
Chinese Oto-HNS Alliance Survey, 2020 n=134[1923]	<2 weeks: 53% 1-3 weeks: 12% 1-4 weeks: 19% 1-6 weeks: 8% >6 weeks: 7%	Not specified	<2 weeks: 81% 1-3 weeks: 7% 1-4 weeks: 5% 1-6 weeks: 4% >6 weeks: 3%

XII.B.1.c. When should AMT be deemed to have failed?

Failure of AMT has been broadly defined as insufficient symptomatic response to AMT in the presence of continued radiological or endoscopic evidence of CRS. However, the question of what exactly constitutes certain metric thresholds in this setting of failure have not been studied specifically. Instead, clinicians have investigated "appropriateness criteria" for surgery, using RAND/UCLA methodology as an attempt to define the transition from AMT to surgical candidacy.[283] This group deemed that in patients with CRSwNP, surgery can be appropriately offered when the Lund-Mackay score is ≥1 and a SNOT-22 of ≥20 following treatment with INCS (8 weeks duration or greater) and a short course of oral corticosteroids (1-3 weeks duration). The recommendation for CRSsNP is similar, but instead of oral corticosteroids, the panel decided upon a short-course of broad spectrum/culture-directed antibiotics (2-3 weeks duration), or a prolonged course of a low dose anti-inflammatory antibiotic (12 weeks duration or greater).

XII.B.1.d. What is the response rate and long-term control rate following MMT/AMT?

The response rate to previous trials of MMT varies between 30.4% and 90% (Table XII-9).[1092,1094,1096,1925,1926] Fewer studies are available regarding AMT specifically. A recent study by Speth *et al.* demonstrated a reduction in systemic corticosteroid and antibiotic use for patients on AMT (INCS and nasal saline rinses).[1927]

It is accepted the CRS has a chronic relapsing course, but the long-term fate following a successful trial of medical therapy is not well reported. However, the success of continued medical therapy can be used as a proxy for this outcome. A 2017 meta-analysis comparing continued medical therapy to sinus surgery demonstrated significantly improved QoL and endoscopic scores for patients undergoing surgery.[1928]

Table XII-9. Reported response rates to medical therapy trials prior to surgery

Study	Intervention	Outcome Measured	Response Rate	LOE
Lal [1094]	4 weeks amoxicillin-clavulanate, 12 days oral corticosteroid, 4 weeks INCS, 4 weeks	Complete resolution of symptoms	51.03% 17.8%	4

	saline rinse	Partial response		
Dilidaer [1925]	Not specified	Complete control	30.4%	3
Young [1092]	3 weeks oral prednisolone, antibiotics, INCS and saline rinses	Improvement in symptoms sufficient to avoid surgery	37.5%	4
Subramanian [1096]	4 weeks antibiotics, INCS, saline rinses, 10 days prednisolone	Improvement in symptoms sufficient to avoid surgery	90%	4
Baguley [1926]	3 weeks prednisolone, 4-6 weeks INCS, saline rinse, optional 20 days antibiotics	Control = symptoms resolved or no longer bothersome	38%	4

XII.B.2. Timing of Sinus Surgery

Capacity issues in the UK's National Health Service, a publicly funded healthcare system, and pathway restrictions result in many patients having sinus surgery after many years of persistent symptoms; more than 50% of patients have an interval of more than 5 years since the onset of CRS symptoms before their first surgery. In this context, Hopkins *et al.*, studied the impact of timing of surgery on outcomes. Data from both the UK prospective audit of surgery for CRS and UK primary care electronic datasets were analyzed.[95,1917] Patients were classified according to the duration of their CRS until their first surgical intervention for CRS. Three cohorts of patients were defined: early cohort – less than 12 months; mid cohort – 12-60 months; and late cohort – more than 60 months of symptoms. 1493 patients having primary surgery were identified; 11.5% in the early group, 50.2% in the mid group and 38.2% in the late group. Patients in the early group had not only a greater percentage improvement in their symptoms, but the improvement was better maintained over five years. At five years there was a significantly higher proportion of patients in the early group maintaining a clinically significant improvement over baseline (71.5%) than in either the mid (57.3%) or late (53.0%) groups. Using healthcare utilization as a proxy outcome in the Clinical Practice Research Datalink, a UK Primary care dataset, the early, mid and late groups were compared. The authors assumed that higher frequency of healthcare visits and prescription medications reflect a poorer outcome from surgery. Patients having early surgery saw their primary care physician less frequently and received fewer prescription medications each year after surgery compared to those patients in the mid or late cohorts. These results were further replicated in a US based electronic dataset using MarketScan.[1918]

Perhaps of even greater interest to the population as a whole, is the impact of ESS on the subsequent development of asthma. It was found, using both UK and US datasets, that ESS was associated with a reduction in the incidence of new asthma diagnoses following surgery, and that the risk of asthma was lowest in those having early surgery, suggesting they had less exposure.[97]

Other groups have subsequently studied the timing of surgery and the impact it has on QoL. A prospective investigation in Sweden found that patients with less than 12 months of sinus disease derived greatest benefit after ESS with respect to improvement in SNOT-22 scores.[241] In contrast, Alt *et al.* performed a prospective multi-centered cohort study in the US enrolling patients diagnosed with CRS

and observed for 14.7 [±4.8] months following primary ESS. Preoperative symptom duration was stratified into short-term (<12 months), middle-term (12–60 months), and long-term (>60 months), using the original criteria as defined by Hopkins *et al.* Disease-specific QoL was measured with the SNOT-22 and the RSDI. The authors found that the length of disease prior to surgical intervention did not predict disease severity or QoL. Further, patients with long-term symptom duration reported the greatest mean postoperative QoL improvement as measured by the SNOT-22 and RSDI, suggesting that delayed surgical intervention may not reduce QoL improvements following ESS.[1929]

Two investigations have evaluated any detrimental effect of surgical wait times In terms of symptomatic benefit from surgery. Newton *et al.* found no association between wait time for surgery (mean wait time 32 weeks) and outcome from surgery in an observational cohort of 150 patients.[1930] The most recently published study (mean wait time 44 weeks) evaluated the effect of surgical wait times and found that prolonged wait times were associated with detrimental outcomes in terms of the total SNOT-22 score and the rhinological domain.[1931]

Although the timing of surgery has not been formally evaluated in a randomized trial, there is a growing body of evidence that suggests that delays in surgical intervention may be detrimental to QoL improvement and increased risk of asthma. The mechanism for this is not yet clear. Reduction in type 2 inflammation and prevention of irreversible remodeling of the mucosa by facilitating improved access to topical therapies are potentially disease-modifying benefits of surgery. However, observation studies are at risk of bias – for example there may be patient behavioral factors, such as compliance with prescribed medications, related to the time that patients seek surgery that influence their post-operative outcomes. Patients included in the observation studies had all received prior medical therapy and therefore it must be highlighted that there is no evidence to suggest that patients should be offered surgery prior to a trial of appropriate medical therapy.

All groups studied in relation to timing of surgery still derived symptomatic improvement therefore surgery can be considered regardless of symptom duration as data suggest that it is never 'too late'.

Timing of Sinus Surgery

Aggregate Grade of Evidence: C (6 level 4 studies)
Benefit: Potential to optimize QoL outcomes of ESS for patients with CRS, though the evidence is indirect and conflicting.
Harm: Risk of encouraging unnecessary or early ESS prior to undergoing appropriate medical management.
Cost: Provided indications for surgery are unchanged, there should be no increase in costs.
Benefits-Harm Assessment: Provided indications for surgery are unchanged, this recommendation will not increase rates of surgery and therefore increased risk of harm is avoided while having the potential to optimize benefit.
Value Judgments: The context in which the studies were initiated was to consider the impact of delayed surgery, and not encourage early intervention, or a change in threshold for surgery.
Policy Level: Recommendation, though weak based on strength of evidence
Intervention: As part of a shared decision-making process with a patient, it is reasonable to avoid prolonged delays in offering surgery if appropriate medical therapy has failed to achieve adequate symptom control. At a health system level, patient pathways should be optimized to avoid unnecessary delays in surgery.

Table XII-10. Evidence for timing of sinus surgery

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusion
Alt[1929]	2019	4	Prospective observational cohort study n-78	Early <1yr Mid 1-5 yrs Late > 5 years	Absolute improvement on SNOT-22, RSDI	Greater symptom improvement in late group
Yip[1931]	2019	4	Prospective observational cohort study N=104	Single cohort of patients on wait list for surgery, mean wait time 44 weeks	Postoperative improvement on SNOT-22	Prolonged wait-time for ESS negatively correlated with outcome. Wait >41 weeks associated with clinically significant reduction in symptomatic benefit
Newton[1930]	2017	4	Prospective observational cohort study N=150	Single cohort of patients on wait list for surgery, mean wait time 32 weeks	Multivariate regression of improvement on SNOT-22	Time spent on waiting list did not adversely impact on symptomatic improvement
Benninger[97]	2016	4	Electronic health records analysis	Patients without asthma at time of CRS diagnosis. Grouped by time between CRS diagnosis and surgery.	Incidence of new onset asthma at time of surgery and postoperatively	Yearly incidence of new onset asthma reduced in all groups after surgery from 4.5% to 0.4% Rates of asthma at time of surgery were 9.4%, 12.8%, 18.2% and 22.4% in each group
Hopkins[95]	2015	4	Prospective observational cohort study N=1493	Early surgery <1yr from diagnosis Mid 1-5 yrs Late > 5 years	% improvement in SNOT-22 score from baseline multivariate regression	Greatest % improvement in early group. Time to surgery significant predictor or outcome in regression
Hopkins[1917]	2015	4	Electronic health records analysis	Early surgery <1 year Late surgery >5 years	Post-operative healthcare utilization – doctor visits and drug	Patients in early cohort had significantly fewer doctor contacts

					prescriptions	and prescription usage after surgery than the late cohort

XII.B.3. Patient Selection and Achieving a Minimally Clinically Important Difference in Sinus Surgery

ESS for CRS with and without NP has been validated in its efficacy and safety.[1932,1933] Surgical success is often measured by improvement in patient reported outcome measures (PROMs), and in particular, CRS-specific QoL metrics. The minimal clinically important difference (MCID) estimates the smallest clinically detectable change of a PROM and therefore is a meaningful endpoint when defining a change threshold for surgical success.[1934] In post-surgical CRS patients the MCID has been defined as 8.9 points on the SNOT-22 using both anchor-based methods that compare change scores to external metrics and distribution-based methods that utilize the statistical properties of a PROM.[71,1935]

Prior studies showed that 70-80% of CRS patients achieve an MCID post-ESS.[1816,1936,1937] A variety of baseline conditions have been explored as potential risk factors for failure to reach an MCID with variable conclusions. The presence of asthma and decreased productivity improve the likelihood of obtaining at least 1 MCID of improvement,[1352,1938,1939] whereas the effects of nasal polyposis, prior sinus surgery, and age are controversial.[1352,1816,1934,1938-1943] Consistently, though, higher baseline SNOT-22 scores have been shown to be predictors of achieving an MCID. Subjects with baseline SNOT-22 >30 points have a >70% chance of achieving an MCID post-operatively.[1934,1940,1944,1945] Conversely, CRS patients with SNOT-22 <20 have a low probability of reaching an MCID due to presumed floor effects.[3,12,18] This finding has prompted the suggestion of a minimal criteria for offering ESS which include a SNOT-22 ≥20 post-medical therapy with topical intranasal steroids and either systemic steroids for CRS with NP or systemic antibiotics for CRS without NP as well as CT Lund-Mackay score ≥1.[283] Following these guidelines appear to result in high post-operative clinically significant improvement in both CRS subsets.[1946]

Despite these recommendations, it is recognized that surgical decision-making remains nuanced, with up to 32% of surgical patients deviating from these criteria.[1947] Patient perceived importance of an individual SNOT-22 domain and achievement of domain-specific MCIDs may impact surgical decision-making.[5] Thus, patients report high levels of satisfaction even without achieving an overall SNOT-22 MCID if their most severe symptoms are addressed.[1948] ESS results in greater improvement of facial pressure, nasal obstruction, and discharge compared to medical treatment.[1949] Those with sleep dysfunction tend to favor surgery, but may ultimately experience lower levels of improvement despite achieving an MCID.[1176,1950] Further research may help us guide appropriate surgical candidacy for CRS, and careful consideration is warranted for patients with low SNOT-22, but a tailored shared decision making process between surgeon and patient remains the guiding principle.

Patient Selection and Achieving a Minimally Clinically Important Difference in Sinus Surgery

Aggregate Grade of Evidence: B (Level 1: 2 studies; level 2: 1 studiy; level 3: 11 studies; level 4 studies: 2 studies).
Benefit: Use of baseline disease-specific QoL metrics (*e.g.,* SNOT-22 score ≥20) as criteria for surgical intervention in CRS patients can help standardize patient selection and improve outcomes by choosing patients who have a high likelihood of achieving an MCID post-op.

Harm: Exclusion of patients based on SNOT-22 scores alone who may otherwise benefit from surgery (*e.g.,* high symptom-specific burden such as smell loss, loss of productivity, co-morbidities such as asthma, odontogenic sinusitis).
Cost: Ignorance of individual specific symptoms or loss of productivity at work if criteria for surgery not met.
Benefits-Harm Assessment: The majority of studies suggest a pre-operative SNOT-22 score may be used to predict likelihood of achieving a minimal clinically important difference after ESS with a recommended SNOT22 score ≥20, but acknowledge certain patients with low pre-op SNOT22 may benefit from surgery.
Value Judgments: Standardizing patient selection and surgical indications may help improve CRS patient outcomes post-operatively.
Policy Level: Option.
Intervention: Patient selection for surgical intervention for CRS with and without NP should take into consideration baseline patient reported symptom burden. Those with greater symptom burdens have a higher likelihood of achieving an MCID and may benefit from surgery. However, each patient should be considered individually with a shared decision making process between surgeon and patient.

Table XII-11. Evidence for patient selection and achievement of MCID in sinus surgery for CRS

Study	Year	LOE	Study Design	Study Groups	Clinical End-point	Conclusion
Le[1352]	2018	1	Systematic review and meta-analysis	3048 CRSwNP pts treated with ESS	SNOT-22	Mean SNOT-22 change of 23.0 points (95% CI 20.2-25.8). Higher preop SNOT-22 scores correlate with greater changes in SNOT-22 scores. Age, asthma, prior ESS correlate with greater improvement in SNOT-22 Tobacco and length of follow up associated with less SNOT-22 change.
Soler[1938]	2018	1	Systematic review and meta-analysis	CRS pts undergoing ESS	Change in SNOT-22 and factors that affect SNOT-22 change	Across all studies (n=40) showed a significant change in mean SNOT-22 12.7- 44.8pt post-ESS (mean 24.4pt change). All studies showed average improvement that meets MCID.
Smith[1816]	2010	2*	Prospective, multi-center cohort study	CRSwNP and CRSsNP 302 pts	RDSI and CSS Medical short form -36 (MSF-36)	72% pts with poor baseline QoL (defined by exclusion of top quintile of QoL scores to avoid ceiling effect) reached clinically significant change for RSDI and 76% for CSS. Patients undergoing primary ESS were 1.8x (CSS) and 2.1x (RSDI)

						more likely improve compared to those undergoing revision ESS.
Mattos[1948]	2019	3	Prospective cohort study	100 CRS pts undergoing ESS	SNOT-22, patient satisfaction questionnaires	Nasal obstruction very important symptom by 93% of patients. -postop satisfaction depends on ESS improving their most important symptoms. -postoperative satisfaction not correlated to achieving MCID, but correlated to change in SNOT-22 ($r=0.35$, $p<0.05$).
Smith[189]	2019	3	Observational cohort study	59 CRS pts s/p ESS	QoL outcomes: RDSI, CSS, SF-6D Health utility values Revision surgery rate Patients satisfaction rate	Clinically significant improvement in symptoms at 6 months post-op typically have sustained improvement long term (at least 10 years follow up).
Yancey[1942]	2019	3	Retrospective analysis of prospective cohort	403 CRS pts	SNOT-22 change SF-8 scores	Elderly patients least likely to achieve a MCID in total SNOT-22 score compared to younger patients (66% reached MCID, $p=0.16$). Similar trends for each SNOT-22 domain.
Singla[1945]	2018	3	Prospective observational cohort study	50 CRS patients	Change in SNOT-22	SNOT-22 > 30 had a > 90% changes of achieving MCID. CRSwNP greater improvement than CRSsNP.
Chowdhury[1935]	2017	3	Prospective observational cohort	276 patients CRSwNP and CRSsNP post-ESS	MCID	MCID values for the rhinologic, extra-nasal rhinologic, ear/facial, psychological, and sleep domain scores were: 3.8, 2.4, 3.2, 3.9, and 2.9, respectively. Improvement in SNOT-22 scores alone does not correlate with health utility as captured by SF-6D.
Levy[1951]	2017	3	Prospective observational	774 CRS patients	SNOT-22 and RSDI scores	Low SNOT-22 patients (<20) were less likely to achieve MCID

			cohort	2 cohorts: Low-SNOT < 20 vs high SNOT22 >=20 points		compared to high-SNOT (>=20) (43% vs. 82%; p<0.001)
Soler[1939]	2016	3	Prospective observational cohort	690 medically refractory CRS patients (medical & surgical tx), 5 clusters based on total SNOT-22, age, and missed productivity	SNOT-22 and RSDI scores up to 18 mo post-enrollment	Odds of achieving MCID was greater with surgery compared to medical therapy in 3 of the 5 patient clusters. 2 of the 5 clusters showed no difference. Factors associated with achieving MCID included pre-operative SNOT-22 score, age and missed productivity.
Hopkins[1934]	2015	3	Prospective observational cohort study	2263 CRSwNP and CRSsNP	Change in SNOT-22 score 3 months post-op	Pre-op SNOT-22 score >30 pts have a >70% chance of achieving MCID. CRSwNP had greater improvement than CRSsNP. Revision surgery rate was lower in those who achieved the MCID (11.3%) compared with those who did not (18.0%), p<0.001.
Rudmik[1940]	2015	3	Prospective observational cohort study	327 pts refractory CRS patients undergoing ESS, grouped based on pre-op SNOT22 score, with polyp subgroup	Change in SNOT-22 post-op, Achievement of MCID	Pre-op SNOT-22 score >30 pts have a >75% chance of achieving an MCID. Pre-op SNOT-22 >20 required for >50% chance of achieving MCID. SNOT-22 <20 have 37.5% of achieving an MCID with relative mean worsening of QoL No difference in NP subgroup.
Smith[1936]	2011	3	Prospective, cohort study	CRS w and w/o NP post-ESS 75 pts	Mean change in RSDI and CSS	73% improvement in RSDI vs 76% CSS post-ESS clinically significant. Greater improvement following surgery vs medical management.
Lehmann[1943]	2018	3	Prospective cohort study	636 CRS patients	SNOT-22, EQ-5D post-ESS at 12, 24 mo	Improvement postoperative SNOT-22 reached MCID across all ages. MCID for change in health utility value exceeded for all ages except age 70-80 years old following ESS.
Lal[1176]	2018	4	Retrospective case series	146 pts undergoing ESS	SNOT-22, achievement	All groups achieved MCID at 3 mo. High baseline scores in the

				divided into 4 clusters based on preoperative SNOT-22 scores	of MCID	psychological-sleep domain group had worse SNOT-22 outcomes at 6 mo.
Kennedy[1944]	2013	4	Retrospective case series	104 pts undergoing ESS, CRS w and w/o NP	SNOT22	SNOT-22 >30 absolute improvement post-ESS 13.6-18.3 pts (95% CI)

*Upgraded due to multicenter study with common disease definition and outcome metrics.

XII.C. Preoperative Management for Sinus Surgery

The primary objective of preoperative management is to create optimal surgical conditions to ensure the best patient outcomes. An unobscured endoscopic view during surgery is one of the most important factors for the success of ESS;[1952] particularly because a bloody field can impair surgical dissection, prolong the length of the procedure and increase the rate of complications.[1952,1953] There are studies that suggest that the extent of preoperative disease may be a predictor for bleeding during ESS.[1954 1955]

In order to create an unobscured surgical field, corticosteroid and antibiotic treatment are both commonly prescribed as preoperative treatment measures because of their potential to decrease inflammation and vascularity of the sinus mucosa. However, to date there is no uniform consensus on dosage or duration of antibiotics or corticosteroids used preoperatively for CRS.

XII.C.1. Preoperative Management in CRSsNP

XII.C.1.a. Effect of Preoperative Corticosteroids in CRSsNP

There are no clinical trials investigating the role of pre-operative corticosteroid use in only CRSsNP patients, as most studies are cohorts comprising both CRSsNP and CRSwNP patients (Table XII-1). Albu and colleagues[1953] demonstrated in an RCT that preoperative INCS treatment for four weeks resulted in significantly less intraoperative blood loss, better surgical field, and shorter operation time. Subgroup analysis demonstrated that these effects were also significant in CRSsNP patients. Although a recent meta-analysis also showed similar blood loss reduction,[1956] Tirelli and colleagues[1957] have shown that chronic topical corticosteroid for at least 3 months prior to ESS caused more intraoperative bleeding in both CRSsNP and CRSwNP patients on the Boezaart score.[1958]

Collectively, non-chronic topical corticosteroid use as preoperative treatment may lead to a better surgical field. However, there are no studies to evaluate the role of preoperative oral corticosteroid before ESS in CRSsNP, and there are significant known risks with their use.[1959,1960]

Preoperative Corticosteroids in CRSsNP

Aggregate Grade of Evidence: C (Level 1: 1 study, Level 2: 1 study, Level 4: 1 study).
Benefit: Objective decrease in intraoperative bleeding, and potential objective improvement in surgical field and less operation time seen with INCS. Subjective reduction in surgical difficulty.
Harm: Possible side effects (see Table II-1).

Cost: Low.
Benefit-Harm Assessment: Preponderance of benefit over harm in INCS. Unknown for oral corticosteroids.
Value Judgment: Improvement in surgical field (less bleeding) is important.
Policy level: Recommendation for INCS. No recommendation for oral corticosteroids.
Intervention: INCS are recommended prior to ESS in CRSsNP.

Table XII-12. Evidence for preoperative corticosteroid administration in CRSsNP

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Pundir[1956]	2016	1	Systematic review of randomized trials	CRSsNP and CRSwNP treated with 4-week course of mometasone furoate	Intraoperative blood loss	Statistically significant reduction in blood loss on Boezaart score
Albu[1953]	2010	2	Individual RCT	CRSsNP and CRSwNP treated with 4-week course of mometasone furoate	Intraoperative blood loss and operation time	Statistically significant reduction in blood loss and operation time
Tirelli[1957]	2019	4	Prospective cohort	CRSsNP and CRSwNP treated with at least 3 months INCS	Intraoperative blood loss	Statistically significant increase in blood loss with no difference between CRSsNP and CRSwNP

XII.C.1.b. Effect of Preoperative Oral Antibiotics in CRSsNP

Similar to INCS, no studies have been identified addressing the preoperative use of systemic antibiotics in only CRSsNP. One study found preoperative antibiotic use led to significantly better SNOT scores but not endoscopic scores, especially in the rhinologic subset. However, the high antibiotic dose group (more than 29 days out of 90 days prior to ESS) was relatively less improved.[1961] In addition, macrolide therapy was reported effective.[1105,1121,1962] Moreover, several studies in CRSsNP patients have found that short term (9-14 days) use of antibiotics improved clinical symptoms with no significant difference in several types of antibiotics.[1102-1104] Although there has been no trial to directly investigate the effect of preoperative antibiotics on intraoperative ESS conditions, patients with impaired nasal patency, impaired sense of smell and more than two nasal symptoms have experienced more intraoperative bleeding and longer surgery time.[1963] Collectively, short term, culture directed oral antibiotic treatment for CRSsNP may be beneficial before surgery, and the disadvantages need to further investigated.[1964] No recommendations are given in this regard because of no direct studies.

XII.C.2. Preoperative Management in CRSwNP

XII.C.2.a. Effect of Preoperative Corticosteroids in CRSwNP

Three articles and one meta-analysis have investigated the effect of oral corticosteroids on CRSwNP and CRSsNP before ESS.[255,1953,1957,1965] Both Pundir[1965] and Hwang's[1966] studies found that preoperative corticosteroids significantly decreased intraoperative blood loss, surgery time and improved surgical field during ESS, compared to controls. Furthermore, Hwang and colleagues' meta analysis[1966] found the effects on intraoperative bleeding were similar for topical or systemic corticosteroids. Wright and Agrawal[255] found that preoperative oral corticosteroid treatment led to significantly greater improvement in inflammation of the nasal mucosa and decreased surgical difficulty, compared to preoperative placebo treatment. Similarly, Atighechi and colleagues[1967] have reported CRSwNP treated with a 5-day course or single dose of systemic corticosteroid could improve the surgical field. Ecevit and colleagues[1616] performed a prospective double blind randomized trial to investigate the effect of preoperative steroids (60mg prednisolone once daily for 7 days and tapered to 10mg every other day then stopped on day 17) for nasal polyps. The authors showed that in addition to improvement of blood loss, surgical field and surgery time, preoperative steroid also decreased the time for hospitalization. In conclusion, preoperative treatment with topical or oral corticosteroids is recommended to ensure better intraoperative conditions in CRSwNP patients in the absence of co-morbidities, which could be aggravated with systemic corticosteroids.

Preoperative Corticosteroids in CRSsNP

Aggregate Grade of Evidence: B (Level 1: 2 studies; level 2: 4 studies; level 3: 3studies; level 4: 1 studies); three studies show contradicting results.
Benefit: Objective improvement in surgical field, decrease in surgery blood loss, and operation time. Subjective reduction in surgical difficulty.
Harm: The possible risks of steroids are well known (see Table II-1) but there were no specific reports about side effect in CRSwNP without co-morbidities.
Cost: Low.
Benefit-Harm Assessment: Preponderance of benefit over harm.
Value Judgment: Improvement in surgical field is important. There is no evidence-based agreement on dosage and duration. For oral corticosteroids, 30-60 mg within 7 days with or without tapering is a commonly prescribed regimen.
Policy Level: Recommended.
Intervention: Recommendation for the use of oral and topical corticosteroids in the preoperative management of CRSwNP.

Table XII-13. Evidence for preoperative corticosteroid administration in CRSwNP.

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Hwang[1966]	2016	1	Meta-analysis	CRSwNP treated with preoperative steroid	Intraoperative bleeding, surgical field visibility and operative time	The treatment of preoperative steroid can reduce intraoperative bleeding, improve surgical field and decrease surgery time

Pundir[1965]	2016	1	Systematic review of randomized trials	CRSsNP and CRSwNP treated with 4-week course of mometasone furoate	Intraoperative blood loss	Statistically significant reduction in blood loss on Boezaart score
Ecevit[1616]	2015	2	Prospective double blinded RCT	CRSwNP who were refractory to topical treatment treated with 60mg prednisolone then reduce 10mg every other day and stop after 10mg for two days	Visual analog scale (VAS), polyp score, Lund-Mackay score, Connecticut Chemosensory Clinical Research Center butanol olfactory threshold test, peak nasal inspiratory peak flow (PNIF), bleeding scoring	The therapy of steroid can decrease intraoperative bleeding, surgery time, improve operative field and reduce the time in hospital
Günel[1968]	2015	2	Individual double blinded RCT	CRSwNP treated with oral prednisolone (1 mg/kg) once daily for 2 days then tapered off	Mean bleeding volume, surgical field quality scores, Lund-Kennedy score, Lund-Mackay score, nasal polyp size and Kennedy Osteitis Scores	There was no significant change on intraoperative bleeding and surgical field after preoperative corticosteroid
Albu[1953]	2010	2	Prospective double blinded RCT	CRSsNP and CRSwNP treated with 4-weeks of mometasone furoate	Intraoperative blood loss and operation time	Statistically significant reduction in blood loss and operation time
Wright[255]	2007	2	Prospective double blinded RCT	CRSwNP treated with 5 day course of 30 mg oral prednisone	Mucosal status and difficulty during surgery	Statistically significant improvement in mucosal status and surgical difficulty
Tirelli[1957]	2019	3	Prospective cohort	CRSsNP and CRSwNP treated with at least 3 months INCS	Intraoperative blood loss	Statistically significant increase in blood loss with no difference between

						CRSsNP and CRSwNP
Atighechi[1967]	2013	3	Individual open label-controlled trial	CRSwNP treated with 5 day course or single dose of systemic corticosteroid	Surgical field quality	Better surgical field following treatment
Sieskiewicz[1952]	2006	3	Individual open label-controlled trial	CRSwNP treated with 5 days of 30 mg oral prednisone	Blood loss and condition of surgical field	Statistically significant reduction in blood loss
Grzegorzek[1963]	2014	4	Case series	Treatment with systemic or topical corticosteroid	Intraoperative blood loss	INCS use was associated with increased blood loss during surgery

XII.C.2.b. Effect of Preoperative Oral Antibiotics in CRSwNP

There are no studies on preoperative antibiotic therapy for CRSwNP. Perica and colleagues[1969] found macrolides can decrease polyp size, but the role of preoperative antibiotic therapy for CRSwNP needs further investigation.Thus no recommendation is therefore given in this regard.

X.D. Surgical Principles/Techniques

XII.D.1: Extent of Surgery

XII.D.1.a. Ostium Size

Since the introduction of endoscopic techniques for the surgical treatment of CRS in the 1980s, the goals of ESS have been to reestablish ventilation and drainage of the paranasal sinuses and improve delivery of topical medications and irrigations through enlargement of the natural ostia.[1970] Modifications to conventional ESS techniques have been described to match the extent and location of a patient's sinus disease. Modifications that reduce the extent of conventional sinus surgery include minimally invasive sinus technique (MIST) and balloon dilation of the sinuses.

MIST is based on the premise that transition spaces, not the natural ostia, serve as bottlenecks for obstruction in the setting of CRS. MIST therefore addresses the clearance of these transition spaces, rather than the enlargement of sinus ostia. For example, MIST involves removal of the uncinate, but does not include direct enlargement of the natural ostium itself.[1971-1973] In comparison to MIST, ESS provides direct enlargement of the natural sinus ostia, which may be beneficial in cases of more severe inflammatory disease or to address anatomic variants, such as an infraorbital ethmoid (Haller) cell. Ostial enlargement may also be advantageous for clearing disease within the sinuses, such as polyps or fungal debris. Large ostial openings can also allow for monitoring and office management of the disease process.

Cohort studies of CRS patients undergoing MIST have demonstrated improvements in sinonasal symptoms maintained up to two years after surgery.[1974,1975] However, improvements were found to be

greater in patients who underwent concomitant nasal polypectomy at time of MIST,[1975] calling into question the extent to which the MIST-specific technique contributed to clinical improvement. Two RCTs have been reported with patients undergoing a MIST procedure on one randomly-chosen side and traditional ESS, including maxillary antrostomy, performed on the other.[1976,1977] Although no significant differences in objective evidence of disease were detected between sides, maxillary sinuses with smaller post-operative ostia were associated with maxillary sinus opacification or OMC obstruction.[1976] In another prospective trial, patients with chronic maxillary RS were randomized to receive either a small maxillary antrostomy, with mean diameter of 6 mm, or a large maxillary antrostomy, with mean diameter of 16 mm. Difference in ostial size was not found to impact symptomatic improvement in facial pain, nasal obstruction or rhinorrhea.[1978] Although most studies of MIST have been related to maxillary ostium size, in a more recent retrospective study of minimally invasive ethmoid surgery, a simple punch sinusotomy led to improvement of symptomatology as well as radiographic resolution of ethmoid disease.[1979]

The necessary extent of ESS has also been addressed through study of balloon dilation for RS. In two prospective randomized trials, [1800,1980] patients with mild CRS (such as chronic maxillary sinusitis with or without concomitant anterior ethmoid sinus disease but excluding posterior ethmoid, frontal or sphenoid sinus disease) received either balloon sinus dilation or ESS. For those patients with mild disease, similar levels of sinonasal symptom improvement, sinus ostium patency, reduction in RS episodes, and improvement in work productivity and daily activity were seen. In a separate non-randomized prospective study of patients with CRS without polyps undergoing ESS or balloon sinus dilation, balloon sinus dilation was associated with a greater frequency of acute exacerbations of CRS and less improvement of nasal drainage symptoms at up to 6 years post-operatively.[1981] Thus, balloon sinus dilation appears to be effective for patients with mild sinus disease.

Extended surgery of the maxillary, frontal and sphenoid sinuses to enlarge the openings of those sinuses beyond traditional ESS principles includes mega-antrostomy, frontal sinus drill out, and sphenoid drill out, respectively. Extended surgeries are generally reserved for recalcitrant disease and most frequently performed in the setting of revision ESS. Clinical studies have shown that a mega-antrostomy and modified endoscopic medial maxillectomy (MEMM) for recalcitrant chronic maxillary sinusitis are effective in reducing sinonasal symptomatology, objective endoscopic and radiographic evidence of CRS, and the need for corticosteroid and antibiotic use.[1982-1988] A recent systematic review reported that MEMM is safe with a low complication rate and may reduce symptoms of recalcitrant chronic maxillary sinusitis in up to 80%.[1989] Presently, the relative efficacies of various extended frontal and sphenoid sinus surgeries are less clear.[1990,1991]

Post-operative distribution of topical medications to the paranasal sinuses may be limited by more conservative ESS techniques, such as MIST or balloon dilation. Studies have suggested that maxillary antrum size correlates with intra-sinus delivery of topical medications.[1992,1993] Evidence suggests that unoperated sinuses receive little topical therapy compared to sinuses that have been surgically opened. More extensive enlargement of the maxillary, frontal and sphenoid sinuses has been associated increased penetration of irrigations.[1993-1995]

Currently available data suggest that MIST and balloon sinus dilation may be a reasonable alternative to ESS for select CRS patients, particularly those with limited disease burden. In comparison, surgeries aimed at creating larger openings may be better suited for patients with more severe disease or nasal polyposis who require greater penetration of topical medications. The current evidence does not

support the routine application of limited or extended techniques for all CRS patients, but they may be considered on a case by case basis.

Ostium Size in ESS

Aggregate Grade of Evidence: B (Level 2, 6 studies; level 3, 4 studies; level 4, 1 study; level 5, 4 studies).
Benefit: Although no studies have demonstrated a direct benefit of more conservative (less extensive) surgical approaches for treatment of CRS compared to traditional ESS, reduced manipulation of sinonasal tissues with these limited approaches, including MIST or balloon dilation, has the potential to reduce surgical time.
Harm: Potential harm of more conservative techniques includes insufficient removal of obstructing sinonasal disease, leading to persistent inflammation, reduced postoperative delivery of topical medications, less access for postoperative care, and potentially faster relapse of symptoms.
Cost: Although no studies have examined the issue of cost related to modified ESS techniques, shorter operative time could translate to lower costs in some circumstances. In contrast, balloon-dilation technology is associated with increased equipment costs per case.
Benefits-Harm Assessment: Over the short-term (up to one year post-operatively), conservative approaches do not appear to increase harm from recurrence of inflammatory sinus disease, particularly in patients with limited sinus disease.
Value Judgments: Conservative approaches (MIST or balloon dilation) appear to provide short-term clinical outcomes that are comparable to traditional ESS in patients with limited disease. For patients with moderate-to-severe CRS, traditional ESS or extended ESS approaches have the potential for improved long-term sinus ventilation and delivery of topical medications. There is no strong evidence for or against the use of less extensive sinus procedures. All studies to date have suggested equivalent short-term outcomes as compared to traditional large-hole technique in patients with minimal sinus disease.
Policy Level: Option.
Intervention: Less extensive sinus interventions are likely reasonable options in patients with minimal OMC or maxillary sinus disease.

Table XII-14. Evidence for ostium size in sinus surgery

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Hathorn[1990]	2015	2	RCT	Patients with CRS and frontal sinus disease who were randomized to receive balloon dilation on 1 side vs. Draf 2a frontal sinusotomy on the contralateral side	Frontal sinus ostial patency Mean blood loss	Balloon dilation was associated with similar ostial patency rate as Draf2a but with lower mean blood loss (58ml vs. 91ml).
Bizaki[1980]	2014	2	RCT	Patients with chronic or recurrent RS without severe findings on sinus CT were randomized to receive ESS or balloon	SNOT-22 score at 3 months post-operatively compared to	Balloon sinus dilation and ESS had similar degrees of improvement in

				sinus dilation.	preoperatively.	SNOT-22 score.
Bikhazi[1800]	2014	2	RCT	Patients with chronic maxillary sinusitis (with or without chronic anterior ethmoid sinusitis) that failed medical therapy received: 1. In-office maxillary sinus balloon dilation 2. Maxillary antrostomy with or without anterior ethmoidectomy	At one year after the intervention: 1. Change in SNOT-20 2. Maxillary sinus ostium patency by CT scan 3. RS episode frequency 4. Change in Work Productivity and Activity Impairment survey scores	Improvement in SNOT-20 and subset scores, Work Productivity and Activity Impairment survey scores and RS episode frequency in both cohorts. No statistically significant difference in outcomes between the two groups.
Myller[1976]	2011	2	RCT	CRSsNP patients in whom: 1. Wide maxillary antrostomy was performed on one side (2x natural ostium size) and 2. Uncinectomy alone was performed on the other side	Post-operative CT scan findings at 9 months. Post-operative maxillary sinus ostium cross-sectional area.	Improvement in overall ipsilateral LM for both surgical treatments. No difference in post-operative overall ipsilateral LM score between surgical treatments.
Albu[1978]	2004	2	RCT (Nonvalidated means of measuring symptoms and 45% follow up)	Surgical CRS patients who underwent: 1. Small maxillary antrostomy (mean diameter 6mm) 2. Large maxillary antrostomy (mean diameter 16mm)	Patient-reported change in symptoms of obstruction, facial pain and rhinorrhea	Maxillary antrostomy size is not associated with post-operative changes in patients' symptoms of obstruction, facial pain and rhinorrhea.
Wadwongtham[1977]	2003	2	DBRCT	In patients with bilateral and symmetric CRSwNP, 1. Wide maxillary antrostomy was performed on one side and 2. Uncinectomy alone	Maxillary sinus ostium obstruction at 3, 6, 9 and 12 months.	Less maxillary sinus obstruction in the large antrostomy group compared to

				was performed on the other side		the uncinectomy group at 3 months but not at 6, 9 or 12 months after surgery
Patel[1991]	2018	3	Prospective non-randomized controlled cohort study	Patients with CRS and refractory frontal sinus disease undergoing Draf2b vs. Draf3 frontal sinus drillout	SNOT-22 Neo-ostium patency Surgical revision rate Complications	At last follow-up (mean 15.6 months), there were no statistically significant differences in clinical endpoints between patients undergoing Draf2b vs. Draf3.
Koskinen[1981]	2016	3	Prospective non-randomized controlled study	Patients with CRS without polyps received maxillary sinus surgery with either maxillary antrostomy or balloon sinus dilation	Change in 19 symptoms on a scale of -3 to 3 Patient reported acute exacerbation of CRS frequency	At a mean of 6 years post-operatively, patients having balloon sinus dilation reported more exacerbations and less improvement in nasal drainage symptoms.
Salama[1975]	2009	3	Prospective cohort study	A consecutive series of patients presenting with CRS and undergoing uncinectomy but not antrostomy to address the maxillary sinuses	Symptoms (VAS) QoL assessments at 1 and 3 years after surgery	Reduction in sinonasal symptoms after MIST, more pronounced in patients with NPs QoL after surgery was sustained 3 years post-operatively
Catalano[1974]	2003	3	Prospective cohort study	Patients undergoing MIST for CRS	CSS Need for revision	Postoperative CSS scores were improved

					surgery	78.8% of patients had improved CSS score 5.9% of patients required revision MIST
Velasquez[1979]	2017	4	Retrospective study	Patients with CRS without polyps who underwent ethmoid punch sinusotomy to address ethmoid sinuses.	SNOT-22 score Lund-Mackay CT score of the ethmoid cavities	SNOT-22 score decreased by a mean of 33.1 points at last follow up Reduction of Lund-Mackay score of the treated ethmoid sinus from 1 or 2 to zero in all cases.
Govindaraju[1993]	2019	5	Cadaveric study	Fresh frozen cadaver heads undergoing MMA, (Mega-A), and EMMA	Penetration of irrigations using a squeeze bottle Surgical access to interior of maxillary sinus	Irrigation penetration improved with increasing antrostomy size Visualization of interior of maxillary sinus and access for surgical instruments was improved with Mega-A and EMMA compared to MMA.
Gantz[1994]	2019	5	Cadaveric study	Fresh frozen cadaver heads undergoing maxillary sinus surgery with balloon sinus dilation followed by ESS (maxillary antrostomy and Draf2a frontal sinusotomy)	Penetration of irrigations using a high-volume, high-flow squeeze bottle	Penetration of irrigations improved with both balloon sinus dilation and traditional ESS. Maxillary antrostomy had better penetration of irrigations than balloon sinus

						dilation. Draf2a frontal sinusotomy had no additional benefit over balloon sinus dilation for irrigations.
Grayson[1995]	2019	5	Cadaveric study	Fresh frozen cadaver heads undergoing sphenoidotomy, sphenoid sinusectomy (type 1), or sphenoid sinusectomy (type 3a)	Penetration of irrigations using a high-volume, high-flow squeeze bottle. Force of irrigation within the sphenoid sinus. Residual pooling of irrigation fluid after the irrigation.	Improved penetration and force of irrigation into larger sphenoid sinus openings. Less residual pooling of irrigation fluid with larger sphenoid opening.
Se[1971]	1996	5	Expert opinion	Patients undergoing uncinectomy but not antrostomy to address the maxillary sinuses	Surgical revision rate: 1. To address the maxillary sinus 2. Overall	Maxillary revision rate was 0.3%. Overall revision rate was 7%.

XII.D.1.b. Mucosal Preservation vs. Mucosal Removal

In recent years, there has been increased discussion about the potential effectiveness of removing paranasal sinus mucosa during ESS for the treatment of CRS. While there is minimal data regarding this technique for patients with CRSsNP, this has been a more widely studied approach for CRSwNP and has been dubbed "nasalization."

In this more radical approach, a complete ethmoidectomy is performed along with removal of lateral, non-olfactory ethmoid mucosa. The middle turbinate is also typically removed during the procedure. Studies, though limited in number, have shown positive results for the nasalization procedure.[1780,1996]

In a retrospective 5-year study, patients with CRSwNP who underwent nasalization ethmoidectomy demonstrated better symptom relief by VAS at 8.41 +/- 0.40 compared to 5.69 +/- 0.83 after ethmoidectomy ($p = 0.002$).[1780] Further, total recurrence rate was 22.7% in the nasalization group, and 58.3% in the ethmoidectomy group ($p < 0.01$).[1780] In a second study looking at patients with CRSwNP failing medical management, a group receiving nasalization was compared to a group receiving a single

course of oral steroids. The nasalization group showed better sustained long term results.[1997] Despite these encouraging results, the data on direct comparison between nasalization to routine, mucosal preserving, ethmoidectomy is quite limited, thus limiting broader applicability of the technique for CRS.

Additional studies have evaluated olfactory improvement after nasalization.[1996] The initial study by Jankowski *et al.* in 2003 noted improvement in olfaction with preoperative steroids and nasalization.[1996] Two more recent studies have also assessed nasalization and olfaction, show promising results when applied to patients with severe hyposmia using the Sniffin stick smell test.[1997,1998] Despite the sustained olfactory improvement after nasalization, the effectiveness of this approach compared to mucosal preserving ethmoidectomy was not studied.

Additional studies have taken a modified approach to removal of inflamed mucosa, called the "reboot" procedure. In this technique, authors have proposed stripping of all polypoid mucosa thereby giving the mucosa the opportunity to regrow in a more functional manner.[55,1999] In a study by Alsharif *et al.*, 50 patients with CRSwNP were surgically treated in one of three groups: traditional, non-stripping ESS; partial reboot; and full reboot with Draf III. They noted that full reboot with Draf III resulted in significantly less polyp recurrence over two years. However, the approach to the frontal sinus was not standardized between groups.

Recently, some authors have found that a more aggressive approach to the maxillary sinus may be effective for treating recalcitrant CRSwNP. These techniques, traditionally used for access for removal of maxillary sinus neoplasms, include the Caldwell-Luc procedure and a modified endoscopic medial maxillectomy. The latter approach includes near total removal of the inferior turbinate, widening the maxillary sinus opening to its anatomic boundaries with the option of extending the window anteriorly into the anterior wall of the maxillary sinus facilitating increased access for topical therapies.[1985,1987,1989,2000]

Mucosal Preservation versus Mucosal Removal in ESS

Aggregate Grade of Evidence: C (Level 2: 3 studies; level 4: 4 studies)
Benefit: In patients with CRSwNP mucosal removal is associated with improvement in QoL scores, sustained improvements in smell, and decreased polyp recurrence.
Harm: Potential for direct damage to olfactory mucosa or CSF leak at middle turbinate attachment. Risk of chronic crusting.
Cost: Direct and indirect costs related to ESS.
Benefits-Harm Aassessment: For patients with CRSwNP, the evidence suggests mucosal removal is associated with sustained improvement in QoL scores, sustained improvements in smell and decreased rates of polyp recurrence. However, substantially more research is required with direct comparison to mucosal preserving ESS. Further, rates of complications such as CSF leak, scarring, or crusting should be considered.
Value Judgments: Evidence is based on very few studies in the literature, virtually all from the same research group.The data available at this time is limited and its broad applicability to additional patient cohorts unclear.
Policy Level: Option.
Intervention: Mucosal stripping is an option in patients with CRSwNP.

Table XII-15. Evidence for mucosal preservation vs. removal

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoints	Conclusion
Jankowski [1996]	2003	3	Prospective, controlled	Preoperative steroids followed by nasalization Nasalization only	VAS for smell at 1, 3, 6, 9, 12 months after surgery	Nasalization and topical steroids leads to sustained improvement in VAS
Jankowski [1996]	2003	3	Prospective controlled	7 day steroid course only Nasalization only	VAS prior to intervention and post intervention at multiple time points	Nasalization had long term improvement in obstruction scores, rhinorrhea, sneezing compared to oral steroid group
Alsharif [*1999*]	2019	4	Prospective controlled cohort study	Mucosal sparing ESS Partial Reboot Full Reboot with DRAF III	Endoscopic scores	Reboot procedure yields lower rate of polyp recurrence in CRSwNP
Sonnet [1998]	2017	4	Prospective controlled cohort study	CRSwNP pre- and post-nasalization	Sniffin stick smell test preop Sniffin stick smell test postop	Patients with profound hyposmia preop trend show improvement postop.
Eluecque [1997]	2015	4	Prospective controlled cohort study	CRSwNP pre- and post-nasalization	Sniffin stick smell test preop Sniffin stick smell test postop	Patients with profound hyposmia preop trend show improvement postop
Jankowski [1780]	2006	4	Retrospective cohort study	Nasalization group Ethmoidectomy group	QoL measures Postop CT Polyp recurrence rate	Nasalization significantly better at 5 years in all 3 outcome measures

XII.D.1.c. Balloon Dilation

Balloon catheter dilation (BCD) was introduced in 2005 as a treatment for surgical management of paranasal sinus inflammatory disease. Despite widespread usage, there is a relative paucity of robust clinical trials evaluating the efficacy of balloon technology in patients with CRS. The CLEAR study, the initial large-scale cohort investigation, demonstrated the safety and technical feasibility of BCD, with improvements in SNOT-20 scores and ostial patency in 109 patients. However, the patient cohort in this study was not clearly defined and management was not standardized.[2001]

The ORIOS study began as an initial prospective, single-arm, non-randomized, multicenter evaluation of in-office BCD in 38 patients with CRS.[1796] In-office technical success was 89% with no adverse complications. Significant reduction of mean SNOT-20 scores at all time points ($p < 0.0001$) was reported. An improvement in mean Lund-Mackay score from 6.62 at baseline to 2.79 was noted at 24 weeks ($p < 0.001$). The follow up ORIOS2 study included a larger cohort and showed similar findings with follow up to 52 weeks.[1797,1798] The use of adjunctive procedures, the lack of a control group, loss to follow-up and non-standardized medical management confounded the secondary outcomes.

A recent prospective, multicenter, nonrandomized, observational, comparative study, the MERLOT study, attempted to assess the utility of BCD in medically refractory CRS.[2002] Patients with CRS self-selected continued medical therapy or BCD with or without adjunctive surgical procedures, including septoplasty, ethmoidectomy, turbinate reduction, uncinectomy, concha bullosa resection, polypectomy, or sinus irrigations (n = 198, 146 surgery and 52 medical management). An initial 24-week evaluation showed improvement in QoL metrics including the CSS, RSDI and SNOT-20.[2003] A follow up evaluation at 52-weeks reported sustained improvement in CSS, RSDI and SNOT-20 over continued medical therapy.[2002] Challenges of the study limiting generalizability include the non-randomized nature of the groups, the variability in medical therapy, the use of adjunctive procedures in the BCD group, and poor follow-up in the medical management group (52% vs. 83% in the BCD group).

Two randomized control trials have been performed to compare the efficacy of BCD to ESS.[2004-2006] The REMODEL trial is the largest of these trials with 92 patients enrolled, it is the only randomized control trial with sufficient power to draw conclusions.[2006] Eligible patients were at least 18 years of age and were diagnosed with either chronic or recurrent RS (68% CRS and 32% RARS in the final cohort). Prior medical therapy was not delineated although patients met criteria per the 2007 Adult Sinusitis Clinical Practice Guidelines. Patients with posterior ethmoid, sphenoid, frontal, fungal and polypoid disease were excluded yielding a fairly uniform study cohort with maxillary disease only (62%) or maxillary and anterior ethmoid disease (38%). Patients were randomized to either in-office balloon dilation of the maxillary sinus or operative ESS, including uncinectomy and maxillary antrostomy with or without anterior ethmoidectomy. Postoperative follow-up assessments were conducted at 1 week, 1 month, 3 months, and 6 months. Primary endpoints included improvement in mean SNOT-20 scores and required number of postoperative debridements by blinded assessment. Timing of baseline SNOT-20 for RARS was not reported. Six-month follow-up was 98.9%. Important findings included equivalent mean SNOT-20 score change between groups (1.67±1.10 in the balloon arm and 1.60±0.96 in the ESS arm). ESS had a higher requirement for debridement (0.1±0.6 in the balloon arm and 1.2±1.0 in the ESS arm, $p < 0.0001$). Secondary findings included a 0% complication rate in both arms and faster return to normal daily activity (1.6 vs. 4.8 days, $p = 0.001$) and less pain medication requirement (0.9 days vs. 2.8 days, $p < 0.001$) in the balloon arm. A follow up study at 12 months demonstrated equivalent improvement in SNOT-20 (-1.64±1.06 in the balloon arm and -1.65±0.94 in the ESS arm).[2005]

Challenges of the REMODEL study include limited disease severity in the study cohort and industry support. Nonetheless, the REMODEL study provides level 1 evidence that BCD may be a potential treatment option for patients with limited disease involving the maxillary and/or anterior ethmoid sinuses, where appropriate medical therapy has failed. A recent randomized, placebo-controlled trial in patients with RARS showed BCD plus medical management proved superior to medical management alone further potentially supporting its role in minimal diseased states.[511]

Balloon Catheter Dilation

Aggregate Grade of Evidence: C (Level 2: 1 study; level 3: 1 study; level 4: 7 studies).
Benefit: Balloon catheter dilation may have potential benefit in patients with limited maxillary and anterior ethmoid disease.
Harm: Minimal harm with risk of minor bleeding and patient discomfort; major harm though uncommon with reported risk of CSF leak and significant eye swelling from orbital entry (see Table II-1).
Cost: Balloon-dilation technology is associated with increased equipment costs and potential for overutilization.

Benefits-Harm Assessment: Benefits balance risks but may not outweigh costs.
Value Judgments: Although numerous prospective studies, including RCTs, have emerged showing benefit, the exclusion of patients with more diffuse paranasal sinus inflammatory disease limits broader applicability to all CRS patients.
Policy Level: Option.
Intervention: Balloon catheter dilation may have benefit for patients with limited maxillary sinus disease with or without anterior ethmoid disease in CRSsNP.

Table XII-16. Evidence for balloon sinus dilation

Study	Year	LOE	Study Design	Study Groups	Clinical endpoint	Conclusions
Bikhazi[2005] Cutler[2006]	2013, 2014	2	Individual RCT	BCD (n=50) vs ESS (n=42); CRS/RARS with minimal maxillary and ethmoid disease only, polyp disease excluded	SNOT-20, 1-year follow up	BCD is as effective as ESS in treatment of CRS with maxillary disease with or without anterior ethmoid disease
Achar[2004]	2012	3	Individual RCT	BCD (n=12) vs ESS (n=12); patients with polyps excluded	SNOT-20, saccharine clearance time at 6-, 12- and 24-weeks	Both groups with similar improvements; study did not reach power calculation
Payne[2003] Stolovitzky[2002]	2016, 2018	4	Prospective cohort study	BCD +/- adjunctive procedure (n=146) vs continued medical management (n=52), limited polyp disease included	Chronic sinusitis survey score, SNOT-20, RSDI at 24-weeks and 52-weeks	Sinus surgery utilizing BCD had significantly greater QoL improvements than medical management alone
Abreu[2007]	2014	4	Prospective cohort study	CRS without nasal polyps (n=13)	SNOT-20, LM scores at 3-6 months	BCD provided improvement in QoL and CT score
Gould[1799]	2014	4	Prospective cohort study	CRS or RARS (n=81), polyp disease excluded	SNOT-20/RSI at 1-month, 6-months and 1 year	BCD provided mean improvement in SNOT-20 and RSI at 1 year
Karanfilov[1797] Sikand[1798]	2013, 2015	4	Prospective cohort study	CRS (n=122 at 1yr), limited polyp disease included	SNOT-20 at 2-, 8-, 24- and 52-weeks LM scores at 24-weeks	BCD provided significant improvements in SNOT-20 at 24-weeks maintained to 52-weeks
Brodner[2008]	2013	4	Prospective cohort study	CRS (n=175), polyp disease included	Safety, patency, SNOT-20 at 1-year	BCD provided significant SNOT-20 improvement at

						1yr (1.9 to 0.8, p <0.01) with 91.6% patency
Raghunandhan[2009]	2013	4	Prospective cohort study	CRS (n=20), limited polyp disease included	SNOT-20, endoscopy, LM scores at 1-, 6- and 12-months	BCD provided significant improvement in subjective and objective findings at all time points
Albritton[1796]	2012	4	Prospective cohort study	CRS (n=37), polyp disease included	SNOT-20 at 1-, 4-, 24-, and 52-weeks LM at 24-weeks	BCD yielded improvement in SNOT-20 at all time points and LM at 24-weeks

XII.D.1.d. Extent of Frontal Surgery

Determining the appropriate extent of frontal surgery can pose challenges. Greater extents of frontal surgery have been postulated to enhance relief of inflammatory burden, improve ventilation, and improve delivery of topical treatments. However, more extensive dissection can be technically challenging and hold greater potential for complications.

In 1991, Wolfgang Draf published a classification system for the extent of frontal surgery, which is still widely accepted and used: Draf I – removal of ethmoidal cells without altering the frontal ostium; Draf IIa – removal of ethmoidal cells in the frontal recess with widening of the frontal sinusotomy from the lamina papyracea to the middle turbinate; Draf IIb – removal of frontal sinus floor to extend the frontal sinusotomy from the lamina papyracea to the septum; Draf III – removal of superior nasal septum and the frontal sinus septum to extend the frontal sinusotomy from medial orbital wall to contralateral medial orbital wall (also known as endoscopic modified Lothrop procedure).[2010,2011]

There is evidence that a Draf I procedure has efficacy as an intervention for selected patients with chronic frontal sinusitis in one retrospective[2012] and one prospective study.[2013] The retrospective study reviewed patients with CT evidence of frontal sinusitis who underwent a Draf I procedure. The success rate of Draf I for treating frontal sinusitis was >90%, with 8.3% of patients requiring revision surgery. Patients with AERD or frontal septal cells were more likely to fail.[2012] The prospective study was a multi-institutional study comparing outcomes of Draf I ethmoidectomy with those of frontal sinusotomy procedures (Draf IIa, IIb or III). Both groups had comparable improvement in SNOT-22 scores, with a 0% revision surgery rate in the Draf I group (vs. 2.6% in the comparison group). Noting a skew towards more severe CRS in the frontal sinusotomy group, the authors cautioned that selection of Draf procedure should reflect severity of the frontal sinusitis.[2013]

Outcomes of Draf IIa procedures have been studied extensively. A recent review identified an overall 67.5%-92% patency rate of Draf IIa frontal sinusotomy,[2014] with diameter over 4.5mm at completion of the procedure being the most significant factor in achieving patency. Years earlier, Hosemann had also shown that the stenosis rate was 16% for an ostium size of 5mm, versus 50% when the ostium size was

2mm.[2015] A large retrospective case series review of 109 patients undergoing a primary Draf IIa procedure by a single surgeon demonstrated significant symptom improvement in 78% of patients, with 92% sinus patency rate and a revision surgery rate of less than 9%.[1813] One challenge in interpreting these studies is that other sinuses are usually surgically treated in conjunction with the frontal sinus, thus making it difficult to determine the degree of subjective symptom improvement attributable to frontal sinusotomy.

The most common indications for a Draf IIb procedure are chronic frontal sinusitis due to lateralized middle turbinate, mucocele or mucopyocele, synechiae from previous surgery, and a frontal sinus mass.[2016] In a case series of 18 patients undergoing a Draf IIb procedure, 13 were revision surgeries, and a 91% long term patency was achieved. In another case series of 21 patients,[1991] all patients had a patent neo-ostium at an average of 15.7 months follow-up, with clinically significant symptom improvements. One patient required revision by conversion to a Draf III procedure. There were no major complications except for hyposmia, which was reported in 14.3% of the patients.

A recent meta-analysis of publications reporting outcomes of Draf III procedure between 2000-2016 reported a symptom improvement rate of 75.9% in 357 patients.[201710] A restenosis rate of 17.1% was identified; however, most studies did not establish a quantitative standard for defining restenosis. Smaller case series have reported a reduction of the restenosis rate using mucosal grafts or stents in the neo-ostium.[1824,2018]

There is sparse comparative evidence to guide the decision-making process between the various extents of frontal surgeries. In one study, Draf III patients were found to require more office visits and debridement, as well as antibiotics, when compared to Draf IIa patients in the early post-operative period.[2019] However, the study period was limited to the first 8 weeks postoperatively, and long term outcome comparison was not available. Another study directly compared Draf IIb and III procedures, and found earlier symptom improvement in the Draf IIb group, and equivalent long term symptom improvement, patency, revision, and complication rates.[1991] This is despite a cadaveric study demonstrating increased frontal sinus penetration with irrigation with Draf III cavities when compared to IIb.[1262] In the presence of co-morbid conditions such as asthma and nasal polyposis, the extent of surgery may influence rates of polyp recurrence. In patients with asthma and nasal polyposis, Zhang *et al.* found that the addition of a Draf III frontal sinusotomy improved polyp recurrence rates in the first year after surgery compared to standard ESS (59% vs 89%); however, by year three there were no differences in polyp recurrence rate, with a 96% rate of polyp recurrence in both groups.[2020]

Newer intermediate hybrid procedures between Draf IIb and III have also been described.[1263,2021-2023] When compared to Draf III surgery, these procedures demonstrated similar rates of frontal patency rates[2022,2023] and comparable patterns of irrigation distribution.[1263]

In summary, a graded approach to frontal sinusotomy is generally supported by evidence for safety and efficacy. High level evidence for the selection of extent of frontal sinus surgery in any given patient is lacking.

Extent of Frontal Surgery

Aggregate Grade of Evidence: C (Level 2: 1 study; level 3: 1 study; level 4: 7 studies).
Evidence is based on mostly uncontrolled studies
Benefit: Frontal sinusotomy is an effective and safe operation for chronic frontal sinusitis.

Harm: Surgeries are associated with potential complications, but the rates are comparable between the extended, Draf IIb and III, frontal sinus operations.
Cost: There is Level 4 evidence to demonstrate Draf III patients requiring more frequent clinic visits and debridement procedures in the early postoperative period, when compared to less extensive frontal sinus operations.
Benefits-Harm Assessment: Balance of benefit and harm for performing extended frontal sinus surgery for chronic frontal sinusitis.
Value Judgements: Patient selection is crucial for advising and performing various extents of frontal sinus surgery.
Policy level. Options for extent of frontal sinusotomy .
Intervention: Frontal sinusotomy is likely beneficial for recalcitrant frontal sinusitis, but in deciding the extent, various patient, surgeon expertise and illness factors need to be taken into consideration.

Table XII-17. Evidence for extent of frontal sinus surgery

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoints	Conclusion
Zhang [2020]	2020	2	Randomized trial	Patients with CRSwNP requiring revision surgery randomized into 3 groups: ESS, "Radical ESS (RadESS)" and RadESS with DrafIII.	Follow-up for minimum 5 years, assessing polyp recurrence, symptom scores, endoscopic scores, revision surgery rates, and clinical control of asthma.	Radical ESS (surgery addressing all sinuses, and performing partial middle turbinate resection), and RadESS with Draf III yielded similar outcomes, both superior than ESS (addressing all sinuses including frontal sinusotomy).
Abuzeid [2017]	2018	3	Meta-analysis of Level 3-5 evidence	All English-language publications between 2000-2016 involving Draf III as a revision procedure for CRS, identifying 357 patients.	Postoperative outcomes, including complication, frontal sinus restenosis and revision surgery rates.	Draf III is an effective salvage procedure for recalcitrant chronic frontal sinusitis.
Patel [1991]	2018	3	Cohort-study	21 patients with bilateral Draf IIb procedures and 17 patients with Draf III.	Postoperative outcomes review, including complications and revision	Comparable long term outcome between the two groups, but with patients achieving this sooner in the

					surgery rates.	Draf IIb group.
Abuzeid [2013]	2016	3	Non-randomized controlled cohort	196 cases undergoing frontal sinusotomy and 30 cases treated with ethmoidectomy without frontal sinusotomy.	Post-operative outcome, subjective and objective, as well as revision surgery rates.	Ethmoidectomy without frontal sinusotomy may achieve similar QoL improvement for those with less severe sinusitis.
DeConde [2014]	2016	3	Systematic review of Level 3-5 evidence	Review of evidence for Draf IIa and III procedures.	Efficacy, safety and long term post-operative outcome review.	While limited data, evidence suggests long lasting quality of improvement with Draf IIa procedure, and efficacy of Draf III as a salvage procedure.
Choby [2023]	2018	4	Case-series	Description of "Cross-court Draf IIb" procedure, with case presentations.	Long term patent frontal sinusotomy.	Description of variation to the Draf procedures.
Jafari [2019]	2017	4	Case-control study.	19 patients undergoing Draf IIa, and 19 patients undergoing Draf III procedures.	Evaluate surgical and QoL outcomes.	Draf III is associated with more postoperative clinic visits, debridements, antibiotic therapy, and extranasal symptoms than Draf IIa in the first 8 weeks after the procedures.
Morrissey [1824]	2016	4	Case-series	213 patients who underwent a Draf III procedure by a single surgeon 2001-2013.	Review of the Draf III outcomes, then rate and indications of revision surgeries. Review of	21% restenosis after Draf III procedures, mainly due to polyp recurrence. Intraoperative pus present at initial surgery,

					outcomes after the revision Draf III.	more than 5 previous sinus operations, or AERD increased risk of failure. Revision Draf III is safe and well-tolerated.
Turner [2016]	2016	4	Case-series	22 patients undergoing Draf IIb procedure.	Review of indications and postoperative outcomes.	Draf IIb is a safe procedure with multiple indications and long term patency. Suggests that this would be a valid alternative to a Draf III procedure in appropriate patients
Al Komser [2022]	2013	4	Case-series	Description of "Draf IIc" procedure, with case presentations – Draf IIb sinusotomy was extended to include the nasal and frontal sinus septum, without extension to the opposite frontal recess.	Long term patent frontal sinusotomy.	Description of variation to the Draf procedures.
Conger [2018]	2012	4	Case-series	29 patients undergoing Draf III procedures, with free mucosal graft to dress the neo-ostium.	Anterior-posterior diameter at 3 months post surgery, as well as reviewing patient demographics and percentage graft viability.	Use of mucosal graft may reduce postoperative stenosis.

Naidoo [1813]	2012	4	Case-series	109 patients undergoing primary Draf IIa procedure.	Postoperative outcome, as well as analysis of factors leading to stenosis.	Frontal ostium size correlates with stenosis, as well as recurrent/residual inflammation. Asthma, eosinophilic mucin, allergy and smoking did not affect outcomes.
Becker [2012]	2007	4	Case-series	77 patients who underwent anterior ethmoidectomy for chronic frontal sinusitis.	Post-operative outcome, including revision surgery rate.	Anterior ethmoidectomy for drainage of frontal sinuses appears to be an effective initial treatment option.
Bhalla [1263]	2019	5	Mechanism-based reasoning	Cadaveric study of "Cross-court Draf IIb" sinusotomy irrigant delivery.	Compare therapeutic benefit of the hybrid procedure with a Draf III cavity.	"Cross-court Draf IIb" sinusotomy provided similar irrigation delivery benefits to a Draf III sinusotomy.
Barham [1262]	2016	5	Mechanism-based reasoning	Cadaveric study	Evaluate and compare distribution of topical irrigation in Draf IIa, IIb and III cavities.	Degree of distribution and rate of lavage increased with increasing dimensions of frontal recess.
Eloy [2021]	2016	5	Mechanism-based reasoning	Description of modifications of surgical approaches to Draf classification.	-	Description of variations proposed classification to the extent of frontal sinus surgery.

XII.D.2. Concurrent Septoplasty with Sinus Surgery

Rhinologic surgeons commonly perform septoplasty as an adjunctive procedure in patients undergoing ESS. Septal surgery may be performed to provide access to the paranasal sinuses, or to address nasal obstruction due to septal deviation. Because the two procedures are often performed together, it may

difficult to separate the benefits of the concurrent procedures. Similarly, while some risks are clearly related to the septoplasty (*e.g.*, septal perforation), attributing other outcomes, such as postoperative pain or epistaxis, may be problematic.

Descriptions of conventional septoplasty (CS) performed in conjunction with ESS are sparse, although the procedure combination seems quite common. Cantrell described the technique and rationale for "limited" septoplasty, presumably performed with traditional headlight illumination.[2024] Most authors describe techniques for endoscopic septoplasty (ES) and report limited outcomes data in case series.[2025-2028] Giles *et al.* compared cohorts of patients undergoing ESS alone, ESS and CS, and ESS and ES and noted good outcomes in the ESS/ES group.[2029] Bothra and Mathur performed a similar comparison of ES and CS in patients undergoing ESS and noted no differences between groups.[2030]

In a prospective, multi-institutional study, Rudmik, *et al.* compared ESS with septoplasty to ESS without septoplasty, and noted no differences in various quality-of-life measures for CRS.[2031] Based upon these data, the authors conclude that patients undergoing concurrent septoplasty should not be excluded from studies evaluating the impact of ESS on CRS.

In a large retrospective case series, Chang *et al.* compared ESS with septoplasty and ESS without septoplasty and noted a lower revision rate in patients who underwent both procedures.[2032] Similarly, Rudmik *et al.* noted that ESS with septoplasty was associated with a lower revision ESS rate in retrospective review.[2033] These studies demonstrate a clear benefit of performing septoplasty and ESS concurrently, at least for patient with both CRS and septal deviation.
Data on opioid usage among patients undergoing ESS and septoplasty vs. ESS alone are inconsistent. One study noted that ESS with septoplasty patients did not request narcotics refills at a higher rate,[2034] while another study did show that concurrent ESS and septoplasty associated with greater opioid usage.[2035] Patients undergoing concurrent ESS and septoplasty have a longer period to pain relief than those patients undergoing septoplasty alone.[2036]

Concurrent Septoplasty with Sinus Surgery

Aggregate Level of Evidence: C (level 2, 2 studies; level 3, 2 studies; level 4, 12 studies; level 5, 1 study).
Benefit: Reduction in nasal obstruction, improved access for ESS, possibly reduced need for revision surgery.
Harm: Risk of bleeding, postop discomfort/pain, septal hematoma, septal perforation, persistent obstruction, intranasal scarring, CSF leak.
Cost: Cost is related to increased operative time when septoplasty is added to ESS
Benefit-Harm Assessment: Preponderance of benefit over harm.
Value Judgment: Septoplasty may be required during ESS for surgical access. Patients with septal deviation and CRS may experience reduced nasal obstruction when septoplasty is performed at the time of ESS. The studies supporting septoplasty at the time of ESS presumably performed septoplasty when a clinically relevant septal deviation was encountered.
Policy Level: Recommendation to perform septoplasty at the time of ESS when a clinically relevant septal deviation is present.
Intervention: Septoplasty for clinically relevant septal deviation (either ES or CS) should be performed at the time of ESS.

Table XII-18. Evidence for concurrent septoplasty with sinus surgery

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoints	Conclusion
Smith[2037]	2017	2	Prospective, multi-center observational cohort	288 ESS procedures performed at 3 sites	Improvements in patient-reported outcome measures	ESS with septoplasty associated with greater improvement.
Rudmik[2031]	2011	2	Prospective, multi-institutional cohort study	ESS with septoplasty (n=108) ESS without septoplasty (n=113)	Rhinosinusitis Disability Index Chronic Sinusitis Survey	No statistically significant differences between groups.
Khanwalker[2036]	2019	3	Prospective cohort series	288 patients undergoing septoplasty, or ESS with or without septoplasty	Patient reported days to pain relief	Septoplasty associated with fewer days to pain relief while ESS with septoplasty associated with more days to pain relief.
Newberry[2035]	2019	3	Prospective cohort series	346 patients undergoing ESS with or without septoplasty	Patient reported narcotic usage	Concurrent ESS and septoplasty associated with greater opioid usage.
Fu[799]	2019	4	Case-control study	72 patients undergoing revision ESS with and without septoplasty	Lund-Mackay CT scores	Patients treated with revision ESS with septoplasty had higher disease burden on CT scan.
Jafari[2034]	2018	4	Retrospective review	121 patients undergoing ESS	Narcotic usage	ESS with septoplasty not associated with narcotics refills.
Marchia[2038]	2018	4	Retrospective review	20 patients undergoing	Postoperative outcomes	Rhinoplasty/septoplasty/ESS and ESS with

				ESS, septoplasty and rhinoplasty and 20 patients undergoing only ESS and septoplasty		septoplasty produce similar results.
Rudmik[2033]	2017	4	Retrospective review of database	2168 ESS procedures performed by 43 surgeons	Need for revision surgery	ESS with septoplasty associated with a lower revision rate.
Chang[2032]	2014	4	Case series	ESS with septoplasty (n=876) ESS without septoplasty (n=3608)	Need for revision surgery	ESS with septoplasty associated with a lower revision rate.
Bothra[2030]	2009	4	Case series	ESS with CS (n=40) ESS with ES (n=40)	Symptoms Physical examination Complications	No statistically significant differences between groups.
Chung[2027]	2007	4	Case series	ESS with ES (n=96) ES alone (n=20)	Symptoms Physical examination Complications	ES is an alternative to CS, especially in patients undergoing ESS.
Su[2026]	2004	4	Case series	ESS with ES (n=81) ESS alone (n=152)	Symptoms Complications	No statistically significant differences between groups.
Castelnuovo[2028]	1999	4	Case series	ESS with CS (n=89) ESS with ES (n=155) Rhinoplasty with ES (n=15)	Complications	ES is the optimal technique in select patients due to excellent visualization, which facilitates less extensive manipulation of the septal framework.

Hwang[2025]	1999	4	Case series	ESS with ES (n=108) ES alone (n=3)	Physical examination Complications	ES is an adjunctive procedure.
Giles[2029]	1994	4	Case series	ESS without septoplasty (n=496) ESS with CS (n=144) ESS with ES(n=38)	Symptoms Physical examination	5 patients had synechiae develop between the septum and lateral nasal wall; all were lysed in the office. No postop obstruction was noted among the ESS patients.
Cantrell[2024]	1997	5	Report of technique	ESS with "limited" septoplasty (n=100)	Not specified	"Limited" septoplasty may be performed with ESS.

XII.D.3. Middle Turbinate Preservation or Resection in Sinus Surgery

Whether to routinely preserve or resect the middle turbinate (MT) during sinus surgery has been a topic of debate for decades. Moreover, partial or total resection of the MT have been performed in endoscopic surgery, which further complicates the interpretation of the literature. Whereas some studies showed beneficial effects of MT resection compared with MT preservation, several others showed no difference.[2039] These various arguments have been examined in the literature over the last thirty years and have shown limited effects of both preservation and resection, in several aspects:

Quality of life (QoL) and Endoscopic Outcomes. Better SNOT-22 improvement, and lower rhinorrhea and olfactory scores were found in radical ESS (ESS with MT resection) and radical ESS combined with Draf III in a randomized study compared to the ESS with MT preservation at one year postoperatively, whereas there were no differences between the groups by 3 and 5 years after operation.[2020] However, a multicenter study demonstrated similar improvements in SNOT-22 and EuroQol 5-Dimension questionnaire between MT preservation and resection groups[2040], which was consistent with Byun's findings[2041] in SNOT-20. Soler and colleagues,[2042] however, found that although MT resection was associated with improved endoscopy scores versus MT preservation, there was no difference in QoL. A recent RCT showed that there was no sustained objective endoscopic benefit of MT resection.[2043] With conflicting results from similar quality studies, it is difficult to definitively determine the possible QoL benefit of MT resection.

Medication Delivery. Only one study showed that after MT resection in 4 cadaver heads, irrigation delivery significantly improved.[2044]

Postoperative Frontal Sinusitis. In 1995 Swanson and colleagues[2045] reported that patients had a higher risk of frontal sinusitis with MT resection. Other studies demonstrated that patients undergoing MT resection had 10-18% postoperative rate of frontal sinusitis.[2046,2047] However, two more recent studies compared MT resection to preservation and found no difference in the rate of frontal sinusitis.[2048,2049] Collectively these results cast doubt on the significance of MT resection as a risk factor for postoperative frontal sinusitis.

Recurrence of Nasal Polyps. Brescia[2050] and Byun[2041] found MT preservation associated with lower nasal polyps scores 12 months after ESS. Similarly, Marchioni and colleagues[2051] found a trend toward a lower recurrence rate (although without statistical significance) effect of MT resection in their prospective cohort. Subsequently, Wu and colleagues[2052] found a longer median time to recurrence of NPs with MT resection compared to that with MT preservation. These authors noted, however, that a greater burden of disease preoperatively might possibly account for the difference in endoscopy scores. Overall, it appears MT resection reduces or slows the recurrence of nasal polyps.

Olfaction. Two prospective cohort studies have shown no effect on olfaction following MT resection,[2053,2054] whereas another two prospective cohort studies[2042,2055] and one retrospective review [2056] have shown a beneficial effect. Akiyama and colleagues[2057] found significantly better olfactory cleft patency in the submucosal MT resection group than in the control group without MT resection. In this prospective randomized double-blind trial, improvements were observed in the olfactory recognition threshold test scores after submucosal middle turbinectomy combined with ESS. Kim and colleagues[2058] investigated the effect of preservation of MT by medialization and found no impairment of olfactory function. With regard to olfaction, the aggregated data of similar low level studies show conflicting results.

Maxillary Ostial Stenosis. Three studies have shown no effect of MT resection on maxillary patency,[2048,2059,2060] whereas there was a positive effect for MT resection in one earlier retrospective study.[2061] However, it appears from these data that MT resection does not have a significant effect on middle meatal antrostomy patency.

Middle Turbinate Synechiae. Two retrospective reviews indicated no effect of MT resection on synechiae formation between the MT and the lateral nasal wall.[2062,2063]

Intraoperative Cerebrospinal Fluid (CSF) Leak. A multicenter case series reported that partial MT resection led to CSF leak in only one case out of 91 patients following partial or complete MT resection.[2064]

Development of "Empty Nose Syndrome". Tan and colleagues[2065] found that partial MT resection did not significantly increase the risk of developing the condition commonly referred to as empty nose syndrome compared to MT preservation.

Postoperative Bleeding. The MT has a rich blood supply from a branch of the sphenopalatine artery. Previous studies have reported that MT resection was associated with the risk of postoperative bleeding.[2050,2066-2069] Recently, Miller and colleagues[2070] found that there was a significantly increased minor bleeding rate correlated with MT resection. However, in the multicenter case series (n = 91) found no postoperative epistaxis after partial or complete MT resection.[2064]

Orbital Complications. One retrospective review found that MT absence after previous surgery was associated with an increased risk of nasolacrimal duct stenosis, lamina papyracea injury and orbital hematoma during revision ESS.[2071]

In conclusion, rigid adherence to MT preservation or routine MT resection is not supported by the available cumulative evidence. Additional, definitive evidence is warranted to investigate the valid indications for MT preservation and resection. To be noted, currently, there are no head-to-head studies comparing partial vs. total MT resection, which should be further studied in the future. At present, management of the MT requires a thoughtful approach with considerations of all potential risks, benefits, and alternatives.

Middle Turbinate Preservation or Resection in Sinus Surgery

Aggregate Grade of Evidence: C (Level 2: 4 studies; level 3: 11 studies; level 4: 15 studies)
Benefit: Lengthening of time to recurrence of NPs, possible improvement in olfaction, improved endoscopy scores
Harm: Loss of landmark for revision surgery, leading to increased risk of intraoperative complications. Possibly increased risk of postoperative bleeding.
Cost: No additional cost beyond those associated with ESS.
Benefits-Harm Assessment: Most of the potential risks and benefits postulated for MT resection have conflicting support in the literature, complicating a definitive assessment.
Value Judgments: MT resection may improve access to the ethmoid cavity during ESS, however, thoughtful consideration must be given to alternatives in removing a non-diseased structure to improve access. The vast majority of the literature purported to support both MT resection and MT preservation is low level and most shows no effect in aggregate.

Policy Level: Option.
Intervention: MT resection may be employed during ESS, especially in cases of CRSwNP.

Table XII-19. Evidence for middle turbinate resection vs. preservation

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Kim [2058]	2019	2	RCT(n=80)	Bilateral CRS patients undergoing ESS: 1. left MT medialization 2. right MT medialization	BTT, OC	MT medialization does not impair olfactory function, and OC status is closely related to olfactory function.
Hudon[2043]	2018	2	RCT (n=16)	CRSwNP patients undergoing ESS: 1. MT resection 2. MT preservation	POSE, Lund-Kennedy score	No sustained objective endoscopic benefit of MT resection within the first six postoperative months.
Gulati[2059]	2010	2	RCT (n=40)	CRS patients undergoing MMA 1. MT resection 2. MT preservation	Subjective symptoms and endoscopy	Patients undergoing MT resection with MMA were more likely to have improvement in nasal obstruction.
Havas[2067]	2000	2	RCT (n=1,106)	Patients undergoing ESS 1. MT resection 2. MT preservation	Atropic rhinitis, synechia and need for revision surgery	MT resection was assocaited with less synechia and need for revision surgery. Patients with MT resection had no atrophic rhinitis after a mean of 4.2 years.
Zhang[2020]	2019	3	Prospective cohort (n=81)	CRSwNP patients undergoing ESS 1. Functional ESS (MT preservation) 2. Radical ESS (MT resection)	symptoms scores, endoscopic scores, CT scores	The clinical efficacies of radical ESS are comparable with functional radical ESS plus Draf 3 surgery.

				3. Radical ESS + Draf 3		
Tan[2065]	2018	3	Prospective nonrandomized cohort (n=177)	CRS patients undergoing ESS: 1. partial MT resection 2. MT preservation	Subjective symptom scores (ADSS, Lund-Mackay) and ENS6Q	No addition risk of developing ENS symptoms.
Scangas[2040]	2017	3	Prospective nonrandomized cohort (n=406)	CRS patients undergoing primary and revision ESS: 1. MT resection 2. MT preservation	SNOT-22, chronic sinusitis survey, euroQol 5	In select patients undergoing revision sinus surgery, the performance of BMTR results in improved disease-specific QoL.
Chen[2055]	2016	3	Prospective nonrandomized cohort (n=47)	CRSwNP patients with asthma: 1. Extensive ESS (EESS), including MT resection 2. ESS with MT preservation	Subjective symptoms and endoscopy	EESS significantly improved the subjective olfaction and endoscopic appearance in patients with CRSwNP and with asthma compared with ESS.
Miller[2070]	2016	3	Retrospective nonrandomized cohort (n=456)	Patients undergoing ESS 1. MT resection 2. MT preservation	Postoperative bleeding	There was a significantly increased minor bleeding rate associated with MT resection, particularly if the patient was on anticoagulants.
Byun[2041]	2012	3	Prospective nonrandomized cohort (n=187)	CRSwNP patients undergoing ESS: 1. MT resection 2. MT preservation	Endoscopy, QoL (SNOT-20 and VAS)	MT preservation group had better endoscopy outcomes. QoL improvement did not differ between groups. Greater burden of disease in MT

						resection group based on preoperative endoscopy, CT imaging, and VAS.
Albu[2060]	2010	3	Prospective nonrandomized cohort (n=411)	Patients with chronic maxillary RS undergoing ESS: 1. MT resection 2. MT preservation	Recurrence of RS	Partial MT resection did not alter the risk of recurrence.
Soler[2042]	2010	3	Prospective nonrandomized cohort (n=242)	CRS patients undergoing ESS: 1. Bilateral MT resection 2. Bilateral MT preservation	Olfaction, endoscopy, and QoL (RSDI, CSS, SF-36)	Patients with bilateral MT resection were more likely to have asthma, AERD, CRSwNP, and prior sinus surgery. No differences in QoL improvement were seen between the two groups postoperatively.
Federspil[2053]	2008	3	Prospective nonrandomized cohort (n=52)	CRSwNP patients undergoing ESS: 1. MT resection 2. MT preservation	Olfaction (Sniffin' Sticks)	Partial resection of the MT had no effect on olfactory threshold, discrimination and identification.
Marchioni[2051]	2008	3	Prospective nonrandomized cohort (n=56)	CRSwNP patients undergoing ESS: 1. MT resection 2. MT preservation	Time to recurrence of NPs;	Trend toward faster relapse in patients with MT preservation (p=0.0589)
Unlu[2049]	2006	3	Prospective nonrandomized cohort (n=61)	CRS patients undergoing ESS: 1. MT resection 2. MT preservation	Postoperative frontal sinusitis (by CT)	MT resection had no effect on development of frontal sinusitis.
Pinther [2064]	2019	4	Case series	Refractory	Postoperative	Complication are

			(n=91)	CRSwNP patients undergoing primary or revision ESS 1. partial MT resection 2. complete MT resection	complications, SNOT-22, revision ESS rates	rare from both partial and complete MT resection during ESS.
Akiyama[2057]	2017	4	Case control studies (n=38)	Eosinophilic CRS patients undergoing ESS: 1. Submucosal MT resection 2. MT preservation	Post-operative MTL, synechia formation, and patency grade of OC	The opening of the OC was significantly superior to that in the MT preserved group.
Kidwai [2044]	2016	4	Case series	Four cadaveric heads undergoing bilateral ESS followed by MT resection	Penatraion of nasal irrigation in the cadaver model	MT resection results in significant improvement in penetration of nasal irrigation.
Wu[2052]	2014	4	Retrospective review (n=299)	CRSwNP patients undergoing ESS: 1. MT resection 2. MT preservation	Time to revision surgery	Patients who underwent MT resection had a longer median time to revision surgery. The beneficial effect of MT resection dissipated by 8 years postoperatively.
Brescia[2050]	2008	4	Retrospective review (n=48)	CRSwNP patients undergoing ESS: 1. MT resection 2. MT preservation	Endoscopy and rhinomanometry	Patients who had MT preservation had better endoscopy results. Nasal airway resistance did not differ between groups.
Giacchi[2048]	2000	4	Retrospective review (n=50)	CRS patients undergoing ESS: 1. MT resection 2. MT preservation	MT lateralization, synechiae, maxillary ostial stenosis, recurrent ethmoiditis, frontal sinusitis	Greater burden of disease in MT resection group based on preoperative CT imaging. Higher risk of

						recurrent ethmoiditis in sides with MT resection. No difference in other outcomes.
Fortune[2046]	1998	4	Retrospective review (n=115)	Patients with CRS undergoing MT resection	Frontal sinusitis following surgery	Patients with MT resection had a 10% rate of frontal sinusitis postoperatively.
Saidi[2047]	1998	4	Retrospective review (n=33)	Patients with CRS undergoing MT resection	Frontal sinusitis following surgery	Patients with MT resection had a 18% rate of frontal sinusitis postoperatively when not present preoperatively.
Jankowski[2056]	1997	4	Retrospective review (n=78)	CRSwNP patients undergoing surgery: 1. Nasalization, with MT preservation 2. Ethmoidectomy including MT resection	Olfaction (VAS)	Patients who underwent nasalization, including MT resection, had better olfaction than patients who underwent traditional ethmoidectomy, with MT preservation.
Friedman[2054]	1996	4	Prospective case-control study (n=64)	CRS patients undergoing ESS: 1. MT resection 2. MT preservation	Olfaction (SIT)	No difference was seen in postoperative olfaction between the two groups.
Kinsella[2062]	1995	4	Retrospective review (n=193)	CRS patients undergoing ESS: 1. MT resection 2. MT preservation	Middle turbinate synechiae	Patients who had MT resection had the same rate of synechia formation as those who had MT preservation.
Ramadan[2063]	1995	4	Retrospective review (n=337)	CRS patients undergoing ESS: 1. MT resection	Middle turbinate synechiae	Patients who had MT resection had the same

				2. MT preservation		rate of synechiae formation as those who had MT preservation.
Swanson[2045]	1995	4	Retrospective review (n=110)	CRS patients undergoing ESS: 1. MT resection 2. MT preservation	Frontal sinusitis following surgery	Patients who had MT resection had a higher rate of frontal sinusitis compared to MT preservation.
LaMear[2061]	1992	4	Retrospective review (n=283)	CRS patients undergoing ESS: 1. MT resection 2. MT preservation	Either closed antrostomy or significant synechia formation	Patients who underwent MT resection had a higher antrostomy patency or less synechia formation.
Vleming[2071]	1992	4	Retrospective review (n=593)	Patients with CRS who had previously had surgery 1. MT resection 2. MT preservation	Complications during surgery	CSF leak, nasolacrimal duct stenosis, lamina papyracea injury and orbital hematoma were all more likely in patients who had undergone previous MT resection.

XII.D.4. Use of Image Guidance for Sinus Surgery

Image-guided surgery (IGS) technology has found support among sinus surgeons seeking to improve clinical outcomes.[2072] In addition to preoperative imaging review, IGS incorporates surgical navigation, which permits surgeons intraoperatively to localize specific points in the operating field against pre-operative imaging data sets.[2073] Since 2002, the American Academy of Otolaryngology-Head and Neck Surgery's position statement on IGS has emphasized the technology for complex procedures of the paranasal sinuses and skull base, at the discretion of the operating surgeon.[2074] Originally developed for the operating rooms setting, IGS is now used in office settings.[1787,2075]

It must be remembered the use of IGS is associated with more extensive surgery, presumably due to the benefits of using the technology.[2076-2078] Both in practice and in published reports, ESS cases performed with IGS tend to be more complex than those cases performed without IGS; thus, a bias exists when interpreting some of the literature on the use of IGS and its benefits.

Surgical navigation requires a target registration error (TRE), informally referred to as "accuracy," of 2 mm or less.[2079] For ENT technology, reported TREs include 2.28 +/-0.91 mm for headset-based, automatic registration[2080]; 1.4 mm (range of 0.61-1.95) for paired anatomical points[2081]; 2.4 +/-0.7 mm for laser surface registration[2082]; and 0.3-0.4 mm for laser/touch registration.[2083] Hardy, *et al.*, compared fiducial, landmark and surface/contour registration in a cadaveric model, and reported TREs of 0.47 +/- 0.36 mm, 3.10 +/- 0.44 mm and 1.05 +/- 0.10 mm, respectively.[2084] Automatic mapping of fiducials is at least as good as manual mapping.[2085] Glicksman, *et al.*, reported a novel registration system based upon photo recognition.[2086] TRE reflects 3 independent factors (1) error of localizing an instrument/sensor; (2) CT scan quality; and (3) robustness/fidelity of registration software algorithm.[2087] The distribution of fiducial points influences TRE.[2088,2089] Also, surgeons tend to achieve better TRE as they acquire additional experiences with the registration process.[2090] Most publications emphasize physician confidence in the technology, suggesting a level of practically-achievable TRE that is clinically meaningful. Failures of registration and surgical navigation have been well categorized.[2091]

IGS does seem to increase operative time.[2076,2081,2092-2095] This increase may reflect the time for IGS set-up. Alternatively, case selection bias may adversely influence operative time. In contrast, IGS does not seem to be associated with increased intraoperative blood loss.[2077,2092]

Numerous publications have examined complication rates.[2096] In a comparison of 400 patients whose ESS was performed with IGS and a historical cohort of patients in whom IGS was not employed, Reardon showed comparable complication rates, despite more extensive surgery in the IGS patients.[2076] Fried, *et al.* were able to associate a reduced complication rate with the use of IGS through a comparison of a patient cohort of ESS cases performed with ESS and historical controls; of note, the IGS patients had greater surgical complexity.[2077] A more recent publication also associated reduced rate of complications with IGS.[2094] Most authors have not detected differences in complications with IGS.[2097,2098] A 2013 systematic review, by Ramakrishan, *et al.* concluded that the peer-reviewed literature does not support conclusions that IGS reduces complications and improves clinical outcomes; these authors recommend IGS as an option, because the consensus of practicing surgeons and expert opinion confirm the utility and acceptance of IGS technology.[2098] Smith, *et al.*, have estimated that such a study designed to detect differences in complication rates would require as many 35,000 enrolled patients.[2099] Dalgorf, *et al.*, in an extensive meta-analysis, concluded that IGS is indeed associated with fewer complications. [2100] In a subsequent meta-analysis, Vreugenberg, *et al.*, who focused on complex cases only, confirmed that IGS is associated with fewer total, major and orbital complications, but not minor complications and severe hemorrhage.[2101] Both of these reports have been criticized because they cannot address the bias intrinsic to the underlying publications that they summarize and review.[2102]

While improvements in clinical outcomes associated with the use of IGS have been difficult to confirm, Javer, *et al.* were able to show improved RSOM-31 scores in patients whose ESS was performed with IGS.[2103] Masterson found a reduction in revision surgery among patients whose ESS was performed with IGS.[2104] In another retrospective study, Galletti, *et al.*, showed that IGS was associated with greater symptom reduction and decreased recurrence rates.[2095] Other studies have not demonstrated similar benefits of IGS.[2105-2108]

Strauss, *et al.* proposed a novel strategy for assessing the impact of IGS on surgical decision-making. In this clinical series, IGS was associated with changes in surgical technique and strategy, even for experienced surgeons.[2109] Presumably, the information provided by IGS, as captured in this study, translates to more complete/effective surgery and greater operative efficiency.

Several studies have looked at the impact of IGS on surgeon stress levels. Survey data show that surgeons believe that IGS reduces their stress levels.[2078] In a prospective trial of trainees, IGS did not impact overall stress levels, although more experienced trainees did experienced a decreased perceived workload with IGS.[2110] In a small study, physiological parameters for stress did not markedly differ if IGS was employed.[2111] Nonetheless, survey data show that surgeons report reduced stress levels with IGS.[2072]

IGS has also been combined with intraoperative fluoroscopy,[2112] CT-MR fusion[2113,2114] and 3D CT angiography.[2115] These reports emphasize technical feasibility of these adaptations and explore potential clinical applications. IGS with an imaging update provided by an intraoperative cone-beam (or volume) CT scanner has been associated with an alteration of the surgical plan in 30% of ESS cases.[2116,2117] Furthermore, IGS also has specific uses for frontal sinus surgery,[2118] orbital surgery,[2107,2119,2120] sphenoidotomy,[2121] skull base surgery,[2122] pediatric sinus surgery,[2123-2125] procedures with skull base erosion,[2126] trephination procedures,[2127] device placement,[2128] orbital surgery,[2107] mucocele marsupialization,[2129] and osteoplastic frontal sinus surgery.[2130-2132]

Surgeon surveys suggest greater availability of IGS technology in ENT operating rooms and confirm that most surgeons are comfortable with the technology, especially for more advanced sinus cases.[2133-2135] Regional variations in the usage of IGS are large, suggesting that factors other than case complexity determine its usage.[2136]

IGS technology entails incremental costs.[2137] One study has proposed that IGS may reduce the overall cost of care, by reducing the need for revision surgery.[2104] From a medico-legal perspective, IGS has not been implicated as a factor in litigation for ESS-related complications.[2138]

Recently, IGS systems have introduced new technology. IGS with virtual reality features has been described.[2139] Augmented reality features have been incorporated into IGS systems.[2140] Advantages of augmented reality-enabled IGS include more intuitive and more detailed imaging data, which should reduce mental workload for surgeons.[2141] Interestingly, an IGS system offering three dimensional modeling did not improve surgeon's efficiency and workload in a cadaveric trial.[2142] In addition, microsensor electromagnetic tracking may be incorporated into conventional instruments or sinus balloons.[2143]

Use of Image Guidance for Sinus Surgery

Aggregate Level of Evidence: B (Level 1: 2 studies; level 2: 1 study; level 3: 11 studies; level 4: 48 studies).
Benefit: Reduction in complications; improved surgical outcomes; more extensive surgery performed under endoscopic visualization; surgeon satisfaction/stress.
Harm: Increased operating time; IGS failure leading to inaccurate localization of instruments.
Cost: Costs are related to greater operating time and the need for specialized equipment and technical expertise.
Benefit-Harm Assessment: Preponderance of benefit over harm in selected cases.
Value Judgment: Image-guided surgery provides important localization information to the surgeon during ESS; such information may reduce complications and improve outcomes. In addition, IGS may reduce operative morbidity by permitting endoscopic techniques for more complex surgical targets. Surgeon acceptance of the technology is high.

Policy Level: Option in patients undergoing ESS, especially in the setting of anatomic complexity or the need for more advanced procedures. Intervention: Image-guided surgery performed at the time of ESS.

Table XII-20. Evidence for the use of image guidance in sinus surgery

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoints	Conclusion
Vreugenberg[2101]	2016	1	Meta-analysis	Comparison of ESS with and without IGS in 'complex' cases	Complication rates	IGS associated with lower complication rates in complicated ESS
Dalgorf[2100]	2013	1	Meta analysis	14 controlled cohorts (including 1 randomized trial)	Complications	IGS reduces major complication rates
Galletti[2095]	2019	3	Cohort study	96 ESS procedures 1. with IGS (n=48) 2. without IGS (n-=48)	Recurrence rate, reduction in nasal resistance, frontal stenosis rate, nasal symptoms	IGS associated with statistically significant better outcomes on these critical measures
Ahn[2144]	2018	3	Cohort study	ESS procedures for inverted papilloma surgery 1. With IGS (n=34) 2. Without IGS (n-24)	Recurrence rate, complication rate	IGS associated with statistically significant better outcomes on these measures
Stelter[2111]	2015	3	Cohort study	ESS with IGS (n=40) and without IGS (n-40)	Physiological markers of stress	IGS not associated with lower levels of physiologic stress
Theodoraki[2110]	2015	3	Cohort study	ESS with IGS (n=32 sides) and without IGS (n=32 sides), by trainees	Physiological markers of stress	IGS neither increases nor reduces the physiological workload of trainees
Tschopp[2108]	2008	3	Prospective case series	ESS procedures With IGS (n=62) Without IGS (n=62)	Extent of surgery; indications for surgery; patient symptoms (VAS); surgeon satisfaction	IGS is associated with few complications; but overall outcomes are similar with and without IGS.
Javer[2103]	2006	3	Prospective case series	ESS procedures With IGS (n=80)	RSOM-31	IGS usage associated with

				Without IGS (n=15)		greater improvement in QoL after ESS.
Woodworth[2083]	2005	3	Prospective case series	15 ESS cases with IGS: Laser registration Touch registration	Time for registration; TRE	Both laser and touch registration produce similar TRE (0.3-0.4 mm), but laser registration is faster.
Raabe[2082]	2002	3	Prospective case series	34 consecutive patients	Calculated TRE	Laser surface registration TRE was 2.4 +/- 1.7 mm.
Metson[2092]	1999	3	Prospective case series	121 patients undergoing ESS: Optical-based system (n=55) Electromagnetic -based system (n=24) No IGS (n=42)	TRE; operative time; EBL; costs; complication rates	IGS is associated with greater costs and operative time.
Fried[2080]	1997	3	Prospective case series (multi-center)	55 patients undergoing ESS	Technical description of new technology; calculated TRE; surgeon satisfaction; case descriptions	Auto-registration TRE was 2.28 +/- 0.91 mm. IGS is an important new technology for ESS.
Casale[2129]	2019	4	Case report	Patient with mucocele	Successful completion of the procedure	IGS helpful in this case
Giotakis[2145]	2019	4	Case series	Postop CTs to identify residual ethmoid cells after ESS (n=10)	Rate of residual ethmoid cells	IGS is associated with fewer "missed" ethmoid cells during ESS.
Itayem[2146]	2019	4	Proficiency testing	Identification of the anterior ethmoid artery on CT with and without segmentation	Percentage correct responses on test	Segmented images improves surgeon's accuracy, confidence, and efficiency in this task.
Sugino[2147]	2019	4	Cohort study	Method for analyzing	Validated data set	IGS can be used for time-series

				surgical performance through use of IGS (n=14 ESS cases)		comparative analysis.
Vicaut[2078]	2019	4	Cohort Study	311 procedures performed by 36 surgeons at 16 hospitals	Surgeon satisfaction, extent of surgery	IGS increased the extent of surgery and reduced surgeons' reported stress levels.
Zeiger[2139]	2019	4	Case series	134 endoscopic procedures performed with virtual model and navigation	Description of technology	Surgeons deemed the technology useful.
Bang[2131]	2018	4	Case report	Description of osteoplastic flap case	Successful completion of the procedure	Novel application of patient tracker described
Rodriguez[2132]	2018	4	Case report	Description of osteoplastic flap case	Successful completion of the procedure	Novel application of patient tracker described
Glicksman[2086]	2017	3	Cohort study	Comparison of 2 registration types in 45 patients: 1. Contour-based 2. Facial recognition	Accuracy	Facial recognition registration was better than contour-based registration.
Grauvogel[2148]	2017	3	Dry lab	Comparison of 3 registration types in cadaveric lab: 1. paired point against bone-anchored fiducials 2. LED mask 3. Contour-mapping	Accuracy	All approaches yielded accuracy <1 mm; bone-anchored fiducials were best, followed by contour and then mask
Lam [2143]	2017	4	Case series	Microsensor navigation with balloon sinus	Effectiveness	Microsensors may be combined with

				surgery (n= 18 sinuses)		sinus balloons.
Wellborn[2149]	2017	4	Dry lab	Novel set-up for fixation of patient tracker tested in lab	Accuracy	Novel device offers more robust accuracy
Al-Qudah[2126]	2015	4	Case series	ESS with IGS in patients with skull base and orbital erosion (n=14)	Complications, effectiveness	IGS is safe and effective during ESS in patients with skull base erosion.
Bergeron[2125]	2015	4	Case series	ESS with IGS in children (n=21) and adults (n=38)	Complications, accuracy	IGS is comparable in adults and children
Stokken[2119]	2015	4	Case series	Endoscopic orbital surgery cases (n=27)	Outcomes	IGS should be employed for complex endoscopic orbital cases.
Taulu[2128]	2015	4	Case series	Device placement with fluoroscopy (n=26) and IGS (n=26)	Description of techniques	IGS is faster, safer and more exact that fluoroscopy
Jiang[2121]	2014	4	Case series	Endoscopic sphenoidotomy with IGS (n=30)	Effectiveness, safety	IGS facilities endoscopic sphenoidotomy
Servat[2120]	2014	4	Case series	Endoscopic orbital surgery with IGS	Complications, effectiveness	IGS aids endoscopic orbital surgery.
Eloy[2138]	2013	4	Medicolegal case review	30 malpractice cases; 4 mentioned IGS	Mentions of IGS in malpractice judgments	IGS is not a factor in ESS litigation.
Ramakrishnan[2150]	2013	4	Database query	62,823 patients undergoing ESS (identified in MarketScan Commercial Claims and Encounters database)	Complication rates	Major ESS complications seem to be decreasing; impact of IGS is unclear.
Sunkareneni[1819]	2013	4	Case series	ESS procedures With IGS (n=333) Without IGS (n=47)	Complication rates; need for revision sinus surgery	IGS is associated lower recurrences in the early postop period; IGS does

						not appear to reduce complication rates.
Masterson[2104]	2012	4	Case series	132 patients underwent 147 ESS procedures for CRS and tumors	Complication rates; need for revision surgery; economic simulation of potential savings	IGS is safe and may reduce need for revision surgery; IGS may also reduce overall costs.
Al-Swiahb[2094]	2010	4	Case series	ESS procedures: With IGS (n=30) Without IGS (n=30)	Operative time, complications, recurrence rates	IGS is associated with greater operative time and fewer complications.
Mueller[2097]	2010	4	Case series	ESS procedures: With IGS (n=108) Without IGS (n=168)	Complications, need for revision surgery	IGS is not associated with lower rates of complications and revision surgery.
Benoit[2123]	2009	4	Case series	Pediatric patients undergoing sinus surgery (n=28) and skull base surgery (n=5)	Complications, surgeon satisfaction, accuracy, uses per procedure	IGS is safe and effective in children; surgeon usage and comfort increases with experience.
Crawley[2151]	2009	4	Case series	ESS with IGS procedures performed by residents (n=102)	Operative times, EBL, case complexity	Residents may safely perform ESS with IGS.
Manzey[2072]	2009	4	Survey	Survey of German ENT surgeons (n=213)	Human factors associated with IGS	Surgeons deem IGS helpful.
Parikh[2124]	2009	4	Case series	33 pediatric patients undergoing ESS with IGS	Indications; complications; surgeon satisfaction	IGS can be used in children, especially for more complex procedures.
Batra[2117]	2008	4	Case series	25 patients whose ESS was performed with IGS and intraoperative	Need for additional intervention	In 6 cases, the intraoperative CT scan led to additional surgical

				update through volume CT scanning		intervention
Dubin[2107]	2008	4	Case series	24 patients undergoing endoscopic orbital decompression with IGS (45 orbits)	Ophthalmological outcomes; surgeon satisfaction	IGS did not improve ophthalmological outcomes after surgery, despite surgeon acceptance.
Jackman[2116]	2008	4	Case series	20 patients whose ESS was performed with IGS and intraoperative update through volume CT scanning	Alteration of surgical plan	In 6 cases, the intraoperative CT scan led to additional surgical intervention
Brown[2112]	2007	4	Case series	14 consecutive patients undergoing ESS with fluoroscopy-enhanced IGS	Feasibility; concept validation	Real-time IGS with fluoroscopy is feasible; additional development is warranted.
Leong[2114]	2006	4	Case series	ESS with IGS and CT-MR fusion (n=25)	Image-to-image TRE; feasibility; surgeon satisfaction	CT-MR fusion provides hybrid images that may be used during IGS for complex procedures of the skull base and sinuses.
Stelter[2152]	2006	4	Case series	ESS with IGS (n=368)	TRE; surgeon satisfaction; complications	Risks associated with inaccurate IGS are minimal.
Strauss[2109]	2006	4	Case series	ESS with IGS (n=29) Other ENT procedures with IGS (n=13)	Change of surgical strategy; surgeon satisfaction; TRE; costs; operative time	IGS usage is associated with a change of surgical strategy, especially as specific subsites.
Tabaee[2106]	2006	4	Case series	ESS procedures Wth IGS (n=60) Without IGS (n=179)	Complications; need for revision surgery; SNOT-20	IGS is not associated with lower complication rates and improved QoL

						measures.
Zaharek[2127]	2006	4	Case series	ESS with trephination and IGS (n=13)	Feasibility; concept validation; indications; surgeon satisfaction.	IGS may be used to guide trephination placement.
Buchwald[2153]	2005	4	Case series	42 patients undergoing endoscopic inverted papilloma resection with IGS	Recurrence rates, complications	Endoscopic inverted papilloma resection with IP is safe.
Chiu[2113]	2005	4	Case series	2 patients undergoing endoscopic skull base surgery with IGS enabled with CT-MR fusion	Feasibility, surgeon's satisfaction	IGS with CT-MR fusion offers advantages over conventional IGS in more complex cases.
Leong[2115]	2005	4	Case series	Patients undergoing ESS with IGS and 3DCTA (n=18)	Feasibility; indications; surgeon satisfaction	IGS with 3D-CTA offers advantages over conventional IGS in more complex cases.
Orlandi[2134]	2005	4	Physician survey	Survey of practicing ENT surgeons (n=340)	IGS availability; surgeon satisfaction; indications	Most surgeons have access to IGS; most surgeons limit use to more complex cases.
Tabaee[2105]	2005	4	Case series	Endoscopic CSF leak repair With IGS (n=16) Without IGS (n=8)	Surgeon satisfaction; surgical success rates	IGS enhances surgeon's confidence, but data supporting improved outcomes is lacking.
Chiu[1823]	2004	4	Case series	Revision endoscopic frontal sinus surgery with IGS (n=67)	Frontal recess patency; complications	IGS is a valuable tool for revision ESS.
Eliashar[2093]	2003	4	Case series	ESS procedures With IGS (n=34)	Operative time; surgeons	IGS is associated with longer

				Without IGS (n=131)	satisfaction; complications	operative time and greater surgeon satisfaction.
Metson[2154]	2003	4	Case series	1000 IGS procedures performed by 42 surgeons	Case volume; surgeon satisfaction	IGS offers both benefits and pitfalls.
Rassekh[2090]	2003	4	Case series	22 procedures in 21 patients	TRE; completion of set-up; complications	IGS carries a learning curve for surgeons.
Rombaux [2081]	2003	4	Case series	32 patients undergoing ESS	Clinical accuracy; complications; preparation time	IGS accuracy is adequate for ESS.
Fried[2077]	2002	4	Case series	Consecutive patients undergoing ESS: With IGS (n=97) Without IGS (n=61)	Patient co-morbidities; extent of surgery; complications; EBL; operative time; repeat surgery	IGS may reduce complications and reduce the need for revision surgery.
Reardon[2076]	2002	4	Case series	ESS procedures performed by 7 surgeons: With IGS (n=400) Without IGS (n=400)	Extent of surgery; complications	IGS usage is associated with more extensive surgery; IGS may be deployed in a community-hospital setting.
Gibbons[2137]	2001	4	Case series	Consecutive patients undergoing ESS with IGS (n=203)	Costs associated with IGS	ESS with IGS is more expensive than ESS without IGS.
Metson[2155]	2000	4	Case series	754 IGS procedures performed by 34 physicians	TRE; operative time; surgeon satisfaction	IGS can be deployed in a multi-surgeon OR.
Olson[2073]	2000	4	Case series	62 ESS with IGS cases	Indications for surgery; surgeon satisfaction; TRE	IGS, including preoperative CT review at the computer workstation, is helpful at specific subsites, especially in the setting of anatomic

						complexity.
Fried[2156]	1998	4	Case series; cadaver dissection	14 patients undergoing ESS; cadaver dissections	Feasibility; complications; surgeon satisfaction	IGS is suited to complex ESS procedures; it is anticipated to reduce surgical complications
Klimek[2122]	1995	4	Case series	14 pediatric patients undergoing skull base surgery	Technical description; completion of procedure	IGS has promise for skull base surgery.
Roth[2157]	1995	4	Case series	Patients undergoing ESS: With IGS (n=12) Without IGS (n=208)	Indications for surgery; operative time; costs; surgeon satisfaction	IGS can be used for the identification of key structures.
Beswick[2102]	2020	N/A	Narrative review	IGS literature	Narrative review	Published evidence (level 2A) suggests that IGS is associated with fewer complications.
Kristin[2085]	2019	N/A	Cadaveric trial	Comparison of automatic vs. manual mapping for paired-point registration	TRE measurements	Automated mapping of metallic markers is comparable to manual mapping.
Lee[1787]	2019	N/A	Survey	Survey of American Rhinologic Society membership	Usage of IGS in ambulatory clinics	IGS now used in ambulatory clinics.
Dixon[2142]	2016	N/A	Cadaveric lab	Comparison of 3D-IGS vs. conventional IGS	Accuracy, efficiency, task work load	3D IGS unlikely to be clinically useful.
Li[2141]	2016	N/A	Cadaveric lab	Novel augmented reality system description	System description	Augmented reality offers advantages over conventional ESS.
Bhattacharyya[2136]	2014	N/A	Data base analysis	ESS with and without IGS in ambulatory surgery centers in 5 states	Rate of IGS usage	Regional variation in IGS usage is considerable.
Citardi[2140]	201	N/	Cadaveric	Novel	Feasibility	Augmented

	4	A	lab	augmented reality system in a cadaveric model of ESS		reality IGS may offer advantages over conventional IGS.
Ramakirshnan[2098]	2013	N/A	Evidence-based review	6 publications from the peer-reviewed literature	Complication rate, clinical outcomes	IGS has not reduced complications nor has it improved clinical outcomes, despite wide support from many surgeons.
Justice[2135]	2012	N/A	Survey	Physician survey (n=337)	IGS usage; surgeon satisfaction	IGS technology is increasingly available, and surgeons favor its use for specific surgical challenges.
Fried[2158]	2008	N/A	Literature review	N/A	Abstracted observations and data from published reports	Definitive trial for IGS has not been done; almost all experts agree that IGS is a significant advance for ESS.
Smith[2099]	2007	N/A	Systematic review	5 peer-reviewed publications	Complications	Studies intended to confirm the impact of IGS on complication rates are not feasible.
Hardy[2084]	2006	N/A	Cadaveric dissection	10 specimens 3 groups: Fiducial registration Landmark registration Surface/contour registration	Time for registration; TRE	Fiducal TRE was 0.47 +/- 0.36 mm. Landmark TRE was 3.10 +/- 0.44 mm. Surface/contour TRE was 1.05 +/- 0.10 mm.
Hepworth[2133]	2006	N/A	Survey	Survey of practicing ENT surgeons	IGS usage; surgeon satisfaction	IGS usage is increasing; surgeons favor

				(n=672)		usage for more complex ESS cases.
Knott[2089]	2006	N/A	Simulation lab	Comparison of contour-based registration and paired-point registration	TRE	Paired-pointed registration offered better TRE, although the differences may not be clinically meaningful. Distribution of points for contour-based registration influences TRE.
Berry[2088]	2002	N/A	Dry lab simulation	N/A	Calculated TRE	Optimal TRE is the center of the fiducial points.

XII.D.5. Use of Packing in Sinus Surgery

Absorbable and non-absorbable materials are commonly used to pack the sinus cavities in the peri-operative period. Proponents of their use suggest that they facilitate hemostasis and improve wound healing while opponents argue that they increase patient discomfort and may increase scarring. This area has been well studied in recent years, with numerous well-performed RCTs.

Evidence exists to support the position that packing for hemostasis is not essential for the vast majority of sinus cases.[2159-2167] Five RCTs comparing packing to no-packing reported no evidence of significant post-operative bleeding requiring intervention in their unpacked arms.[2159-2161,2165,2167] This is further supported by a large retrospective series by Orlandi and Lanza of 165 patients undergoing ESS.[2162] This study observed that only 11.2% of patients required packing at the end of their sinus procedure, with no reports of significant post-operative bleeding in those left unpacked.

Intraoperative Hemostasis. Level 1 evidence now exists to support the findings of earlier case series that packing with absorbable biomaterials can help achieve rapid hemostasis within the sinuses.[2168-2171] Both Floseal® (Baxter Inc, Deerflied, Illinois, USA), an absorbable matrix of bovine-derived gelatin with human-derived thrombin and HemoStase® (CryoLife Inc, NW Kennesaw, USA), a purified plant polysaccharide, resulted in complete cessation of intra-operative bleeding within 5 minutes of application.[2168,2169] Although Jameson *et al.*[2170] reported a slower mean time to hemostasis of 16.4 minutes in their RCT using Floseal, hemostasis was still considerably faster than no intervention. When compared to Merocel (Medtronic ENT , Jacksonville, Florida, USA), a non-absorbable, highly porous polyvinyl acetyl sponge, Floseal did not appear to achieve significantly faster hemostasis.[2171] Other absorbable agents that have been evaluated include chitosan-dextran (CD) gel (Chitogel®), a biopolymer derived from the treatment of crustaceans (Chitogel Pty ltd, Wellington New Zealand); Sepragel®, a hyaluronan-derived gel (Genzyme Co, Cambridge, USA); Quixil®, a fibrin-based glue (OMRIX Biopharmaceuticals Ltd, Nes-Ziona, Israel); and Surgiflo® hemostatic matrix (Johnson & Johnson, Ethicon division Somerville, NJ, USA) used in combination with thrombin (King Pharmaceuticals, Bristol, TN, USA).[2159,2160,2172,2173] An RCT by Valentine at al.[2159] showed CD gel (Chitogel®), to achieve hemostasis in a mean time of 2 minutes, which was significantly lower than the average time of 10 minutes in untreated sinuses cavities. Sepragel® has also been compared to no intervention, but did not appear to confer the same advantage in the time to hemostasis.[2160] Vaiman *et al.* showed Quixil® to be significantly superior to Merocel® in the control of intra-operative bleeding and bleeding on pack removal, but no significant difference was observed in post-surgical bleeding > 30 hours after the procedure.[2172] Although Surgiflo® with thrombin was shown in one case series to have an impressive time to hemostasis (median=61 seconds) and success in 95% of patients, these findings have not yet been validated in a well-designed RCT.[2173]

Post-Operative Hemostasis. For situations where packing is necessary, a number of trials have compared various materials. Vaiman *et al.* reported significantly less bleeding in sinus cavities treated with fibrin sealant (Quixil®) compared to Merocel®, within the first 24 hours post surgery but not beyond.[2172] Yu *et al.*'s study[2174] did not replicate this finding in their study of an aerosolized form of a fibrin sealant but did report a decreased rate of bleeding on pack removal in favor of the fibrin sealant. Raghunandhan *et al.* (2014) in a DBRCT compared Nasopore® (Stryker, Hamilton, ON, Canada) with Merocel and showed that the Merocel had better hemostasis in the first 24 hours. Floseal®,[2171] Surgicel®,[2175] Cutanplast®[2176] (Mascia Brunelli S.p.A., Milan, Italy), and oxidized cellulose[2177] have also been found in RCTs to be associated with less bleeding than Merocel® at the time of pack removal. Al-Shaikh *et al.*'s[2177] study also showed oxidized cellulose to be associated with significantly less bleeding

than Merocel®, immediately after surgery and on post-operative days 4,6 and 7. Kim *et al.*[2178] investigated whether gloving Merocel® prior to its insertion had any effect on hemostasis and found that sinus cavities packed with the gloved Merocel® had 40g less bleeding on removal than sides packed with ungloved Merocel®. Mehan *et al.* performed an RCT with polyvinyl acetate (PVA) packing on one side for a day after which it was removed and compared this to no packing. There was significantly more bleeding on the unpacked side on day 1 but significantly more bleeding after pack removal on the packed side on days 2 and 3 with no difference thereafter.[2167]

Nasopore®, a fully synthetic absorbable dressing, has also been studied extensively. Two different RCTs comparing Nasopore® to Merocel® have shown contrasting results. While Verim *et al.*[2179] showed a benefit of Nasopore® in all areas of post-operative morbidity including bleeding on packing removal, this was not replicated in Shoman *et al.*'s RCT.[2180] More recently a DBRCT by Kastl *et al.*[2181] showed no post-operative hemostatic benefit of Nasopore® over not packing at all. Jung *et al.* in an RCT compared aerosolized fibrin sealant to Nasopore® and found no difference post-operative bleeding.[2165]There is some evidence to suggest that pre-soaking Nasopore® with lidocaine may improve its hemostatic effect within the first 24 hours after surgery,[1887] without causing adverse hemodynamic effects, but studies comparing this treatment to no packing have not yet been performed.

A recent systemic review and meta-analysis compared fibrin tissue adhesive (FTA) vs. nasal packing in which 4 studies were identified.[2182] Bleeding trended toward improvement in the packing group but not statistically significantly. Nasal obstruction, granulations were better in the FTA group.

Wound Healing. Critical to good surgical outcomes is optimal wound healing. Various studies have investigated the effects of different packing materials on adhesion formation, crusting, mucosal edema, inflammation, and cilia regeneration. Packing materials that have been evaluated against not packing at all include Merocel®[2183] and absorbable materials such as Floseal®, [2170] HemoStase®[2184] carboxymethylcellulose (CMC),[2185] Merogel®, [2186] Sepragel®[2187] and CD gel (Chitogel®).[2159] Only CD gel (Chitogel®), Merocel® and Sepragel® were shown to confer any advantage over not packing at all, with both showing lower adhesion rates in their active treatment arms.[2159,2183] CD gel (Chitogel®) was also shown, in another RCT, to be associated with significantly larger sinus ostial sizes at 3 months, although this study did not report any difference in adhesion rates between treated and untreated cavities.[2188] In a more recent study CD gel (Chitogel®) showed a significant improvement in frontal, maxillary and sphenoid ostial size at 12 months.[2189] A small noncontrolled study by Kim *et al.*, suggests that gloving the Merocel® pack prior to insertion may further reduce its post-operative adhesion rate, however this finding has yet to be validated in a controlled study.[2178] Given the perceived benefits of Merocel® in reducing adhesion formation, several RCTs have evaluated different packing materials directly against Merocel®. Floseal®, [2171] fibrin sealant,[2174] oxidized cellulose,[2177] and Nasopore®[2179,2180] have all been found to have similar effects on postsurgical wound healing, including rate of adhesion formation. Contrasting results exist in RCTs comparing Merogel® to Merocel® however. While an RCT by Berlucchi *et al.*[2190] suggested better early and long-term wound healing for Merogel®, no difference between these agents was observed in two other independent RCTs.[2191,2192] A RCT by Park *et al.* 2016 comparing Calcium alginate (Algi-pack®) and carboxymethylcellulose (Sinu-knit®) showed a statically better outcome with respect to adhesions and edema for the calcium alginate pack. Interestingly an RCT by Shi *et al.* evaluating a hyaluronan-based gel, PureRegen Gel® (BioRegen Bio- medical, Changzhou, China), observed improved wound healing in terms of adhesion formation, edema and crusting when the gel was applied to Merocel® prior to packing.[2193] This does suggest a possible benefit of hyaluronan gel.

Floseal® and CMC have also been extensively investigated for their effect on wound healing. Although studies by Jameson *et al.*[2170] and Baumann *et al.*[2171] reported no difference in wound healing or adhesion rates when Floseal® was compared to no treatment or packing with Merocel®, concerns have been raised regarding Floseal®'s possible pro-adhesion properties. Two studies by Chandra *et al.*,[2194,2195] suggest that Floseal® may actually incite early granulation tissue formation, with a higher rate of symptomatic adhesion formation. Their histopathological finding of incorporated foreign material within a mature synechiae supports this concern.[2195] Like Floseal®, CMC has not been shown to confer any significant benefit on wound healing compared to leaving a cavity unpacked.[2185] Two separate RCTs do suggest however that CMC dressings may be associated to a lower rate of adhesion formation when compared to commonly used non-absorbable dressings.[2196,2197]

Yan *et al.* in a systemic review and meta-analysis of biodegradable packing showed that biodegradable packing was better than removable packing for bleeding on removal of packs, pain and nasal obstruction but could not determine whether biodegradable packing was better than no packing at all.[2198] Stern-Shavit *et al.* did a decision analysis model which showed that packing was not advantageous for patients undergoing ESS but that absorbable packing had less adverse effects than non-absorbable packing.[2166]

Patient Comfort. Sinus surgery itself is not characteristically associated with significant amounts of pain, although patients do frequently report discomfort from nasal packing and its removal. Level 1 evidence suggests that packing with absorbable dressings such as Nasopore®,[2181] HemoStase®,[2161] Sepragel®[2187] and Floseal®[2170] is not associated with any increase pain, compared to unpacked cavities. In fact in the studies that evaluated Sepragel® and Floseal®, patients reported less subjective discomfort on the treated side.[2170,2187] Both studies were small in number however and did not use validated pain scoring systems. Bugten *et al.*[2183] also reported no significant difference in pain scores between patients packed bilaterally with Merocel® and those left unpacked, although a patient self-controlled study has not yet been performed to validate this observation. Several RCTs have directly compared pain and comfort levels of packing using absorbable vs non-absorbable materials. Nasopore® and Merogel® (Medtronic, Jacksonville, Florida, USA) have both been found to better tolerated than non-absorbable Merocel® while *in situ*,[2179,2180,2190] with Merogel causing less discomfort on removal.[2190] Park *et al.* in a single blinded randomized controlled study found no difference in pain when comparing calcium alginate packing to carboxymethylcellulose but showed less edema and adhesions with the latter.[2164] Finally, studies have also investigated whether modifications to existing dressings can also improve their tolerance and discomfort level during removal. The addition of lidocaine to Nasopore®, intra-operatively and 8 hours post-surgery appeared to be significantly reduced immediate post-operative pain for up to 16 hours after surgery,[1887] while gloved Merocel® packs were found to cause less discomfort on removal than standard Merocel® packs.[2178] In an RCT Yayik *et al.* showed that adding bupivacaine and dexamethasone to the nasal pack decreased pain and analgesic requirements in the first 24 hours after surgery.[2199] In another RCT Garzaro *et al.* showed that adding 5ml of lidocaine to a PVA sponge did not result in less pain then a saline soaked sponge in a gloved finger.[2200] Yan[2198] did a systemic review and meta-analysis of biodegradable vs. standard packing and showed that biodegradable packing showed significant improvements in bleeding at the time of removal, pain *in situ*, pain on removal and nasal obstruction. No difference could be found in wound healing. Hobson *et al.* conducted another systemic review and meta-analysis in 2015 and showed that middle meatal packing did not significantly reduce the incidence of middle meatal adhesions.[2201]

In summary, packing does not appear to be necessary in the majority of ESS cases. If packing is chosen, available evidence indicates packing achieves hemostasis without significant adverse effects on postoperative wound healing.

Use of Packing in Sinus Surgery

Aggregate Grade of Evidence:

- Intraoperative Hemostasis: A (Level 2: 6 studies; level 3: 1 study; level 4: 2 studies)
- Postoperative Hemostasis: A (Level 1: 2 studies; level 2: 14 studies; level 3: 1 study; level 4: 1 study)
- Wound Healing: A (Level 1: 2 studies; level 2: 27 studies; level 4: 1 study)
- Patient Comfort: A (Level 2: 14 studies)

Benefit: Rapid control of intra-operative bleeding. Potential reduction in adhesion formation with some materials. CD (Chitogel®) appears to improve ostial sizes postoperatively.
Harm: Potential for increased discomfort while *in situ* and on removal. Rare risk of toxic shock syndrome. Potential for an increased rate of clinically significant adhesions with some materials.
Cost: There is a cost associated with all packing materials, with absorbable materials being more costly than nonabsorbable packing.
Benefits-Harm Assessment: Balance of risks and benefits.
Value Judgments: For the majority of sinus surgical cases packing is not required for intraoperative hemostasis and will not reduce the risk of post-operative epistaxis. Although evidence does exist suggesting packing may reduce adhesion formation, it is limited and has not been compared to studies employing early and frequent debridement.
Policy Level: Option
Intervention: When bleeding cannot be controlled, packing may help achieve hemostasis, without significant adverse effects on postoperative wound healing

Table XII-21. Evidence for use of packing in sinus surgery

Author	Year	LOE	Study Design	Materials	Outcome Measure	Findings
Intraoperative Hemostasis						
Kameswaran [2202]	2014	2	DBRCT 30 patients - 60 sides	Nasopore vs. Merocel	Post op bleeding	Less bleeding in the first 24 hours
Beyea[2169]	2011	2	RCT 18 patients - 36 sides	Floseal® vs. HemoStase®	Total blood loss	No significant difference
Valentine[2159]	2010	2	DBRCT 40 patients – 80 sides	CD gel (Chitogel®)vs. no packing	Time to hemostasis	CD gel: 2minutes No packing: 10 minutes
Jameson[2170]	2006	2	Double Blind RCT 45 patients - 90 sides	Floseal® with patties vs. patties alone	Time to Hemostasis	Statistically significant difference with Floseal® added to patties (16.4 min vs.. 30.8 min)
Vaiman[2172]	2005	2	RCT 91 patients undergoing ESS 48 sides	Merocel® vs. Quixil®	All types of bleeding Bleeding after removal Late bleeding	Quixil significantly better in #1 and #2. No significant difference in #3.

			Merocel 43 sides Quixil		>30 hours	
Frenkiel[2160]	2002	2	RCT 20 patients – 40 sides	Sepragel® vs. no packing	Intra-op hemostasis	No significant difference in total blood loss
Baumann[2171]	2003	3	Individual case control 50 patients - 100 sides	Floseal® vs. Merocel®	Hemostasis	No significant difference (mean 3 minutes)
Woodworth[2173]	2009	4	Noncontrolled case series 30 patients - 30 sites	Gelatin-thrombin matrix (Surgiflo®) with thrombin	Intraoperative hemostasis	29/30 sites had complete hemostasis within 10 minutes
Gall[2168]	2002	4	Cohort Study 18 patients - 30 sites	Floseal®	Time to hemostasis	Average time 2minutes Unable to stop bleeding 18 sites
Postoperative Hemostasis						
Yan [2198]	2014	1	Meta-analysis	19 studies 11 comparing absorbable with non-absorbable dressing	Bleeding at removal	Better outcomes for bleeding at removal
Coey [2182]	2019	1	Meta-analysis	4 studies comparing fibrin tissue adhesive and nasal packing	Post-operative bleeding	Improved bleeding in the packing group but not statistically significant
Mehan R [2167]	2017	2	RCT 50 patients – 100 sides	PVA sponge for 24 hours vs. no packing	Post-operative Hemostasis	Less bleeding on packed side first 24 hours
Al –Shaikh[2177]	2014	2	RCT 47 patients - 94 sides	Oxidized cellulose powder vs. Merocel®	Postoperative bleeding	Oxidized cellulose use had significantly less bleeding than Merocel®
Kastl[2181]	2014	2	DBRCT 47 patients – 94 sides	Nasopore® vs. no packing	Post op bleeding	No significant difference
Verim[2179]	2014	2	Partly blinded RCT 56 patients – 112 sides	Nasopore® vs. Merocel®	Postoperative hemostasis	Significantly better for Nasopore®
Jung [2165]	2017	2	RCT 35 patients – 70 sides	Aerosolized fibrin sealant vs. nasopore®	Bleeding	No difference with respect to bleeding post-operatively
Kameswaran [2202]	2014	2	DBRCT 30 patients -	Nasopore vs. Merocel	Pain and healing	Nasopore more comfortable and

			60 sides		(adhesions)	less adhesions
Yu[2174]	2014	2	Nonblinded RCT 41 patients – 82 sides	Aerosolized fibrin sealant vs. Merocel®	Bleeding	Increased in incidence in bleeding on removal of packing compared to fibrin sealant but not on follow up
Cho[2176]	2013	2	RCT 100 patients – 200 sides	Cutanplast® vs. Merocel®	Bleeding and pain on pack removal	Cutanplast® had less bleeding and pain on removal and less time to control bleeding following pack removal
Mo[1887]	2013	2	DBRCT 63 patients – 123 sides	Nasopore® soaked in lidocaine vs. Nasopore®	Post-operative bleeding as determined by the number of gauze changes	The number of gauze changes at 1,4,16,20 hours were not significantly different between the two groups
Kim[2178]	2012	2	RCT 15 patients – 30 sides	Gloved Merocel® vs. Merocel®	Bleeding on pack removal	Gloved Merocel® had 40g less blood loss than ungloved Merocel®
Antisdel[2161]	2009	2	Single blinded RCT 40 patients – 80 sides	Microporous polysaccharide hemospheres vs. no packing	Post-operative hemostasis	Only significant difference on post-operative day 1
Shoman[2180]	2009	2	RCT 30 patients – 60 sides	Nasopore® vs. Merocel®	Postoperative hemostasis	No significant difference
Vaiman[2172]	2005	2	RCT 91 patients undergoing ESS 48 sides Merocel 43 sides Quixil	Quixil® vs. Merocel®	All types of bleeding Bleeding after removal Late Bleeding >30 hours	Quixil® significantly better for all types of bleeding and bleeding upon removal. No difference in late bleeding.
Shinkwin[2175]	1996	2	RCT 60 patients - 120 sides	Surgicel® vs. Merocel® or petroleum ointment gauze	Post-operative Hemostasis	Surgicel® use had less bleeding on pack removal compared to Merocel® or petroleum ointment gauze

Baumann[2171]	2003	3	Individual case control 50 patients - 100 sides	Floseal® vs. Merocel®	Hemostasis	Removal of Merocel® associated with increased bleeding
Orlandi[2162]	2004	4	Retrospective case series 165 patients - 169 sinus surgical procedures	147 unpacked 19 packed 4 hemostatic agents used	Significant postoperative bleeding requiring intervention	No significant postoperative bleeding complications reported
Wound Healing						
Hobson [2201]	2015	1	Meta-analysis	18 studies	Adhesion formation	Middle meatal packing does not significantly reduce the risk of middle meatal adhesions
Yan [2198]	2014	1	Meta-analysis	19 studies 11 comparing absorbable with non-absorbable dressing	Mucosal healing Pain at removal Pain *in situ* Nasal blockage	No difference in mucosal healing Varied outcomes for pain and nasal blockage
Stern- Shavit [2166]	2017	2	Decision analysis model			Packings post ESS was not advantageous for patients but absorbable packing had less adverse effects
Akiyama[2196]	2014	2	RCT single blinded 44 patients – 88 sides	Silver CMC vs. chitin-coated gauze	Synechiae	Silver CMC had significantly less adhesions (0% vs. 14%)
Al –Shaikh[2177]	2014	2	RCT 47 patients - 94 sides	Oxidized cellulose powder vs. Merocel®	Crusting, adhesions, infection	No significant difference
Verim[2179]	2014	2	Partly blinded RCT 56 patients – 112 sides	Nasopore® vs. Merocel®	Edema, crusting, secretions, synechiae, granulation tissue, percentage re-epithelization	No significant difference in wound healing at any time point in the first 6 months after surgery
Jung [2165]	2017	2	RCT 35 patients	Aerosolized fibrin sealant vs. Nasopore®	Endoscopic findings of	No significant difference for

			– 70 sides		crusting, infection, adhesions, frontal stenosis, granulation tissue	infection, adhesions or frontal ostial size; fibrin sealant showed less crusting and granulation tissue compared to Nasopore®
Yu[2174]	2014	2	Nonblinded RCT 41 patients – 82 sides	Aerosolized fibrin sealant vs. Merocel®	Endoscopic findings of crusting, infection, adhesions, frontal stenosis, granulation tissue	No significant difference for infection, adhesions or frontal ostial size; fibrin sealant showed less granulation tissue at 2 and 4 weeks and less crusting a 1 week compared to Merocel®
Ha[2189]	2018	2	Single surgeon DBRCT 36 patients – 72 sides	CD gel (Chitogel®) vs. Chitogel + budesonide vs. no packing vs betamethasone cream	Wound healing including adhesion rate Ostial size at 3, 6, 12 months for maxillary, frontal and sphenoid	Significant improvement in ostial size for Chitogel alone and Chitogel + budesonide compared to no packing
Garzaro [2200]	2020	2	RCT	Gloved PVA pack vs. PVA pack + lidocaine	Pain in 24 hours post surgery	Gloved PVA pack had less pain
Yayik [2199]	2019	2	RCT 72 patient – 144 sides	Lidocaine soaked pack vs. lidocaine + dexamethasone soaked pack	Pain post surgery	Less pain in first 24 hours post surgery
Ngoc[2188]	2013	2	Single surgeon DBRCT 26 patients – 52 sides	CD gel (Chitogel®) vs. no packing	Wound healing including adhesion rate Ostial size at 3 months for maxillary, frontal and sphenoid	No significant difference in wound healing. Significantly larger ostial sizes for CD treated cavities
Grzeskowiak [2203]	2018	2	DBRCT 80 patients 160 sides	Nasopore + saline vs. nasopore + steroid vs. nasopore + antibiotic	Healing and secretions	Steroid _ nasopore had improved

						healing and less secretions
Shi[2193]	2013	2	RCT 54 patients – 108 sides	PureRegen® gel plus Merocel® vs. Merocel® alone	Re-epithelialization, adhesions, edema, and crusting.	PureRegen® gel had better % re-epithelization, Incidence of non-obstructing adhesions, edema, and crusting
Kim[2178]	2012	2	RCT 15 patients – 30 sides	Gloved Merocel® vs. Merocel®	Adhesion rate Postoperative Lund-Kennedy endoscopic score	Higher adhesion rate for ungloved pack Significantly better endoscopic score at 4 weeks but no difference later
Antisdel[2184]	2011	2	RCT 40 patients – 80 sides	Microporous polysaccharide hemospheres vs. no packing	Synechiae Edema Infection	No significant difference in any outcomes.
Szczygielski[2197]	2010	2	RCT 60 patients – 120 sides	CMC packing bilaterally vs. latex gloved cotton gauze bilaterally	Synechiae at 8 weeks	CMC packing had significantly less synechiae (6.5% vs. 35.7%)
Valentine[2159]	2010	2	DBRCT 40 patients – 80 sides	CD gel vs. no packing	Adhesion formation	Lower at all time points in first 3 months postoperatively for CD-treated group
Berlucchi[2190]	2009	2	RCT 66 patients -88 sides	Merogel® vs. Merocel®	Adhesions % re-epithelization Granulation Edema Crusting	Merogel showed superiority in most outcomes and at some time points.
Kastl[2185]	2009	2	RCT 26 patients – 52 sides	CMC mesh vs. CMC gel vs. nothing	Wound healing	No significant difference among the groups
Shoman[2180]	2009	2	RCT 30 patients – 60 sides	Nasopore® vs. Merocel®	Postoperative edema	No significant difference
Franklin[2192]	2007	2	RCT	Merogel® vs. Merocel®	Lund-Kennedy	No significant

			35 patients – 70 sides		endoscopic score	difference
Bugten[2183]	2006	2	RCT 59 patients 31 packed with Merocel 28 unpacked	Merocel® for 5 days vs. no packing	Middle meatal adhesion rate at 10-14 weeks	More bilateral adhesions in unpacked patients. No difference in unilateral adhesions.
Jameson[2170]	2006	2	DBRCT 45 patients - 90 sides	Floseal® with patties vs. patties alone	Wound healing	Only significant difference was that Floseal® showed less crusting at 1 week postoperatively
Wormald[2186]	2006	2	Blinded RCT 42 patients – 84 sides	Merogel® vs. nothing	Adhesion, edema, infection	No difference at 2,4,6-8 weeks for any parameter
Chandra[2195]	2005	2	RCT 13 patients – 36 sides	Floseal® vs. thrombin soaked gelatin foam	Adhesions at 1 year	Floseal® showed a higher number of adhesions overall and a higher number requiring lysis
Chandra[2194]	2003	2	RCT 20 patients – 40 sides	Floseal® vs. thrombin soaked gelatin foam	Granulation and adhesions at 6 weeks	Floseal® had significantly more adhesions
Miller[2191]	2003	2	RCT 37 patients – 74 sides	Merogel® vs. Merocel®	Postoperative edema at 8 weeks	No significant difference
Kimmelman[2187]	2002	2	RCT 10 patients – 20 sides	Sepragel® vs. nothing	Synechiae, middle meatus stenosis, mucosal status	All significantly better in Sepragel® treated sided at week 2.
Baumann[2171]	2003	4	Individual case control 50 patients - 100 sides	Floseal® vs. Merocel®	Middle meatal synechiae and stenosis	No significant difference
Patient Comfort						
Kastl[2181]	2014	2	DBRCT 47 patients – 94 sides	Nasopore® vs. nothing	Pain, breathing, sleep disturbance,	1. No significant difference in any of these

					headache, well-being Pressure Subjective assessment of which side felt better	parameters 2. Packing showed slightly less on days 2 and 3 3. No significant difference
Park[2164]	2016	2	Single blinded RCT 27patients – 54 sides	Calcium alginate vs. Sinu-Knit (carboxymethylcellulose)	Pain Adhesion Infection Edema	No difference in pain Less adhesions and edema with Ca Alginate
Verim[2179]	2014	2	Partly blinded RCT 56 patients – 112 sides	Nasopore® vs. Merocel®	Pain, bleeding, facial edema, nasal obstruction	All significantly less with Nasopore®
Yu[2174]	2014	2	Nonblinded RCT 41 patients – 82 sides	Aerosolized fibrin sealant vs. Merocel®	Visual Analogue Symptom Score	No significant difference while pack *in situ* but greater pain and nasal bleeding during removal of pack
Cho[2176]	2013	2	RCT 100 patients – 200 sides	Cutanplast® vs. Merocel®	Pain on pack removal	Cutanaplast® had significantly less pain on removal.
Mo[1887]	2013	2	DBRCT 63 patients – 123 sides	Nasopore® soaked in lidocaine vs. Nasopore®	Pain at 1, 4, 8, 16, 20, and 24 hours	Significantly less pain at 1, 4, 8, and 16 hours in lidocaine soaked group. Same at 20 and 24 hours.
Akbari[2204]	2012	2	DBRCT 37 patients - 74 sides	Gloved Merocel® vs. Merocel®	Discomfort on removal	Ungloved pack had more discomfort on removal than gloved pack.
Antisdel[2161]	2009	2	single blinded RCT 40 patients – 80 sides	Microporous polysaccharide hemospheres vs. no packing	Pain, obstruction, and nasal discharge	No significant difference
Berlucchi[2190]	2009	2	RCT 66 patients -88 sides	Merogel® vs. Merocel®	Pain on packing removal	Significantly decreased in Merogel® group
Shoman[2180]	2009	2	RCT 30 patients	Nasopore® vs. Merocel®	Postoperative pain	1. Significantly decreased pain

			– 60 sides		Pain on packing removal	with Nasopore® 2. No significant difference
Bugten[2183]	2006	2	RCT 59 patients 31 packed with Merocel 28 unpacked	Merocel® for 5 days vs. no packing	Pain, congestion, headache, sleep quality for 10-14 weeks after surgery	No significant difference in any parameter scores between the groups,
Jameson[2170]	2006	2	DBRCT 45 patients - 90 sides	Floseal® with patties vs. patties alone	Pain in first week	Significantly less in Floseal® group
Kimmelman[2187]	2002	2	RCT 10 patients – 20 sides	Sepragel® vs. nothing	Post-operative subjective pain and congestion	Significantly less in packed group
Shinkwin[2175]	1996	2	RCT 60 patients -120 sides	Surgicel® vs. Merocel® or petroleum ointment gauze	Patient comfort	Surgicel® had less discomfort on removal than Merocel® and ointment gauze.

XII.D.6. Inert Stents in Sinus Sugery

Ostial stenosis, synechiae formation and middle turbinate lateralization (MTL) represent three of the most common complications following ESS, with up to 27% of patients being found to develop adhesions despite meticulous post-operative care.[2205-2207] A 2004 review of 80 revision sinus surgeries found that 50% of frontal recesses and 39% of middle meati (MM) had stenosis.[2208] Moreover, a 2014 review of 66 patients requiring revision frontal sinus surgery found a 48% rate of MTL.[2209] The importance of preventing post-operative adhesions was demonstrated in a 2013 multi-institutional study of 286 patients: patients with synechiae had less improvement in two QoL instruments even after controlling for differences in disease severity. [2210]

To prevent the formation of synechiae formation and MTL, surgeons may deploy the use of non-medicated, non-absorbable inert stents into the MM.[2211] Two double-blind RCTs[105,2212] (patient, reviewing surgeon), comparing MM silastic stents to no MM stenting, demonstrated that MM silastic stenting reduced MTL, synechia, and crusting, but had no effect on symptoms or other endoscopic scores. A DBRCT performed by Manji, *et al.*[2213] compared a silastic MM stent to a gloved Merocel spacer (randomly placed, intrapatient control) and found no difference in synechiae between both sides although removal of silastic stents was rated more painful. Numerous case series[2214-2218] found silastic middle meatus stents to be well-tolerated and to reduce postoperative synechiae. A recently developed balloon-expandable polyurethane/nitinol alloy stent[2219] designed to be removed at 4 weeks has been proposed as a means of easily stenting the ethmoid cavity, preventing adhesions, and reducing MTL. A comparison of 14 to 28 days of a polyurethane/nitinol stent to 2 to 3 days of polyethylene terephthalate stenting revealed a 9.3 times greater risk of adhesions and a 44% (v 3.8%) risk of MTL in the polyethylene terephthalate group. Patients in the polyurethane/nitinol group also experienced

significantly better QoL outcomes.[2220] The unbalanced nature of this study demands further investigation.

The frontal sinus, with its narrow diameter, has been stented with inert material post-operatively for over 100 years, beginning with a gold tube in 1905.[2221] There are currently no randomized studies evaluating post-operative inert stents in the frontal sinus. Some authors proposed that stenting should be considered when the neo-ostium is <5mm or has been significantly demucosalized (>50%), and that stents should be maintained for at least 6 weeks.[2211,2222] Numerous case series[2223-2231] have evaluated soft silicone stents, either fashioned or proprietary, in the postoperative frontal sinus. These uncontrolled studies and have found that inert frontal sinus stents reduce stenosis and reoperation rates. The longest duration of stenting described is 6 years.[2228] Despite the conclusion that these frontal sinus stents are well-tolerated and may reduce stenosis, evidence exists that biofilm formation may complicate their use long-term.[2232]

Middle Meatus/Ethmoid Stenting

Aggregate Grade of Evidence: B (Level 2: 4 studies; level 4: 5 studies)
Benefit: Well-tolerated; reduction in synechiae; improved sinus patency
Harm: Biofilm formation, pain upon removal, potential restenosis, may not change symptoms or endoscopic score
Cost: Minimal to moderate
Benefit-Harm Assessment: Preponderance of benefit over harm
Policy Level: Recommendation
Intervention: Use of inert stents after ethmoid/middle meatus sinus surgery

Frontal Sinus Stenting

Aggregate Grade of Evidence: D (Level 4: 10 studies)
Benefit: Well-tolerated; reduction in synechiae; improved sinus patency
Harm: Biofilm formation, infection related to stent, pain upon removal, potential restenosis, may not change symptoms
Cost: Minimal to moderate
Benefit-Harm Assessment: Balance of risks and benfits
Policy Level: Option
Intervention: Use of inert stents after frontal sinus surgery

Table XII-22. Evidence for inert middle meatus stenting in sinus surgery

Author	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Yaniv[2220]	2019	2	RCT	Unilateral MM ST stent 2-4 weeks Contralateral telfa pack 2 days	3-6- and 12- week endoscopic inflammation (VAS), MT adhesion, MTL 12 week SNOT-22	The ST stent is more effective than telfa packing in reducing sinonasal inflammation,

						MT adhesions, MTL, and SNOT-22 scores
Manji[2213]	2018	2	DBRCT, <80% full follow-up	Unilateral MM silastic stent x 1 week Contralateral MM gloved merocel x 1 week	Patient pain with stent/packing removal at 1 week 5- and 12-week MLK score and synechia presence	MM silastic is more painful to remove at 1 week than MM gloved merocele There is no difference in healing and synechia formation at 12 weeks between MM silastic stent and gloved merocel
Chan[105]	2015	2	DBRCT	Unilateral MM silastic stent x 2 weeks Contralateral MM no stent	VAS 6 months MLK score 6 months	MM silastic stents effectively reduce MTL, adhesions, and crusting but have no effect on PROMs
Baguley[8]	2012	2	RCT, <80% full follow-up	Unilateral MM silastic stent x 2 weeks Contralateral MM no stent	6- and 12- week ethmoid and synechia grading 12-week symptom scores	MM silastic splints reduce adhesions at 12 weeks MM silastic splints do not significantly change symptom or endoscopic scores at 12 weeks
Mantovani[221 8]	2014	4	Descriptive case series	25 patients (35 stents) polypropylene bi-winged (dragon-fly) stents x 4 weeks – both MM and nasal valve stent	3-, 6-, 12-, and 18-month presence of synechia	No synechia observed at any time point Dragon-fly stents are well-tolerated and highly efficient at preventing synechia
Khwaja[2217]	2011	4	Descriptive cases series	MM silastic Park stents in all patients with deficient MT x 2	9- to 36- month presence of MTL or adhesions	Park MM silastic stents are well-tolerated and

				weeks		may be associated with decreased synechia
Lee[2214]	2007	4	Case control	MM silastic x 10-14 days MM no stent	5- month rate of synechia	Silastic in the MM in setting of floppy/deficient MT prevents lateral synechia formation
Shikani[2216]	1994	4	Cohort, poor data reporting	Unilateral silicone OMU stent x 10-14 days Contralateral OMU no stent	3- to 18- month symptoms, antrostomy size, adhesions	Silicone OMU stent improved antrostomy patency rate
Salman[2215]	1993	4	Descriptive case series	Silicone MM stent x 10-14 days	2 years (not specified endpoints)	No complications as a result of using this stent

Table XII-23. Evidence for inert frontal sinus stenting in sinus surgery

Author	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Rotenberg[2231]	2016	4	Descriptive case series	30 patients undergoing EMLP with biliary T-tube placement	Intra- and post-operative bleeding, infection, and post-operative frontal cavity re- stenosis	4 patients required antibiotics, 1 patient had re-stenosis Biliary T-tube stent is well-tolerated and effected
Mansour[2230]	2013	4	Descriptive case series	5 patients (7 sinuses) undergoing revision frontal surgery with silicone double J stents x 6 months	10- to 36- month frontal sinus patency	4/5 patients had patent FSOTs Double J stenting of the frontal sinus is safe and effective
Hunter[2229]	2010	4	Descriptive case series	3 frontal sinuses with silicone Rains stents x 19-60 months	19- to 60- month follow-up of symptoms	2 patients required revision surgery and then stent re-insertion after which became asymptomatic. Long-term

						stenting is viable option in select patients
Orlandi[2228]	2009	4	Descriptive case series	9 frontal sinus Rains stents x at least 6 months	Evaluation of stent condition after at least 6 months	1 patient had stent removed for infection and 1 was removed for discomfort/ edema 7 patients had stents from 15 to 73 months with no ill-effects. Long-term frontal sinus stenting is well-tolerated
Banhiran[2227]	2006	4	Case-cohort	72 EMLP patients with 25 silastic stents x 2 months	6- to 75- month evaluation of FS patency and symptom improvement/ worsening	No difference between stented and non-stented patients 2-month EMLP cavity stenting does not appear to reduce post-operative FS stenosis
Perloff[2232]	2004	4	Descriptive case series	6 patients with frontal sinus silicone stents x 1-4 weeks	Presence of biofilm	6 of 6 patients had biofilm formation
Rains[2226]	2001	4	Descriptive case series	102 silicone FS stents x 6-130 days (avg 35)	8- to 48- month follow-up of FS patency or revision requirement	6% of FS stenosed requiring revision Rains frontal sinus stent is safe and effective
Weber[22]	2000	4	Descriptive case series	12 patients (21 FS stents: 7 rains, 7 U-stents, 4 H-stents) x 6 months	10- to 36- month endoscopic evaluation of FSOT patency and subjective symptoms	Majority (10/12) patients experienced major symptom improvement. 9 of 12 patients had patent or aerated FS Frontal stents

						left in place x 6 months are more effective than those used earlier
Freeman[2224]	2000	4	Descriptive case series	73 frontal sinus silicone semi-rigid stent, duration not specified	12- to 45- month stent functionality and need to remove	All stents remained functional and were relatively well-tolerated 6 patients went on to require FSS obliteration Freeman stent is safe and prevent FSOT blockage
Amble[2223]	1996	4	Descriptive case series	196 fronto-nasal duct stents with rolled silicone x up to 8 weeks all after external Lynch approach	1- to 47- month presence of symptoms or need for revision	2 and 7 patients of 196 required revision or had symptoms attributable to frontal sinusitis, respectively. Rolled silicone stent after lynch approach in frontal sinus surgery is safe and effective

XII.D.7. Drug Eluting Packing, Stents, and Spacers in Sinus Surgery

While ESS is quite successful in treating medically resistant CRS, postoperative inflammation may hamper the ultimate recovery of patients. Postoperative failures may be caused by synechiae formation, ostial stenosis, neo-osteogenesis, middle turbinate lateralization and recurrent polyposis.[2205,2233-2236] These complications are currently mitigated by saline irrigations to reduce crusting, postoperative debridement, adhesion lysis, as well as topical and systemic corticosteroids. Postoperative debridement can be painful and the use of systemic corticosteroids carries potential side effects. Topical corticosteroids can be useful in improving healing but efficacy is limited by patient compliance as well as the inability to deliver sufficient drug to the ethmoid bed in the setting of post-operative edema.[2237]

In order to improve postoperative healing, a wide variety of techniques have been developed including the use of packing, stents and spacers. Nasal packing is principally designed for postoperative hemostasis and in animal models some packing materials demonstrate improved wound healing. Stents and spacers on the other hand are designed to maintain middle meatal patency and allow irrigation without obstruction. If the stents also elute drug, they can potentially provide local medical therapy to the sinus mucosa, independent of patient compliance with minimal systemic side effects.[2238]

Non drug-eluting stents can act as spacers to prevent adhesion formation and provide a scaffold for mucosal regrowth, however there is conflicting evidence on their effectiveness.[2227,2236] Controversy also exists in regard to duration of placement and the type of stent employed.[2238] Silastic stents have been associated with biofilm formation postoperatively which may be counter-productive in the treatment of CRS.[2232]

The off-label addition of steroid to dissolvable packing has shown improved outcomes for wound healing post ESS. In a DBRCT, Grzeskowiak 2018 showed that the addition of a steroid to Nasopore® demonstrated significant improvement in wound healing and secretions, when compared to Nasopore® alone. In a three armed study, Ha *et al.* showed that the addition of Budesonide to CD gel (Chitogel®) showed a significant improvement in ostial size when compared to Chitogel® and to no packing.[2189] In a retrospective cohort study, Xu *et al.* showed that Merogel® soaked in triamcinolone had no significant difference in adhesion formation than Merocel® in a finger cot.[2163]

In an "off-label" use, non-biodegradable spacers such as the Relieva Stratus Microflow Spacer™ (Acclarent, Irvine, CA) have been used as a drug eluting stent by filling the spacer with triamcinolone.[2238,2239] However, these can be difficult to remove with a case report of retained spacers leading to inflammation and infection 7 months after initial insertion.[2240,2241] There has also been a case report of orbital violation leading to pain and a permanently dilated pupil.[2242] One downside to the"off-label" addition of drug to materials is the unpredictable and unknown local release dynamics of the drug as well as the potential for systemic absorbtion.

Biodegradable drug eluting stents offer the benefit of having both a mechanical spacer combined with precise sustained release of medication into the sinus cavity over a known period of time.[2243] Unlike non-biodegradable stents, they may not require potentially painful postoperative removal. Currently, the only drug eluting postoperative stent approved by the US FDA is the Propel™ corticosteroid-releasing implant (Intersect ENT, Palo Alto California, USA). It consists of a self-expanding, bioabsorbable, drug eluting stent with the active ingredient of 370µg mometasone furoate embedded in a polymer matrix composed of polylactide-co-glycolide that degrades over 30 days. Once inserted, its spring-like action helps maintain the patency of the middle meatus allowing continued sinus irrigation. In animal studies, this stent showed minimal mucosal inflammatory reaction.[2244]

The Propel™ stent has been investigated in 1 cohort study and 2 RCTs, which have demonstrated its efficacy and safety. All three studies found similar outcomes with improvements in symptom scores and endoscopic findings (decreased polyposis and adhesions) as well need for postoperative intervention when compared to the stent without corticosteroids. There was also no significant corticosteroid systemic absorption or ocular toxicity.[1612,2237,2245] A meta-analysis combined the results from the 2 RCTs to demonstrate statistically significant reductions in the need for postoperative intervention, oral corticosteroid usage, polyposis and adhesions.[1611] An economic evaluation also demonstrated that Propel™ is cost-effective via a decrease in the need for postoperative interventions.[281] Other drug-eluting stents have been developed but as yet remain unapproved by the US FDA. Adriaensen *et al.* looked at the safety and efficacy of a bioabsorbable fluticasone eluting stent (Sinuband FP, BioInspire Technologies, Palo Alto, California) and showed it to be safe with some improvement in post-operative edema and wound healing when compared to Merocel.

Concerns raised regarding the data to date have included the lack of a non-stented arm in these studies, which might show that the stenting material without the corticosteroid is pro-inflammatory. Previous

work in biomaterials in the sinuses has shown the potential for some materials to induce inflammation.[2246,2247] The lack of a non-stented arm was identified in a recent Cochrane review of steroid eluting sinus stents[2248] in which the authors stated that no conclusion was possible on whether steroid-eluting stents had any potential advantages and disadvantages because the 2 RCTs and the meta-analysis based on these 2 studies used within patient comparisons. A recent RCT by Rawl *et al.* compared Merocel in a finger cot to Propel and found that the Merocel in the finger cot had less adhesions and a better SNOT 22 on day 20. The QoL differences disappeared after that time point.

Corticosteroid eluting materials appear to have promise in the postoperative period.[2249] Additional indications and devices are on the horizon.[1605]

Drug Eluting Stents in Sinus Surgery

Aggregate Grade of Evidence: A (Level 1: 3 studies; level 2: 6 studies; level 3: 1 study; level 4: 4 studies).
Benefit: Reduction in polyposis and adhesions formation, which translates to a reduction in postoperative interventions.
Harm: Potential for misplacement and local reaction.
Cost: Variable depending on stents and medication. The Propel™ system is estimated at USD$700 per implant.
Benefits-Harm Assessment: Preponderance of benefit over harm
Value Judgments: Corticosteroid-eluting stents have been demonstrated to have beneficial impact on postoperative healing although one study showed that Merocel in a finger cot had superior healing with less middle meatal adhesions. One study has shown steroid eluting stents to be cost-effective in preventing additional postoperative interventions. Specific usage should be at the clinician's discretion taking into consideration various important patient-specific factors.
Policy Level: While the authors recognize the high cost of these implants, given the level of evidence, absorbable steroid-eluting implants are recommended in carefully selected patients that are similar to those included in the underlying clinical trials.
Intervention: Corticosteroid-eluting stents can be considered in the postoperative ethmoidectomy cavity.

Table XII-22. Evidence for use of drug eluting stents with sinus surgery

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Smith	2020	1	Evidence based review with recommendations	Review of steroid-eluting sinus stents	Included all RCTs of steroid-eluting sinus stents	31 studies evaluated; concludes a recommendation for their use to be considered in carefully selected patients.
Huang [2248]	2015	1	Cochrane database of systemic reviews	Review of steroid-eluting sinus stents	Included all RCTs comparing steroid-eluting sinus stents with non-	No RCTs that met inclusion criteria largely due to within-patient comparison. Conclusion that

					steroid-eluting sinus stents, nasal packing or no treatment – 21 trials with potential identified	there currently is no evidence of benefit in high-quality RCTs over no packing or nasal packing
Han[1611]	2012	1	Meta-analysis	2 RCTs of outcomes at postoperative day 30.	MT lateralization Adhesions Frank polyposis Need for postoperative intervention Need for postoperative corticosteroids	Relative reduction of adhesions and polyposis. 35% reduction in postoperative intervention. 40% reduction in oral corticosteroid usage.
Rawl [2250]	2020	2	RCT 40 patients – 80 sides	Propel vs. merocel in finger cot	Adhesions Lund Kennedy Snot 22	Merocel in finger cot had less adhesions and better SNOT 22 scores at day 20 but differences disappeared after that time point
Grzeskowiak [2203]	2019	2	DBRCT 80 patients 160 sides	Nasopore + saline vs. nasopore + steroid vs. nasopore + antibiotic	Healing and secretions	Steroid + nasopore had improved healing and less secretions
Ha [2189]	2018	2	Single surgeon DBRCT 36 patients – 72 sides	CD gel (Chitogel®) vs. Chitogel® + budesonide vs. no packing vs betamethasone cream	Wound healing including adhesion rate Ostial size at 3, 6 12 months for maxillary, frontal and sphenoid	Significant improvement in ostial size for Chitogel® alone and Chitogel® + budesonide compared to no packing
Adriaensen [2251]	2017	2	Single blind RCT 27 patients – 54 sides	fluticasone propionate (FP)-eluting implant, SinuBand FP (non-US FDA approved)	Sinuband FP vs. no packing, Sinuband without steroid vs. no packing and Mercoel vs. no packing	No side effects, Sinuband FP and Sinuband better than Merocel for polyps
Marple[2237]	2012	2	Prospective,	ESS for CRS	Postoperative	Decrease in

			multicenter, DBRCT using intrapatient control design (n=105)		interventions at 30 days Endoscopy Safety	postoperative intervention. Decreased adhesions and polyposis. No safety concerns.
Murr[2245]	2011	2	Prospective multicenter intrapatient DBRCT (n=43)	ESS for CRS	Endoscopic assessment at day 21 Safety.	Decreased polyposis and adhesions, no difference in MT lateralization No device related adverse effects No systemic absorption.
Forwith[1612]	2011	3	Prospective multicenter single cohort study (n=50)	Unilateral (n=10) or bilateral (n=40) stent placement.	SNOT-22 and RSDI at 6 month Safety Endoscopic follow up to 60 days	Improvement in SNOT-22 and RSDI Safety with no ocular risk. 1.1% adhesion rate 4.4% MT lateralization
Xu [2163]	2016	4	Retrospective sequential cohort study Patients 274 – 548 nasal sides	First cohort of 146 received Merocel® in finger cot vs. second cohort 128 received Merogel® soaked with triamcinolone	Adhesions	No significant difference
Lavigne[1806]	2014	4	Prospective, multicenter nonrandomized cohort study (n=12)	Recurrent NP following ESS treated with non-US FDA approved stent	Safety of device Efficacy of device	1 case of ocular irritation and 1 nasal irritation. 21/24 successfully inserted. NP size decreased. Need for revision surgery eliminated in 64%
Matheny[2252]	2014	4	Prospective, single center, nonrandomized cohort study using Propel ™	20 patients post ESS had stent inserted within 7 days postop	Feasibility of insertion and safety of device	100% insertion rate 90% of patient very satisfied with experience Improvement in SNOT-20 and

						endoscopic scores
Ow[2253]	2014	4	Prospective single center non-randomized cohort study	5 patients with recurrent NP treated with non-US FDA approved stent	Safety of device	No systemic absorption or adrenal suppression. 10/10 successful implant insertion

XII.E. Postoperative Management following Sinus Surgery

In studies of postoperative management, one problematic issue is the continued heterogeneity of reported postoperative health metrics which is likely related to the need for clinicians to optimize for both short-term and long-term patient outcomes. For example, short-term patient-centered outcomes (*e.g.*, pain and return to work) need to be considered within a context that aims to reduce the risk of needing long-term revision surgery (*e.g.,* reduced synechia formation and endoscopic control of inflammation). For example, some articles report on reduction in pain, and while that may be a legitimate short-term outcome, many surgeons are using treatments to reduce synechia, or reduce endoscopic mucosal inflammation, to reduce the risk of requiring long-term revision surgery. So even though some evidence might assess a certain outcome, it might not address the entire clinical spectrum.

Postoperative care was thoroughly reviewed in ICAR-RS-2016[1] and the following discussion highlights additions to the evidence since then. Recommendations are based on the totality of the evidence.

Saline irrigations. There have been no new studies comparing normal saline irrigation with no irrigation. There was one new study comparing hypertonic saline with normal saline irrigation, and one systematic review with meta-analysis (SR/MA) on the effects of nasal irrigation with different solutions. Peric, *et al.*[2254] performed a single-center RCT in 30 patients with AERD; 15 subjects per group. They compared postoperative irrigation with seawater solution containing 2.3% NaCl with normal saline (0.9% NaCl). Primary outcome was a non-standardized symptom score and secondary outcome was a non-standardized endoscopic score, both at one month. They found that the hypertonic group achieved improved symptom and endoscopic scores, with statistical significance ($p<0.001$). However, the absolute differences were quite small (*e.g.,* symptom score preop to postop: 38 to 6 hypertonic, 40 to 9 saline), and it is likely that these differences were not clinically meaningful.

Chen *et al.*[2255] performed a SR/MA with a broad question. They evaluated the efficacy of nasal irrigation after ESS with various solutions, compared to normal saline. Outcome measures included the SNOT-22, visual analogue symptom score, endoscopic score, CT score, eosinophil count, and adverse events. They identified 824 potential trials, but only 5 trials (n=331) met all inclusion criteria, and only 3 could be included in the meta-analysis and those 3 trials used 4 different irrigants: Ringer's lactate, hypertonic saline, electrolyzed acid water, and Amphotericin B. The authors found no significant difference in symptom scores or endoscopic scores between the groups treated with saline and other solutions. They concluded that additional solutions were no better than saline alone, although the treatments were quite heterogeneous.

The overall evidence supporting the use of saline irrigations remains grade B, and we make a recommendation for normal saline irrigations.

Sinus cavity debridements. There were no new RCTs reported in the review period however there was a Cochrane review[2256] on this topic, which included the studies reviewed in ICAR-RS-2016. The primary outcomes were health related quality of life (HRQoL) scores, disease severity, and adverse effects. Secondary outcomes included endoscopic appearance, use of post-operative medical treatment, and revision surgery rate. Four studies (n=152) were included in the review. One reported SNOT-22 data, with a non-significant difference between the two groups at 6 months follow up. Two RCTs (n=118) reported Lund-Kennedy score data; mean scores were better in the debridement group but the difference was not statistically significant (effect size = -0.31, 95% CI = -1.35 to 0.72). Four RCTs (n=152) reported on adhesion rate and the debridement group had a lower adhesion rate which was statistically significant (relative risk = 0.44, 95% CI = 0.28 to 0.68). Revision surgery rates were not reported in any study. The authors concluded that the evidence was relatively low quality, however the available evidence suggested that postoperative debridement was associated with a significantly lower risk of adhesions at 3 months follow-up.

The evidence for this treatment remains grade B, and we make a recommendation for postoperative outpatient debridement.

Topical corticosteroids. There were three new papers identified – one RCT and two SR/MAs. Rawal *et al.*[1588] reported on 42 patients with CRS with polyps, who were randomized to topical irrigations with budesonide versus saline; outcomes were validated HRQoL questionnaires and olfaction scores at 3-6 months. The authors found no statistically significant differences in HRQol or olfaction between groups, although they noted that both groups did show improvement in HRQOL over time, demonstrating the benefit of saline irrigation.

One SR/MA was reported in 2015.[1956] There were 18 RCTs (n=1309) identified comparing topical steroids with placebo, including several different delivery mechanisms for the steroid – topical spray, steroid-impregnated spacer, and steroid irrigation. Twelve studies addressed symptom score and 8 addressed endoscopic score. Their meta-analysis found no significant difference in postoperative symptom scores between the steroid and no steroid groups, however they found significant improvement in endoscopic score in the steroid group at 6 and 12 months in pooled patients with CRSwNP and CRSsNP, and lower polyp recurrence rate in the subgroup of patients with CRSwNP. Also, four studies found no significant increase in postoperative infection rate with use of topical corticosteroids..

Another SR/MA was reported in 2018,[2257] which specifically focused on steroid high-volume irrigations. They found that the pooled data on the effect of steroid irrigation showed large differences in QoL scores (mean difference = 21.9, minimal clinically important difference (MCID) =~9) and endoscopic scores (mean difference = 4.23, MCID =~4), which were both statistically and clinically significant. The comparative data however showed no benefit when compared to saline irrigations in QoL scores (mean difference = 3.0) and endoscopy scores (mean difference = 0.33). They did not identify any adverse effects from steroid irrigation, such as increased intraocular pressure or adrenal suppression.

The evidence remains grade A, and supports a strong recommendation for the use of topical nasal steroids.

Oral antibiotics. We identified two new RCTs on the postoperative use of oral antibiotics. Amali *et al.*[1115] reported a placebo-controlled RCT of 60 patients after ESS, where 40 patients received oral placebo, and 20 received azithromycin 250 mg daily, both for 12 weeks. Primary outcome was SNOT-22

score at 12 weeks. The azithromycin group showed a statistically significantly larger score reduction than the placebo group: azithromycin 34.05 preop to 5.85 postop; placebo 36.20 preop to 10.07 postop (p<0.001). However, the absolute difference between the two groups is 4.22, and the minimal clinically important difference on the SNOT-22 is approximately 9. So the small difference noted was likely not clinically meaningful.

Haxel *et al.*[1116] reported a single-center, prospective, double-blinded RCT of 58 patients on the use of low-dose erythromycin after ESS. Group 1 (n=29) received erythromycin 250 mg daily and group 2 (n=29) received placebo, both for 3 months. The primary outcome measures were eosinophilic cationic protein and myeloperoxidase levels in nasal mucus, and a number of secondary outcomes, assessed at 3 and 6 months. The authors reported no significant differences between groups in primary outcome measures. They only noted a single statistically significant difference in endoscopy scores favoring the erythromycin group at 3 months, however at 6 months the differences were not statistically significant, and there were no significant differences between groups in any other secondary outcomes.

The evidence remains level B, and we make a recommendation of option for use of antibiotics, citing both benefits and potential side effects.

Topical decongestants. No new studies were identified in the review period which addressed topical decongestants. ICAR-RS-2016 review found insufficient evidence to support their use, and made a recommendation against topical decongestants, because of potential side effects and no clear benefit.

Packing/spacers without medication impregnation. There were no new studies addressing packing or spacers without medication impregnation. The prior review identified individual RCTs and a systematic review with meta-analysis. There was heterogeneity in the outcome measures, and in the packing materials used, however there were improvements (fewer synechia, better cavity appearance) demonstrated with packing compared to no packing, and there was a trend toward less pain with dissolvable packing versus removable packing. The overall evidence was grade B, but because of the data heterogeneity, the recommendation was option for the use of packing or spacer.

Drug-eluting spacers/stents. There were three new studies identified in the review period: a Cochrane review, an RCT and an economic analysis. In the Cochrane review by Huang *et al.* (9), their primary outcome measure was symptom improvement. They reviewed 159 possible abstracts, and found 21 trials which potentially answered their question, however none met all inclusion criteria. So, their conclusion was that they were "unable to provide evidence to establish whether steroid-eluting sinus stents have potential advantages and disadvantages for patients with CRS undergoing ESS."

Gyawali *et al.*[2258] reported an RCT of 58 patients comparing triamcinolone-impregnated polyvinyl alcohol packs placed as a spacer, with saline-impregnated packs, which were removed on day two. The side for the triamcinolone pack was chosen randomly and the opposite side served as the saline control; observers were blinded to side. Primary outcomes were the Lund-Kennedy endoscopic score and the Peri-Operative Sinus Endoscopy score (POSE), at 3 weeks. The authors found statistically significant differences favoring the steroid-receiving side on both endoscopy scores: Lund-Kennedy, steroid 0.53 vs. saline 1.31 (p<0.0001); POSE, steroid 1.21 vs. saline 1.95 (p=0.004). While there is no established MCID for these tools, given the overall range of the scales, certainly the Lund-Kennedy difference seems clinically meaningful, and perhaps also the POSE. The follow-up assessment was only at 3 weeks however, so it is not clear whether the improvements were sustained.

Rizzo *et al.*[285] reported the theoretical budget impact on a healthcare system from use of a drug-eluting sinus implant. However, it was not patient-based research so it was not included.
Prior studies summarized in ICAR-RS-2016 assessed outcome measures such as clinician-based endoscopic score, number of adhesions, presence of polyps, etc. There was clear evidence that steroid-eluting implants improved these endoscopic outcomes compared to non-impregnated implants. However, there were no RCTs which assessed patient-based outcomes such as HRQoL. Therefore, we conclude that there is Grade A evidence supporting benefit in endoscopic appearance, and we make a recommendation for the use of steroid-eluting implants or spacers in select patients with CRS and / or nasal polyposis (see Section XII.D.7).

Systemic Steroids. There was one new report on this topic.[2259] It was a sequential (non-randomized) trial in 60 patients with eosinophilic polyps, comparing two groups where the initial treatment group received topical steroids daily and a subsequent treatment group received topical steroids daily plus two 20-day tapering courses of oral methylprednisolone every year (further details of treatment timing were not provided). Patients were enrolled over two year periods, and were treated daily with topical steroids, so different patients had different durations of treatment, but all patients were followed at least 36 months after surgery. The authors found no differences in polyp recurrence rate, or in disease-free interval between groups at one year. This is level 4 evidence, which does not change the prior evidence-based recommendation that the use of systemic steroids is an option.

Mitomycin C. There was no new evidence on this treatment in the review period. The ICAR-RS-2016 review found no clear evidence of benefit with topical use of Mitomycin C, and there were potential side effects, so there was a recommendation against the use of Mitomycin C.

Other treatments. Mozzanica *et al.*[2260] performed a multicenter, prospective, double-blinded RCT comparing postoperative irrigation with normal saline BID (control, n=30) versus normal saline with 9 mg Sodium Hyaluronate BID (n=26) for 6 weeks. Outcomes were the Lund-Kennedy endoscopic score, SNOT-22, NOSE, and a visual analogue symptom scale, at 3 and 6 weeks. They found no statistically significant differences in any outcome at 6 weeks. The authors focused on a few small subscale differences, and concluded that sodium hyaluronate "may be a useful adjunct," but their actual data do not support a recommendation.

Although not exactly a "treatment," there was one study addressing outcomes with nose blowing after ESS.[2261] It was a small RCT (n=39) comparing nose blowing twice a day for 1 week with no nose blowing. The study was very small and likely underpowered to detect small differences, and based on the outcomes they concluded that judicious nose blowing after ESS "may be permissible."

Table XII-24. Summary of recommendations for postoperative care following sinus surgery

Intervention	Grade	Benefit	Harm (see Table II-1)	Cost	Benefit-Harm Assessment	Policy Level
Saline irrigations	B	Well-tolerated. Improved symptoms and endoscopic appearance	Local irritation, ear symptoms	Minimal	Preponderance of benefit over harm	Recommendation for use of nasal saline irrigation
Sinus cavity debridements	B	Improved symptoms and endoscopic appearance. Reduced risk of synechia and turbinate lateralization	Inconvenience, pain, epistaxis, syncope, and mucosal injury.	In-office procedure with cost	Preponderance of benefit over harm	Recommendation for postoperative debridement
Topical corticosteroids	A	Improved symptoms and endoscopic appearance. Reduced recurrence rate of polyps	Epistaxis, headache	Moderate	Preponderance of benefit over harm	Strong Recommendation for topical corticosteroids
Oral antibiotics	B	Improved symptoms and endoscopic appearance. Reduced crusting.	GI upset, colitis, anaphylaxis, bacterial resistance.	Moderate to high	Balance of benefit and harm	Option for oral antibiotics
Topical decongestants	N/A	Potential reduced mucosal swelling and bleeding.	Increased pain, possible rhinitis medicamentosa	Minimal	Preponderance of harm over benefit	Recommendation against topical decongestants
Packing/spacers without medication	B	Improved symptoms and endoscopic appearance.	Pain, inconvenience, potential for creating synechia or	Moderate to high, depending on material	Balance of benefit and harm. Potential small benefit	Option for packing or spacer

		Reduced risk of synechia and turbinate lateralization	granulation.		of absorbable vs. nonabsorbable packing.	
Drug-eluting spacers/stents	A	Reduction in inflammation, polyps, adhesions.	Possible systemic absorption, pain, inconvenience.	Moderate to high, depending on material and medication.	Balance of benefit and cost.	Recommendation for steroid-eluting spacer or stent
Systemic corticosteroids	C	Improvement in endoscopic appearance, reduction in polyp recurrence.	Insomnia, mood changes, hyperglycemia, gastritis, increased intraocular pressure, avascular necrosis	Minimal	Balance of benefit and harm	Option for systemic corticosteroids
Mitomycin C	B	Reduction in synechia formation, improvement in maxillary ostium patency	Off-label use, systemic absorption, local toxicity	Moderate to high.	Balance of benefit and harm	Recommendation against Mitomycin C

Table XII-25. Evidence for postoperative care following sinus surgery, published since ICAR-RS-2016

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoints	Conclusion
Chen [2255]	2018	1	SR and MA	3 RCTs comparing nasal irrigation (n=226) with normal saline and various solutions (hypertonic saline, Ringer's lactate, electrolyzed acid water, Amphotericin B)	SNOT-20 or SNOT-22. Endoscopic score. Several others, not pooled.	Unable to identify a solution which had improved outcomes compared with normal saline. Heterogeneity of treatments and outcomes made pooled analysis difficult.

Tzelnick [2256]	2018	1	Cochrane review	4 RCTs (n=152) comparing debridement with no debridement.	Disease-specific HRQol. Disease severity. Adverse events. Lund-Kennedy endoscopic score. Adhesion rate. Revision surgery rate.	Overall low-quality evidence with risk of bias. The evidence suggests a significant reduction in risk of adhesion at 3 mos. Other outcomes did not demonstrate significant differences.
Yoon [2257]	2018	1	SR and MA	12 RCTs (n=360) addressing nasal steroid irrigation versus saline irrigation	Symptom and HRQoL scores. Endoscopy scores. Adverse events.	Steroids showed statistically and clinically significant improvements in symptoms and endoscopic score when steroids were used; comparative studies of steroids vs. saline irrigation showed no additional benefit from steroids. No adverse effects noted.
Pundir [1956]	2016	1	SR and MA	18 RCTs (n=1309) addressing topical nasal steroids, which included some studies of intra-operative steroid use. Different delivery methods were included. 12 RCTs addressed postop symptom scores; 8 RCTs addressed postop endoscopic scores; 4 studies addressed postop infection rate	Multiple symptom scores. HRQol scores. Endoscopic scores.	No significant differences in postop symptom scores. Significant improvement with steroid irrigation in postop endoscopy scores for pooled group (CRSsNP and CRSwNP). Lower polyp recurrence rate with steroids in patients with CRSwNP. No increased rate of postop infection in steroid group.
Huang [2248]	2015	1	Cochrane review; 21 trials reviewed, none met all	Steroid eluting stents vs. plain stents	N/A	No recommendation can be made based on lack of high-quality evidence.

			inclusion criteria			
Gyawali [2258]	2019	2	Single-institution, prospective, blinded RCT (n=58)	Triamcinolone impregnated PVA pack vs. saline impregnated PVA pack, on opposite side. Other side (randomized) on each patient was control. Both removed at 2 days. No topical steroids until week 3.	Lund-Kennedy endoscopic score (LKES). Perioperative sinus endoscopy score (POSE). Both assessed at 3 weeks.	Statistically significant differences favoring steroid at 3 weeks: LKES, 0.53 vs. 1.31 ($p<0.0001$) and POSE, 1.21 vs. 1.95 ($p=0.004$).
Mozzanica [2260]	2019	2	Prospective, multi-center, double-blind RCT (n=56)	Saline irrigation BID (n=30) vs. saline + 9 mg Na Hyaluronate BID (n=26), both for 6 wks.	Lund-Kennedy endoscopy score. SNOT-22, NOSE, and VAS for symptoms.	No significant differences in endoscopy score or SNOT-22, NOSE, or VAS at 6 wks.
Peric [2254]	2019	2	Prospective, single-center RCT (n=30)	2.3% NaCl seawater (n=15) vs. normal saline (n=15) Patients with AERD	Nonstandard symptom score at 1 month Nonstandard endoscopic score at 1 month	Statistically significant difference favoring hypertonic irrigation, but differences are likely not clinically significant.
Ayoub [2261]	2018	2	Prospective, single-center RCT (n=39)	Blew nose BID for 1 wk (n=20) vs. no nose blowing (n=19) for 1 wk; then both groups nose blowing prn	NOSE, SNOT-22, LK endoscopy score	No difference in symptom or endoscopy outcomes.
Amali [1115]	2015	2	Prospective, single-center RCT (n=60)	Azithromycin 250 mg daily (n=20) vs. placebo (n=40) for 12 wks; both groups received standard postop therapy	SNOT-22	Statistically significant difference with larger improvement in azithromycin group, but difference (4.2) was smaller than MCID of ~9.
Brescia [2259]	2015	4	Sequential, non-randomized, single-center comparative study	Daily topical steroid spray(2009-10, n=32) vs. Daily topical steroid spray plus 20 day oral	Polyp recurrence rate. Disease-free interval.	No differences between groups.

			(n=60). Pts with eosinophilic polyps.	methylprednisone taper twice a year (2011, n=28), follow-up at least 3 years.		
Haxel [1116]	2015	2	Prospective, single-center RCT (n=58)	Erythromycin 250 mg daily (n=29) vs. placebo (n=29) for 2 months; both groups received standard postop therapy	Eosinophilic cationic protein; myeloperoxidase in nasal mucus. Endoscopy score, saccharin transit time, olfaction, SNOT-20, VAS. All at 3 & 6 mos	No difference in primary outcomes. Only difference noted in secondary outcomes was statistically significant difference favoring erythromycin at 3 month interval; at 6 months there was no difference, and at the 3 month interval the clinical significance of the difference was questionable.
Rawal [1588]	2015	2	Prospective, single-center RCT (n=42)	Homemade saline irrigations (n=18) versus homemade saline plus budesonide 0.5 mg (n=24)	RSOM, RSDI and SNOT-22 scores UPSIT	No statistically significant difference between groups for any outcome measure.

XII.F. Outcomes of Sinus Surgery

There are many outcome metrics by which the efficacy of surgery for CRS can be determined, including objective and patient-reported. In general, current literature broadly demonstrates that ESS improves both objective and patient-reported metrics in patients that have failed previous appropriate medical treatments, including endoscopy scores,[1816,2262] sinus-specific QoL,[1816] cardinal symptoms,[1949] non-cardinal symptoms,[2263] and overall health utility.[2264] Patients undergoing revision surgery also experience significant improvement, although the magnitude is slightly less than primary surgery patients, likely because of the selection bias of more severe inflammatory disease in those requiring revision surgery.[1814,1816,1936]

Although the above outcome measures are all relevant, there has been general agreement that sinus-specific QoL is particularly important from the patient perspective.[1773] The SNOT-22 is perhaps the most widely utilized instrument currently and has been found to be valid and reliable.[2265] A recent systematic review with meta-analysis identified 40 unique studies reporting SNOT-22 outcomes after ESS for CRS, totaling 5,547 patients.[1938] The summary change in mean SNOT-22 across all studies was 24.4 (95% CI: 22.0–26.8) at an average follow-up of 10.6 months, a change well above the minimal clinically important difference of 8.9. A similar review focused on CRSwNP, identifying 15 unique cohorts encompassing 3,048 patients.[2266] Pooled analyses of SNOT-22 scores revealed a mean change of 23.0 points (95% CI, 20.2-25.8; P < .001).

The majority of data supporting the efficacy of ESS for CRS comes from uncontrolled cohort studies; however, there has been a recent push toward the inclusion of comparison groups. Comparative effectiveness studies of patients treated medically vs. surgically can be divided into RCTs and real world, non-randomized observational comparison studies. The most recent Cochrane Review highlights the lack of high quality RCTs from which to draw firm conclusions.[2267] The reality is that formal RCTs comparing medical treatment to surgery are challenging given the difficulty recruiting patients into protocols that randomize to surgical arms, as well as ethical concerns with blinding and sham procedures. Smith *et al.* have published non-randomized real-world, multi-center observational studies. These studies have demonstrated significant benefits of ESS over continued medical therapy in patients who have failed an initial trial of appropriate medical treatment, including at least culture-directed or broad spectrum antibiotics, topical corticosteroids, and in most cases, a trial of oral corticosteroids.[1936,1937,2268-2270] These benefits were reflected in substantially greater QoL improvements as well as decreased used of antibiotics, oral corticosteroids, and reduced absenteeism in the group treated surgically.[245,1936,1937,2268-2270] Finally, several modeling based economic evaluations have demonstrate that an ESS strategy has a higher probability of being the more cost-effective intervention in patients with refractory CRS compared to continuing with medical therapy alone.[235,2271]

There is an immense body of literature which attempts to identity factors which impact outcomes after ESS for CRS. Individual studies have suggested differential impact related to demographics (age,[1942,1943] gender[2272]), comorbidities (asthma,[2273] aspirin sensitivity,[2274] depression[80]), disease severity (steroid dependence[2033]), disease duration,[95,1917,1918] surgeon,[2037] prior surgery,[1816] extent of surgery,[1781] and length of follow-up, among others.[1938] Despite possible differences across groups defined by these measures, all groups generally experience statistically and clinically significant improvement. There has generally been no difference in overall QoL outcomes between CRSsNP and CRSwNP patients,[1816] although the latter likely have a higher revision surgery rate.[189]

Current research efforts are focused on rigorously defining endotypes to categorize subsets of patients with CRS. Presumably, patients with different CRS endotypes may differ in their long-term response to ESS. If and when putative endotypes are defined, it will be important to determine whether outcomes of ESS differ across groups. These future studies will be critical in developing personalized approaches.

XII.G. Complications of Sinus Surgery and Prevention Strategies

ESS is an effective treatment modality for medically recalcitrant CRS. ESS outcomes have improved over the years due to advances in technology and surgical training. Despite these improvements, complications still occur during surgery due to the close proximity of the sinuses to the skull base and orbit. The reported complication rate of ESS for CRS ranges from 0.36 – 5.8%, with minor and major complications occurring in up to 5.7% and 1.5% respectively.[98-104] Minor complications include epistaxis (unilateral blood loss > 100 ml), adhesions, infection, and lamina papyracea violation (subcutaneous periorbital emphysema, preseptal ecchymosis).[99] Major complications consist of hemorrhage (requiring arterial ligation, orbital decompression, transfusion, or greater than > 1000 ml), skull base injury, CSF leak, meningitis, and orbital injury.[98,104,2275] Up to 15% of patients will require revision surgery, with reported major complication rates of 0.46% in revision surgery.[98,105] While altered anatomy and adhesions can increase the risks of complications during revision ESS, the actual revision ESS complication rate was not shown to be significantly different than primary ESS rates.[98,106] Table XII-26 summarizes sinus surgery complications.[100,101,104,2275,2276]

Several studies have identified factors associated with higher risks of intraoperative complications. For instance, age greater than 40, frontal sinus work, Medicaid insurance, and use of image-guided navigation were factors associated with higher risk of complications.[98] Other intrinsic factors to consider include the presence of asthma, polyp burden[100], disease burden, and overall health.[102] Anatomic variations can add to the risk of complications.[102,2277-2280] Surgeons should perform a detailed review of a patient's CT imaging and possess a thorough understanding of the regional anatomy to avoid complications. Several anatomic features should be identified before surgery, including the maxillary to ethmoid sinus ratio, the position of the anterior ethmoid artery to the skull base, the Keros classification or depth of the lateral lamella of the cribriform plate, the overall slope of the skull base, the pneumatization of the sphenoid sinus and presence of an Onodi cell, and any asymmetry of the skull base. Further attention should be directed towards any areas of bony dehiscence over the lamina papyracea, optic nerve, or cavernous carotid. Error, *et al.* implemented a preoperative ESS radiographic checklist and demonstrated improvement in the identification of critical anatomic sinus variations.[2281] Table XII-28 further characterizes these anatomic features and the associated potential complications.[102,2276-2280]

Extrinsic factors that may lead to intraoperative complication include the surgeon experience, balloon sinus dilation, use of IGS, and use of powered machinery.[2275,2282-2286] The microdebrider is an excellent instrument which decreases surgical time and bleeding as well as promotes faster healing.[2282] While complications are rare, they can be extensive and encompass major complications such as severe ophthalmic damage[2284,2285] and CSF leaks.[2286] As mentioned previously, it is important to have a thorough understanding of the surgical anatomy and be cognizant of the location of critical structures during surgery, particularly when using powered instrumentation.

The value of IGS and its impact on complication rates during ESS is an area of much debate. The popular belief is that IGS is an important tool, which if used appropriately, can minimize complications during

sinus surgery. Currently, there are no prospective, randomized studies evaluating the impact of IGS – nor is one ethically feasible. A few population-based database studies have shown a higher incidence of complications with IGS use, however these studies do not take into account the surgeon experience or the complexity of the case.[98,2275]

Aside from preoperative preparation, several strategies can be utilized to mitigate intraoperative and postoperative complications. Bleeding during surgery can significantly affect visibility of the surgical field. Intraoperatively, blood loss can be mitigated by positioning the patient in reverse Trendelenburg, maintaining tight blood pressure control (MAP between 60 – 70 mmHg), using TIVA (propofol and remifentanil), and applying topical agents such as 1:1000 epinephrine or oxymetazoline in a deliberate fashion.[1838,1847,2276,2287] Although a minor complication, adhesions resulting in middle turbinate lateralization and synechiae formation can contribute to suboptimal outcomes and potentially a need for revision surgery.[105,2210,2288] The use of middle meatal spacers, both absorbable and non-absorbable material, controlled synechiae formation, or middle turbinate suturing can reduce middle turbinate lateralization and adhesion formation.[105,2207]

Complications of Sinus Surgery

Aggregate Grade of Evidence: B (level 1: 4 studies; level 2: 4 studies; level 3: 6 studies; level 4: 5 study; level 5: 3 study)

Table XII-26. Evidence for complications of sinus surgery

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoints	Conclusion
Brunner [1838]	2018	1	Double-blind randomized controlled trial	72 patients undergoing ESS (total intravenous anesthesia vs inhaled anesthesia cohorts)	Evaluate effect of TIVA for ESS in patients with high-grade CRS	TIVA resulted in significantly less blood loss and improved intraoperative visualization for patients with severe CRS
Lee [2207]	2012	1	Systematic review & meta-analysis of RCT	CRS patients undergoing ESS	Effectiveness of middle meatal (MM)l spacers vs no spacers in pts undergoing ESS	Nonsignificant trend towards MM spacers for prevention of synechiae Subgroup analysis: nonabsorbable spacers may be more effective than absorbable spacers for reducing risk of synechiae compared to no spacers
Rudmik [2289]	2011	1	Systematic review	Adult CRS patients	Evidence based approach to early postoperative care following ESS	Recommended: nasal saline irrigations, sinus cavity debridement, standard topical nasal steroid spray Options: postop abx, systemic steroids, nonstandard topical

						nasal steroid solution, drug-eluting spacers/stents
May[104]	1994	1	Meta-analysis	2108 of the authors' CRS patients undergoing ESS compared to 17 series of patients undergoing sinus surgery	Evaluate incidence and prevention of sinus surgery complications	Incidence of major complications was 0.85%, with CSF leak being the most common. The incidence of minor complication was 6.9%, with the most common complications consisting of middle turbinate adhesions and those related to orbital penetration.
Chan [105]	2015	2	Double blind, randomized controlled trial	35 CRS ±NP undergoing ESS	Evaluate efficacy of middle meatal silastic stent in reducing synechiae	MM silastic stents significantly reduce MTL, adhesions, and crusting
Suzuki [101]	2015	2	Retrospective cohort study	50,734 CRS pts	Evaluate complication rates associated with different types of ESS	Overall complication rate 0.50% Revision surgery not associated with increased rates of CSF leak, hemorrhage, toxic shock syndrome; there was a higher rate of orbital injury
Henriquez [2210]	2013	2	Prospective, multi-institutional cohort	286 CRS patients	Evaluate impact of synechiae formation on HRQoL outcomes	Pts with synechiae had significantly less improvement on RSDI total scores and less on CSS scores
Asaka[100]	2012	2	Prospective cohort study	706 CRS pt	Evaluate complications of ESS and identify patient risk factors	5.8% perioperative complications (5.7% minor, 0.1% major) Risk factors: asthma and polyp scores
Berlucchi [2190]	2009	2	Multicenter, blinded prospective randomized controlled trial	66 patients with CRS	Evaluate efficacy of MeroGel (absorbable packing at reducing postop adhesions	Lower proportion of adhesions in MeroGel group at 4 and 12 weeks post op
Krings [98]	2014	3	Retrospective cohort analysis	78,944 CRS patients undergoing ESS	Determine incidence of major complications following primary and revision ESS	Rate of major complications for primary ESS -- 0.36%; revision ESS – 0.46% Age >40, Medicaid, frontal sinus work, and IGS use were factors at higher risk for complications

Chaaban [1839]	2013	3	Prospective, randomized controlled trial	33 CRSs/wNP undergoing ESS	Compare blood loss during ESS under TIVA with propofol vs inhalational anesthesia (sevoflurane)	No significant difference in blood loss or surgical conditions
Heaton [2277]	2012	3	Retrospective case-control	18 CRS pts with CSF leak after ESS 18 CRS pts without CSF leak after ESS	Compare preoperative sinus imaging of ESS pts with and without CSF leak	Pts with CSF leak had greater angle of skull base in sagittal plane and slope in coronal as well as higher Keros score
Ramakrishnan [2150]	2012	3	Retrospective review	62,823 pts undergoing ESS	Determine nationwide incidence of major complications in ESS	Major complication rate 1% (0.17% CSF leak, 0.07% orbital injury, 0.76% hemorrhage)
Stankiewicz [102]	2011	3	Retrospective study	3,402 CRS pts	Review complications of ESS by single surgeon	Most common complications were hemorrhage, orbital complications, and CSF leak Risk factors: age, revision surgery, nasal polyps, anatomic variation, extensive disease, overall health, medication, use of powered instrumentation
Bassiouni [2288]	2015	4	Retrospective chart review	151 CRS patients undergoing ESS	Investigate clinical significance of middle turbinate lateralization after ESS	Middle turbinate lateralization is not associated with patient-reported symptoms however may be correlated with earlier need for revision surgery.
Siedek [99]	2013	4	Retrospective study	2596 ARS & CRS patients	Evaluate complication rates of ESS	3.1% minor complications (bleeding, lamina papyracea violation) 0.9% major complication (severe bleeding, CSF leak 0.04% serious complication (meningitis)
Thacker [2285]	2005	4	Retrospective Chart Review	14 patients with strabismus after ESS	Characterize ocular muscles injured in ESS and correlate it to factors in surgical procedure	Medial, inferior, and/or superior oblique muscles were involved. Use of microdebrider resulted in more extensive muscle damage.
Alam [2283]	2018	5	Case Report/Series	Patients undergoing balloon	Review orbital and intracranial complications of	Appropriate patient selection, thorough knowledge of anatomy, and use of sound surgical

				sinus dilation for CRS	balloon system dilation/power dissector-assisted balloon dilation	techniques are necessary to avoid significant complications with balloon dilation and powered instrumentation
Stankiewicz [2282]	2002	5	Review/Expert Opinion	Patients undergoing sinus surgery	Use of microdebrider can lead to complications due to high-suction pressure	When using microdebrider, surgeon should be aware of location within the sinuses and point the suction/cutting side away from vital structures
Ohnishi [2278]	1993	5	Expert Opinion	188 CRS patients; 2 papilloma	Identify high-risks areas within the paranasal sinuses	High risk areas within ethmoid sinuses: lamina papyracea, ethmoid roof near anterior ethmoid and posterior ethmoid, lateral lamella, area between sphenoid and posterior ethmoid sinuses

Table XII-26. Complications of endoscopic sinus surgery

Minor
Temporary, no intervention
Violation of lamina papyracea
Subcutaneous periorbital emphysema
Periorbital ecchymosis
Dental/lip pain or numbness
Temporary, with intervention
Adhesions
Epistaxis (requiring packing)
Infection (frontal, maxillary, or sphenoid sinus)
Permanent despite intervention (persist beyond 1 year)
Dental/lip pain or numbness
Major
Orbital
Orbital hematoma
Vision loss
Diplopia
Epiphora (requiring dacrocystorhinostomy)
Blindness
Hemorrhage requiring transfusion (>1000 ml)
Carotid artery injury
Intracranial
Cerebrospinal fluid (CSF) leak
Meningitis
Brain abscess
Focal brain hemorrhage
Pneumocephalus
Stroke

Central nervous system deficit Death

Table adapted from May *et al.*[104] and Asaka *et al.*[100]

Table XII-27. Anatomic relationships to consider during sinus surgery

Anatomic Findings	Description	Importance
Maxillary-to-Ethmoid Ratio	Ratio of the maxillary sinus height to the posterior ethmoid height (just posterior to the basal lamella) in the coronal plane	Inadvertent injury to the skull base is more likely to occur if the maxillary to ethmoid vertical height ratio is greater than 1:1.
Height of the lateral lamella (Keros Classification)	The length of the lateral cribriform lamella relative to the fovea ethmoidalis - Keros I: 1-3 mm - Keros II: 3-7 mm - Keros III: 8-16 mm	Risk for intracranial injury is positively correlated with higher Keros classification. It is critical to note for any asymmetry of the skull base or areas of bony dehiscence.
Ethmoidal Arteries	Determine if the location of the anterior and posterior ethmoid arteries are traversing through the skull base or suspended below	Arteries suspended below the skull base are more susceptible to injury during sinus surgery. Damage to the artery can result in hemorrhage, CSF leak, or orbital hematoma.
Sphenoid Sinus Pneumatization/Onodi Cell	Classify the pneumatization pattern of the sphenoid sinus (conchal, presellar, sellar). Identify the presence or absence of: - Onodi cell - Intersinus septation inserting onto carotid canal - Dehiscence over the carotid canal or optic nerve	The sphenoid sinus is helpful in identifying the anterior skull base. There is an increase risk of optic nerve injury if an Onodi cell is present or there is bony dehiscent present. Risk of carotid artery injury increases if there is an insertion of a intersinus septation or overlying bony dehiscence.
Skull base asymmetry/bony dehiscence	Evaluate for any areas of asymmetry (height and thickness) within the skull base. Examine the continuity of the bone overlying the lamina papyracea, carotid canal, and optic nerve	Inadvertent injury to the skull base is more likely in the presence of an asymmetric skull base or areas of bony dehiscence. Similarly, injury to the orbit, carotid artery, and optic nerve is increased with areas of bony dehiscence/abnormalities.

XIII. Pediatric Rhinosinusitis

XIII.A. Pediatric Acute Rhinosinusitis

XIII.A.1. Pediatric ARS: Incidence and Prevalence

Acute rhinosinusitis (ARS) is a common disorder in children, usually occurring in the context of an URI.[31-33,2290] In a longitudinal study of 112 children aged 6-35 months, 623 URIs were observed over a 3-year period, and episodes of ARS were documented by the investigators in 8% of cases.[2291] In an older study, 244 full term infants were followed prospectively for 3 years, and the incidence of URIs complicated by ARS was evaluated.[474] The authors defined ARS as the duration of URI symptoms exceeding two standard deviations (range 16-22 days) above the mean (7.3 days). The incidence of ARS as a complication of a URI ranged from 4-7.3% and was highest for children in their first year of life and in day care or group care as compared to home care. Another study evaluating 2,135 children with respiratory complaints found that 139 fulfilled diagnostic criteria for ARS (6.5%).[35] In 2 studies that queried children presenting to pediatric practices for any reason, ARS was identified (based on symptoms) in 9.3% (121/1307)[2292] and 8.3% (249/3001).[2293] respectively. In another study of 2,013 children, the addition of a positive Water's view to clinical symptoms decreased the incidence estimate negligibly (7.2% to 6.7%).[2294]

More recent studies have used large databases to study the incidence of ARS in children. An analysis of United States national survey databases evaluated ambulatory visits to office-based physicians as well as visits to hospital emergency and outpatient departments between 2005 and 2012.[36] A total of 2.1 billion visits by patients 0-20 years of age were included, and diagnoses were based on ICD-9 codes. Analysis showed that ARS was diagnosed in 13.1 million visits, or 0.6% of the total. In comparison, CRS accounted for 2.1% of visits, upper respiratory tract infection for 8%, allergic rhinitis for 2.6%, and acute otitis media for 6.7%. One study from Canada suggests a recent decline in the incidence of pediatric ARS. The Canadian Disease and Therapeutic Index and Statistics Canada databases were queried from 2007 to 2013. There was a 44.4% reduction in pediatric ARS cases (1,025 to 569 ARS diagnoses per 10,000 inhabitants) during the study period.[2295]

Pediatric ARS is a common diagnosis, but the interpretation of data regarding incidence and prevalence is limited by heterogeneity of individual studies' diagnostic criteria, methodology, and study population.

XIII.A.2. Pediatric ARS: Contributing Factors

Conditions that can contribute to ARS include allergic (AR) and non-allergic rhinitis (NAR), coexisting medical conditions (CF, immune deficiency, ciliary dyskinesia), and environmental factors (smoking, daycare).[2296,2297] Influenza in 5-14 year old at risk children (chronic cardiovascular disease, bronchitis, asthma, diabetes mellitus and malignancy) increases the occurrence of ARS.[2298] Chronic conditions such as CF, immune deficiency, and ciliary dyskinesia are more likely to be associated with CRS.

Allergic Rhinitis. There are scant data on the correlation of AR and ARS in children. In a retrospective study of 92 patients with RARS, children with positive skin tests to common inhalant allergens sustained 1.09 more sinus infections than non-allergic patients, a significant difference.[2299] In another study of children with ARS and CRS, there were statistically significantly more patients with a clinical history of AR in the CRS group (90.2%) vs. the ARS group (74.8%).[223] The percentage of positive skin prick test results was similar in both groups (96.4% in ARS and 96.9% in CRS). In a prospective study evaluating the incidence of ARS in allergic children during the grass pollen season, Leo *et al.* enrolled 242 children with grass pollen allergic rhinitis (mean age=13.2 years) and 65 children with no allergies (average age=12.3 years).[357] Symptom diaries and drug use were monitored and ARS was confirmed by nasal endoscopy. Seventeen out of 242 allergic children (7%) had confirmed ARS compared to 3 out of 65 (4.6%) in the control group. The difference was not significant suggesting the lack of importance of grass allergy in the occurrence of ARS. Lin and colleagues used a population-based retrospective cohort study design to analyze data based on the Longitudinal Health Insurance Database in Taiwan in children aged 5-18 years.[351] The intent of the study was to investigate whether allergic rhinitis was associated with an increased incidence of ARS, as defined by ICD-9 codes. The authors identified a cohort of children with newly diagnosed allergic rhinitis between 2000 and 2012 and compared them to a matched cohort without such a diagnosis. They followed the children until a diagnosis of ARS was made or until the date of the last outpatient visit. In this large cohort of 43,588 patients, the overall incidence of ARS in the allergic cohort was 111.8 per 1000 person-years, significantly higher than 33.9 per 1000 person-years in the non-allergic control cohort. Most of the available studies suffer from some limitations, which include referral bias (conducted in allergy practices), failure to distinguish positive skin tests from clinical allergic disease, and making the diagnosis of ARS based on diagnostic codes.

Adenoiditis. Adenoiditis in children can have a very similar clinical presentation to ARS, including anterior and posterior purulent drainage and cough, and is part of the differential diagnosis. In an attempt to differentiate between adenoiditis and ARS based on endoscopic findings, Marseglia and colleagues performed a cross sectional study of 287 consecutive children in whom ARS was suspected based on symptoms lasting for more than 10 days.[2300] The diagnosis of ARS was made if purulent discharge was identified in the OMC or sphenoethmoidal recess on nasal endoscopy, and the diagnosis of adenoiditis was made if there was purulent drainage over the adenoids. Based on those criteria, ARS was confirmed in 89.2% of the patients; it was isolated in 80.8% and coupled with adenoiditis in 19.2%. Adenoiditis alone was confirmed in 7% of the cohort. Combined involvement of the sinuses and adenoids was more frequent in younger patients (2-5 years age group), whereas isolated ARS was more frequent in older children. These data suggest a correlation between pediatric adenoiditis and ARS, although the differentiation between these diagnoses based on clinical presentation alone is difficult.

Immune Abnormalities. Veskitkul and colleagues retrospectively reviewed the records of 94 children presenting with RARS between 2010 and 2012.[489] The most common predisposing factor for RARS was immunoglobulin G subclass deficiency (78.7%), followed by NAR (64.9%) and AR (35.1%). A similar single-center retrospective study examined the prevalence of abnormal results on immunologic testing in pediatric patients with RARS.[2301] There were variable results in the 10 patients with RARS. Among the relevant results were high IgE in 2 patients, and low, non-protective, *S. pneumonia* titers in 4/10 patients.

Table XIII-1. Risk factors for pediatric ARS

Study	Year	LOE	Study Design	Study Groups	Clinical End-point	Conclusion
Lin[351]	2019	3	Retrospective cohort study between 2000 and 2012	Children with newly diagnosed allergic rhinitis (n=23,046), and a matched cohort without an allergy diagnosis (n=23,046)	Incidence rate of ARS determined by diagnostic codes	Having an allergic rhinitis diagnosis was associated with a significantly higher incidence rate of ARS.
Leo[357]	2018	3	Prospective cohort study	Children with allergic sensitization to grass pollen and rhinitis symptoms (n=242), and children without inhalant allergies (n=65)	ARS prevalence during the allergy season	7% of allergic children had confirmed ARS compared to 4.6% in the control group. The difference was not significant.
Marseglia[2300]	2007	3	Cross sectional study	287 consecutive children in whom ARS was suspected based on symptoms	Diagnosis of ARS or adenoiditis made by nasal endoscopy	ARS confirmed in 89.2% of the patients (isolated in 80.8% and coupled with adenoiditis in 19.2%). Adenoiditis alone was confirmed in 7% of the cohort.
Li[2301]	2020	4	Retrospective pilot study	Children with a diagnosis of CRS (n=17) or RARS (n=10) between 2008-18	Immunologic abnormalities on clinical testing	High IgE in 2/10 and non-protective, *S. pneumonia* titers in 4/10 patients with RARS.
Veskitkul[489]	2015	4	Retrospective record review	94 children with RARS.	Reviewed clinical characteristics of the children	Most common predisposing factor was IgG subclass deficiency (78.7%), non-allergic rhinitis (64.9%) and allergic rhinitis (35.1%).
Poachanukoon[223]	2012	4	Prospectively collected cohort	Children with either ARS or CRS	Clinical history of AR and	Statistically significantly more patients with a

					percentage with positive skin prick tests	clinical history of AR in the CRS group (90.2%) vs. the ARS group (74.8%). Percentage of positive skin prick tests similar in both groups.
Furukawa[22] [99]	1992	4	Retrospective review	Children with either positive or negative skin tests to inhalant allergens	Occurrence of acute sinus infections	Children with positive skin tests had 1.09 more sinus infections than children with negative skin tests ($p<0.012$)

Table XIII-2. Aggregate grade of evidence for studies on contributing factors for pediatric ARS

Contributing Factor	Impact of Factor	Grade of Evidence
Allergic Rhinitis	Tendency of the aggregate studies to suggest a contribution of AR to ARS, with reservation based on study limitations	C (Level 3: 2 studies; level 4: 2 studies)
Adenoiditis	Coexistence of ARS and adenoiditis, difficult to distinguish	C (Level 3: 1 study)
Immune Function	Some evidence of immune defects in RARS	C (Level 4: 2 studies)

RARS, recurrent ARS; AR, allergic rhinitis.

XIII.A.3. Pediatric ARS: Diagnosis

Pediatric ARS is a common problem in children.[31,32,2290] and is defined as the onset of two or more of the following symptoms: nasal blockage/ obstruction/congestion, discolored nasal discharge, or cough (daytime and nighttime) for <12 weeks.[26,31,2290] Because these symptoms are similar to those of a viral URI, there is a strong relation between URIs and ARS.

The clinical diagnosis of pediatric ARS can be made in the following situations. Post-viral RS is defined as URI symptoms persisting for more than 10 days, or an abrupt increase in severity of symptoms after an initial improvement (known as double sickening). Pediatric ARS can also present as the acute onset of 2 or more signs and/or symptoms: discolored nasal discharge with unilateral predominance, purulent secretions, severe local pain with unilateral predominance, fever (>38^{o}C), elevated ESR/CRP, or "double sickening," which is the worsening of clinical status after initial improvement.

The clinical diagnosis of ARS in children is challenging as symptoms are often subtle and the history may be limited to a caregiver's observations of the child. When evaluating a child with suspected ARS, there is a wide differential diagnosis including acute viral RS, acute post-viral RS, intranasal foreign body, adenoiditis, and structural anatomic pathology such as choanal atresia/stenosis. The initial diagnostic work-up for such patients should include a thorough history and physical examination, including nasal endoscopy when appropriate.[31]

Prospective studies have been used to evaluate the diagnostic utility of plain X-rays of the sinuses in the context of suspected pediatric ARS. In one of these studies, 54/258 (21%) children with suspected ARS had normal sinus radiographs, suggesting an uncomplicated URI and not ARS.[2302] The absence of green nasal discharge and disturbed sleep, as well as milder symptoms, were associated with a normal radiograph and the diagnosis of an uncomplicated URI. No physical exam findings were particularly helpful in distinguishing between children with normal vs. abnormal radiographs. In another study of 69 children between the ages of 3 and 12 years, ARS was diagnosed by purulent nasal drainage for more than 7 days and abnormal findings in the maxillary sinuses on Waters' view X-ray. In these children, the most troublesome symptoms were postnasal drainage, nasal obstruction, and cough.[2303] In a mail survey of American general pediatricians, symptoms thought to be very important in the diagnosis of ARS included prolonged symptom duration, purulent rhinorrhea, and nasal congestion.[2304] In another survey of pediatric primary care, urgent care and otolaryngology providers, the diagnostic criteria for ARS used most frequently by all providers (95%) was persistent nasal drainage of any quality, day or nighttime cough, or both lasting more than 10 days without improvement.[2305] Other commonly used criteria were symptoms of a classic viral URI with worsening of symptoms at day 5–7 (69.7%) and severe onset of illness with concurrent fever and purulent nasal discharge for at least 3 consecutive days (46.97%). A pediatric RS symptom scale which includes questions about congestion, rhinorrhea, cough (daytime and nighttime), tiredness, irritability, and sleeping problems has been developed.[2306] After testing in children with ARS, it was found to correlate with objective measures and be responsive to change as disease improved.

Physical exam in the evaluation of children with possible ARS includes anterior rhinoscopy to examine the middle meatus, inferior turbinates, mucosal character, and presence of purulent drainage. This is often accomplished using the largest speculum of an otoscope, or alternatively, a headlight and nasal speculum. Topical decongestion may be used to improve visualization. Nasal endoscopy allows superior visualization of the middle meatus, adenoid bed, and nasopharynx, and is strongly recommended in children who are able to tolerate it. An oral cavity exam may reveal purulent postnasal drainage, "cobblestoning" of the posterior pharyngeal wall, or tonsillar hypertrophy. Because some younger children might not tolerate nasal endoscopy and endoscopy is not available to primary care practitioners and pediatricians, who are the most likely to diagnose ARS in children, clinicians must rely on history and/or imaging studies for appropriate diagnosis.

Other diagnostic tests have sparse supporting evidence in the pediatric age group. In a study of 217 patients between the ages of 4 and 61 years, an assay of protein, pH, leukocyte esterase and nitrite in nasal secretions allowed the accurate diagnosis of bacterial sinusitis (as supported by history and positive CT or X ray) in 90% of patients.[2307] This approach and testing would be impractical to perform in physicians' offices. Obtaining a culture is usually not necessary in the context of uncomplicated ARS. However, it should be considered in patients who have not responded to empiric antibiotic treatment within 48-72 hours, in immunocompromised patients, in the presence of complications, or if the child presents with severe illness and appears toxic.[2308] Although a maxillary sinus tap would confirm the diagnosis, this is a relatively invasive procedure and is difficult to perform in a child in the office. Wen and colleagues measured nasal and fractional exhaled NO in a study of pediatric patients with perennial allergic rhinitis (PAR) with and without acute unilateral maxillary sinusitis as defined with clinical signs and symptoms, radiographic examination, and nasal fibroendoscopy.[2309] They found significantly lower mean nasal NO and higher fractional exhaled NO levels in patients with PAR and RS compared to patients with PAR and normal controls without RS. Lindbaek and colleagues evaluated 201 primary care patients aged $\geq$15 years with a clinical diagnosis of ARS.[321] Fluid level or total opacification of any sinus

on CT were used as diagnostic of ARS. Blood tests including erythrocyte sedimentation rate (ESR), C-reactive protein, and white blood count were obtained. A total of 127 (63%) patients had fluid levels or total opacification in one or more sinuses. "Double sickening," purulent rhinorrhea, purulent nasal secretions, and ESR > 10 had the highest likelihood ratios and were independently associated with CT-confirmed ARS.

The diagnosis of pediatric ARS is generally made on clinical grounds, and imaging is usually not necessary. A combination of symptoms and clinical presentation helps differentiate uncomplicated URIs from ARS. Physical exam findings support the clinical impression, and additional diagnostic testing is usually unnecessary.

XIII.A.4. Pediatric ARS: Management

Both the 2012 EPOS guidelines and 2013 AAP guidelines recommend only symptomatic treatment for children with uncomplicated ARS given the likely viral etiology in the first 10 days.[32,2290] The 2013 AAP guidelines recommend antibiotic treatment for patients with severe onset of disease or worsening course. Patients with a persistent illness defined as “nasal discharge of any quality or cough or both for at least 10 days without evidence of improvement” can be offered antibiotic treatment or 3 days of outpatient observation. The AAP recommends amoxicillin with or without clavulanate for empiric treatment of ABRS. For patients allergic to amoxicillin, the AAP guideline recommends a second or third generation cephalosporin as monotherapy for ABRS as the vast majority of patients with penicillin sensitivity tolerate cephalosporin therapy.[2290] For patients under two years of age with a documented type-1 hypersensitivity to penicillins and moderate to severe ABRS, a combination of clindamycin and cefixime is suggested.[2290] A fluoroquinolone, such as levofloxacin, may also be used to treat ABRS in patients with a severe penicillin allergy.[2290] It should be noted that levofloxacin does not have a US FDA approved indication for ABRS in children and has potentially serious side effects, including tendonitis and tendon rupture, which should be considered prior to the initiation of therapy.

In contrast, the 2012 Infectious Disease Society of America clinical guideline for the management of ABRS recommends amoxicillin-clavulanate for empiric therapy for ABRS in children.[31] The ISDA guidelines also recommended that high-dose amoxicillin-clavulanate, defined as 90 mg/kg/day orally twice daily, be used as a first line therapy in children who live in a geographic region with high endemic rates of penicillin-nonsusceptible *S. pneumoniae*, with a severe infection. Additionally this regimen is recommended for children who attend daycare, are less than 2 years old, who have had a recent hospitalization, who have used an antibiotic within the past month, or who are in an immunocompromised state.[31] Macrolides, trimethoprim-sulfamethoxazole, as well as second-and third-generation cephalosporins were not recommended for empiric monotherapy of ABRS. The recommendation against the use of cephalosporins for empiric monotherapy in penicillin allergic patients is in contrast to that made by the AAP. The combination of a third-generation cephalosporin with clindamycin was recommended as second-line therapy for children with non–type I penicillin allergy or from geographic regions with high endemic rates of penicillin-nonsusceptible *S. pneumoniae*.[31] Levofloxacin was the antibiotic of choice for children with a history of type I hypersensitivity to penicillin, and clindamycin plus a third-generation cephalosporin was recommended for children with a history of non–type I hypersensitivity to penicillin.[3] The ISDA recommends antibiotic treatment for a duration of 10 to 14 days.[31]

While these cited guidelines provide us with expert opinion, a 2013 meta-analysis of randomized control trials for the treatment ARS yielded only 4 articles.[2310] The authors concluded that evidence supports the use of antibiotics for ARS but efficacy could not be adequately demonstrated given the variance in study diagnostic and inclusion criteria.[2310]

A 2014 Cochrane review failed to detect any evidence supporting the efficacy of nasal decongestants, antihistamines, or nasal irrigations in the management of pediatric ARS.[33] A subsequent 2018 meta-analysis of nasal saline irrigation (NSI) for both ARS and CRS in children yielded only one article supportive of NSI for ARS.[2311] This lone article by Ragab *et al.* demonstrated equivalent improvement in ARS outcomes on two weeks of NSI with or without antibiotics (amoxicillin).[2312] This article suggests that NSI may be as effective as amoxicillin without the noted observed side effects of antibiotics (*e.g.,* diarrhea).[2312] It is difficult to provide a broad recommendation for the use of NSI for ARS based on a single RCT - further investigation is warranted.

Table XIII-3. Management of pediatric ARS.

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Wald[2290]	2013	1	Systematic Review	N/A	N/A	Definition, evaluation, and management recommendations.
Fokkens[31]	2012	1	Systematic Review	N/A	N/A	Treatment evidence and recommended management algorithm provided
Chow[32]	2012	1	Systematic Review	N/A	N/A	Definition, evaluation, and management recommendations.
Cronin[2310]	2013	1	Meta-Analysis	4 RCTs	Symptom Improvement	Increased odds ratio of 2.0 favors the use of antibiotics for ARS in children
Shaikh[33]	2014	1	Systematic Review	0 of 662 studies reviewed met inclusion criteria	Efficacy of decongestants, antihistamines or nasal irrigation for ARS in children	No studies met inclusion criteria to support the use of decongestants, antihistamines, or nasal irrigation for ARS in children
Gallant[2311]	2018	1	Systematic Review	Only 1 of 272 studies met inclusion criteria	Efficacy of nasal saline irrigation for ARS or CRS in children	Nasal saline irrigation may provide benefit for ARS in children
Ragab[2312]	2015	1	Randomized Control Trial	Single Site, 62 patients	Nasal symptom scores for ARS in children	Treatment of ARS with nasal saline/placebo equally effective as nasal saline/antibiotics

Management of Pediatric ARS

Aggregate Grade of Evidence: A (Level 1: 7 studies).

Recommendation 1:
Given the likely viral etiology, antibiotics should not be given for the first 10 days of uncomplicated acute rhinosinusits.

Benefit: Avoidance of unnecessary medications.
Harm: Potential progression of disease
Cost: None
Benefits-Harm Assessment: Benefits likely outweigh harms and costs.
Value Judgements: Parental preference often plays a large role in decision-making
Policy Level: Recommendation.
Intervention: Antibiotics should not be given for the first 10 days of uncomplicated ARS.

Recommendation 2:
For patients without penicillin allergy, amoxicillin or amoxicillin-clavulanate may be prescribed for ABRS (defined as two nasal symptoms lasting greater than 10 days, or acute onset of severe symptoms).

Benefit: Reduction in duration and severity of symptoms.
Harm: Antibiotic resistance, gastrointestinal complications, risk of allergic reaction (see Table II-1).
Cost: moderate for antibiotics other than amoxicillin.
Benefits-Harm Assessment: Benefits likely outweigh harms and costs.
Value Judgements: Parental preference often plays a large role in decision-making
Policy Level: Recommendation.
Intervention: For patients without penicillin allergy, amoxicillin or amoxicillin-clavulanate may be prescribed for ABRS (defined as two nasal symptoms lasting greater than 10 days).

XIII.A.5 Pediatric ARS: Complications

Complications arising from pediatric ARS are uncommon but require immediate medical attention. The main complications from pediatric ARS are orbital (60-75%), intracranial (15-20%), and osseous (5-10%).[31,2290] Orbital complications range from pre-septal cellulitis to orbital abscess as described by Chandler.[462] Additional orbital complications can include blindness, optic neuritis, corneal ulceration, and panophthalmitis. Intracranial complications can include epidural abscess, subdural abscess, parenchymal brain abscess, meningitis, cerebritis, as well as superior sagittal and/or cavernous sinus thrombosis. Osseous complications include osteomyelitis of the frontal and maxillary bones. Signs and symptoms of complications arising from pediatric ARS include lethargy, headache, eye pain, pain with eye movement, periorbital edema, high fever, nausea/vomiting, diplopia, photophobia, papillary edema, seizures, cranial neuropathies, and focal neurologic deficits.

Early orbital complications can sometimes be managed with IV antibiotics alone while the more severe complications of pediatric ARS require a combination of IV antibiotics and emergent surgical treatment. A recent systematic review indicates that cases of pre-septal and post-septal cellulitis as well as some subperiosteal abscesses can be managed non-surgically. This same paper supports urgent surgical intervention for patients with orbital abscesses and cavernous sinus thrombosis.[2313] The volume of subperiosteal abscess or proptosis severity may predict the likelihood of requiring surgical intervention.[2314,2315] CT scan with contrast is the diagnostic study of choice except when intra-cranial complications are suspected. In such cases, MR Imaging may have superior sensitivity to detecting intracranial findings.[2313]

Surgical management of complications of ARS often require multi-disciplinary care with infectious diseases, ophthalmology, and neurosurgical specialists. Particular attention should be paid to antibiotic choice in regions with high MRSA or pneumococcal vaccination prevelance.[2316,2317] For intra-orbital complications, both external and trans-nasal endoscopic techniques have been described with good outcomes. For intracranial complications, combined otolaryngology – neurosurgery intervention may be required with both ESS and craniotomy and drainage being performed under the same anesthetic. In a systematic review of intracranial complications of ARS, the majority were adolescent males (70%) that required multi-disciplinary surgical intervention. Only 73% of the patients in this review regained baseline neurological status.[2318]

XIII.B. Pediatric Chronic Rhinosinusitis

XIII.B.1. Pediatric CRS: Incidence/Prevalence

Epidemiologic data regarding pediatric CRS (PCRS) are limited compared to adult CRS, but recent data provide some insight into the prevalence of this condition. A US National Health Interview Survey in 1994 reported a PCRS prevalence of 8%, although this survey predates current diagnostic definitions.[2319] A 2017 study examining data from the US Centers for Disease Control National Center for Health Statistics found that CRS was diagnosed in 2.1% of patients younger than 20 years in ambulatory health care visits per year.[36] This study was limited by reliance on administrative diagnostic coding rather than on established diagnostic criteria. A prospective study of a Swedish population-based cohort estimated a 12-month prevalence of self-reported CRS symptoms to be 1.5% in adolescents. At the time of follow-up (average 16 months) prevalence of self-reported symptoms dropped to 0.8%, with nasal endoscopy confirming a diagnosis of CRS in 0.3% of all adolescents.[37]

A family history of CRS significantly increases the incidence of a PCRS diagnosis in children 12 years or younger. Having a sibling with CRS increases the risk 57.5-fold of a child developing PCRS; having a first- or second-cousin also increases the risk albeit less so. Likewise, adult relatives of children with PCRS have an increased incidence of CRS.[2320]

The exact prevalence of PCRS in patients with underlying conditions such as CF, PCD, or immunodeficiency is unknown but may be higher than in healthy children. Depending on the diagnostic criteria used for PCRS, some studies estimate the incidence of PCRS in children with CF to be 11-38%,[38,2321] for children with PCD to be as high as 40%,[39] and for children with CVID to be as high as 36%.[40]

Healthy children with chronic rhinorrhea, nasal congestion, and cough are commonly seen in primary care and otolaryngology settings. One study of 196 children (ages 3 to 14 years) with chronic rhinorrhea, nasal obstruction, and cough found on CT that maxillary sinus inflammation was noted in 63%, ethmoid in 58% and sphenoid in 29% of children, with sinus involvement decreasing with age.[2322] Another study examined sinus CT scans of 91 children (ages 2 to 17 years) presenting to an allergy clinic with 3 months or longer of two or more symptoms of rhinorrhea, postnasal drip, and cough. Sinus inflammation was seen on CT in 63% of children, and younger age was a risk factor for abnormal CT findings.[2323]

XIII.B.2. Pediatric CRS: Contributing Factors

Several medical comorbidities have been identified as contributing factors in the pathogenesis of PCRS. In children with asthma, as many as 48% may have endoscopic signs of RS.[2324] In children with asthma and PCRS, treating PCRS often leads to better asthma control. In a series of 48 children with moderate to severe asthma refractory to medical treatment, 79% of children were able to discontinue their asthma medications after their CRS was managed with oral antibiotics alone. Seventy-nine percent of these children had normal findings on sinus radiographs after treatment. Asthma symptoms returned when RS recurred.[2325] In another study of 18 children with poorly controlled asthma, RS was treated with oral antibiotics, intranasal and systemic corticosteroids. Subjects were evaluated at baseline and 1 month later, and sinonasal symptoms resolved after treatment, with 8 of 18 children having intermittent asthma and 10 of 18 children having mild asthma based on symptoms and spirometry.[2326] These data support the concept that in children sinonasal and pulmonary inflammation often occur simultaneously and improve or worsen together.

The association between AR and PCRS is controversial. In a 2007 study, 2200 children were referred for chronic respiratory symptoms and 351 were diagnosed with CRS. Subjects underwent skin prick testing, of which 29.9% were found positive, an incidence similar to that noted in the general population (31.8%).[2327] Similarly, in a retrospective study of 4044 children with PCRS, AR was found to be present in 26.9% of patients.[2328] In one cohort of children with AR, those who developed PCRS did not have any evidence of more severe AR than those without PCRS.[2329] On the other hand, in a 2019 study of 110 children with PCRS, 52.7% had positive skin prick testing, and patients with atopy had worse endoscopy and QoL scores.[2330] It is important to note that positive skin testing does not necessarily equate to clinically meaningful allergic disease, which may explain the discrepancy in rates of positive skin testing between this and other studies. The potential association between AR and PCRS is thought to be multifactorial and remains a topic of investigation.

Immunodeficiency has been reported to be a factor in several studies of PCRS. Abnormalities commonly seen include IgG subclass deficiencies, IgA deficiency and poor response/deficiencies in pneumococcal titers.[492,2331,2332] Management with systemic therapy directed at immunodeficiency, such as IVIG, was associated with improvement in CRS in a case report.[2333] Children with CRS may benefit from a quantitative Ig evaluation and specific titers for antibodies to polysaccharide antigens including *S. pneumoniae*, *H. influenzae*, and consideration of testing for response to tetanus and diphtheria immunization.[2301,2334]

Cystic fibrosis is an autosomal recessive disease that adversely impacts MCC throughout the upper and lower airways. This disease is associated with a high incidence of CRS and nasal polyposis in both pediatric and adult patients, and nearly all individuals with CF have sinonasal inflammation. Cystic

fibrosis-related CRS is often refractory due to the underlying genetic defect and requires multidisciplinary care, including consideration of surgical intervention as well as targeted therapies.[2335] A diagnosis of CF should be considered in children with NPs or severe CRS, with evaluation via a sweat chloride test and/or genetic testing.[2336,2337]

Rhinosinusitis is common in patients with PCD,[39] though overall PCD is a rare cause of PCRS based on its low prevalence. A diagnosis of PCD should be considered in cases of refractory PCRS, particularly with concomitant chronic otitis media. Primary ciliary dyskinesia is an autosomal recessive disorder involving dysfunction of cilia with an incidence of 1 in 15,000 individuals. In 50% of the cases of PCD, situs inversus and bronchiectasis are present and, with the association of CRS, is known as Kartagener's syndrome.[2338] Screening tests include nasal NO and *in vivo* tests such as the saccharin transit test, which shows increased mucociliary transit times. However, screening tests may be falsely negative in some children. Definitive diagnosis can be made by high speed videomicroscopy analysis and transmission electron microscopy of ciliated epithelium, obtained either from a nasal turbinate or bronchial brushing. The most common ciliary structural abnormality is lack of outer dynein arms or a lack of both inner and outer dynein arms.[2339,2340]

The role of GERD in the pathogenesis of PCRS remains unclear, and no consensus among experts exists. In a recent PCRS consensus statement and in a European Position paper, there was agreement that routine empiric treatment for GERD is not indicated in the management of PCRS.[26,2341]

Table XIII-4. Contributing factors for pediatric CRS

Study	Year	LOE	Study Design	Study Groups	Clinical End-point	Conclusion
Leo[2327]	2007	3*	Cross sectional study	351 children with PCRS who underwent skin prick and serum IgE testing	Sensitization to at least one inhalant allergy by skin test Elevated total IgE	The incidence of allergen sensitization is similar to the overall pediatric population.
Li[2301]	2020	4	Pilot case series	Children with PCRS (n=17) or RARS (n=10) from a single center	Serum Ig Thyroid evaluation Complete blood count Titers to *Streptococcus*, *H Influenzae,* Diptheria, Tetanus	Testing for titers to *Streptococcus* and *H Influenzae* appears high-yield in the workup of PCRS. Testing for Tetanus, Diptheria and thyroid function is lower yield.

Anamika[2330]	2019	4	Case series	110 Children with PCRS between ages 7 and 18	Skin prick testing Sinus and Nasal QoL Survey	Children with PCRS had higher rates of aeroallergen sensitivity than the general population; those with PCRS+atopy had worse QoL.
Bhatt[39]	2019	4	Case series	54 patients with PCD from a single center	CRS symptoms Management required for CRS	CRS was common among patients with PCD; most patients did not undergo surgery.
Sedaghat[2328]	2014	4	Case series	4044 children with PCRS over a 10-year period at an academic center	Diagnoses of AR, CF, immunologic disorders, PCD	The incidence of AR in children with PCRS is similar to the overall population.
Sedaghat[2329]	2013	4	Dual cohort study	117 children with AR without PCRS 37 children with AR and PCRS	Aeroallergen sensitivity	Children who developed PCRS did not have more severe AR or aeroallergen sensitivity than those without PCRS.
Babinski[2336]	2008	4	Case series	126 individuals with CF from a single center	Cytological examination of nasal mucosa	Multiple histologic types of inflammation, including nasal polyps, are present in individuals with CF.
Costa[2331]	2005	4	Case series	27 children with asthma, AR and	Serum Ig and antibodies to multiple bacterial	Humoral immunodeficiency is not the main cause of

				PCRS/RARS	antigens before and after immunization Sweat test Complete blood count	PCRS in children with AR/Asthma.
Tosca[2326]	2003	4	Case series	18 children with moderate asthma and PCRS treated with antibiotics, nasal and oral steroids	Symptoms Spirometry Endoscopy Inflammatory cytokines	Treatment of PCRS improved asthma symptoms and respiratory function in asthmatic children.
Sethi[492]	1991	4	Case series	20 patients with refractory CRS or rhinitis	Serum Ig Vaccine response	Immunodeficiency was common among patients with refractory PCRS.
Shapiro[2332]	1991	4	Case series	61 children with CRS referred for allergy evaluation	Serum Ig levels Response to *pneumococcal* and *H Influenzae* vaccines	The majority of patients with PCRS had immunologic deficits, suggesting immunodeficiency may play a role in PCRS.
Rachelefsky[2325]	1984	4	Case series	48 children with asthma and PCRS treated with antibiotics +/- antral lavage	Asthma medication usage Sinus radiographs Pulmonary function tests Symptoms	Multiple asthma outcomes were improved after treating PCRS.

* Level 3 study based on study quality and magnitude of effect

Table XIII-5. Aggregate grade of evidence for contributing factors to pediatric CRS

Item	Explanation
Asthma as a contributing factor to PCRS	C (Level 4: 2 studies)

AR as a contributing factor to PCRS	D, (conflicting Level 4 studies)
Immunodeficiency as a contributing factor to PCRS	C (Level 4: 4 studies)
PCD as a contributing factor to PCRS	N/A (Level 4: 1 study)
GERD as a contributing factor to PCRS	N/A, lack of direct evidence

XIII.B.3. Pediatric CRS: Diagnosis

PCRS is defined as the presence of two or more of the following cardinal symptoms lasting for 12 weeks or longer: nasal obstruction, nasal discharge (anterior or posterior), facial pain/pressure, and cough. Symptoms must be accompanied by objective evidence of inflammation, demonstrated on rhinoscopy, nasal endoscopy, or radiography. Nasal endoscopy may demonstrate purulent discharge, mucosal edema, or polyposis, and allows for examination of the adenoids.[31,2341] One study found that rhinorrhea is the most common symptom of PCRS, followed by nasal obstruction, cough, and lastly facial pain.[2342]

Plain X-rays have poor specificity and sensitivity for PCRS. One prospective study of 70 infants and children (age 4 months to 19 years) with sinus disease found that plain radiographs failed to correspond to CT scans in 75% of patients. About 45% of patients in the study had normal plain film findings of at least one sinus, with abnormalities of that sinus seen on CT scan; 35% of patients had an abnormality of at least one sinus on plain films, with that sinus found to be normal on CT.[2343] A subsequent study confirmed that CT scans were more sensitive and specific than plain films and also correlated to intraoperative findings of sinus inflammation.[2344]

One study compared sinus CT scans of 66 children undergoing ESS for PCRS (mean age 8 years) to sinus CT scans of 192 children undergoing imaging for non-RS diagnoses (mean age 9 years). The mean Lund-Mackay score was 10.4 in the PCRS group and 2.8 in the control group. A Lund-Mackay score cutoff of 5 for diseased versus non-diseased patients conferred a sensitivity of 86% and specificity of 85%.[2345]

With history and physical exam alone, it may not be possible to distinguish PCRS from chronic adenoiditis, especially in younger children. However, since adenoidectomy alone is often an effective treatment option in this population, this distinction may not be critical. For PCRS, although CT imaging may be used to provide objective evidence confirming the diagnosis of PCRS,[31,2341] the diagnosis is typically made by the clinical impression[31] and physical examination and/or nasal endoscopy. To minimize pediatric radiation exposure, CT imaging can then be saved for when sinus surgery is being considered.

Diagnosis of Pediatric CRS

Aggregate Grade of Evidence: C (Level 3: 2 studies; level 4: 2 studies)

Table XIII-6. Evidence for the diagnosis of pediatric CRS

Study	Year	LOE	Study Design	Study Groups	Clinical End-point	Conclusion
Brietzke[2341]	2014	1	N/A	N/A	N/A	Clinical consensus statement
Fokkens [31]	2012	1	N/A	N/A	N/A	Clinical consensus statement
Bhattacharyya[2345]	2004	3	Prospective cohorts	CTs of children with PCRS undergoing ESS CTs of children for non-RS diagnosis	Lund-Mackay Score	PCRS mean LM score 10.4; control mean LM score 2.8. LM cutoff of 5 has high sensitivity and specificity.
McAlister[2343]	1989	3	Prospective observational cohort study	Plain films of children with chronic sinus symptoms CT scans of same children	Radiographic evidence of inflammation in the sinuses	CT has higher sensitivity and specificity than plain films.
Leo[2342]	2015	4	Cohort study	228 children with CRS and evidence of inflammation on nasal endoscopy 47 children with CRS symptoms, normal nasal endoscopy	Prevalence of Halitosis, cough, facial pain, rhinorrhea, nasal obstruction, epistaxis	Downgraded from Level 3 because of poor control group matching (nasal endoscopy findings not quantified). This limitation does not affect the data cited in text above.
Lazar[2344]	1992	4	Retrospective cohort	Plain films of children who underwent ESS for CRS CT scans of children who underwent ESS for CRS Intraop findings	Presence of inflammation	Downgraded from Level 3 because outcome metrics are not clearly defined or blinded from surgeon/reviewer

XIII.B.4. Pediatric CRS: Management

The goals of PCRS management include control of sinonasal symptoms, restoration of normal sinonasal function, reduction of the inflammatory burden, and minimizing the side effects of therapeutic interventions.

PCRS management begins with medical therapy. Consensus exists that nasal saline irrigations (NSI) are beneficial in the pediatric population as a sole treatment modality or as a treatment adjunct.[26,2346] However, there is no consensus about the optimal method of delivery or concentration of saline. In a recent systematic review of NSI for PCRS, Gallant *et al.* reported that the magnitude of benefit from NSI is unknown, as prior studies have lacked control arms or used inconsistent outcome metrics.[2311] A retrospective study and cross-sectional survey in 104 CRS children aged 5-9 years concluded that the use of once daily NSI for a 6-week period is effective and leads to symptom resolution in PCRS.[2347] A phone survey of parents of 61 children aged 2-16 years diagnosed with CRS, AR and NAR, reported high tolerance and subjective improvement in nasal symptoms with NSI.[2348]

There is limited data regarding topical antibiotic irrigations for PCRS. One prospective randomized double-blinded study found equal efficacy of once-daily nasal irrigations and once-daily saline plus gentamicin irrigations in reducing symptom scores and CT scores. Both groups achieved statistically significant improvement of these outcome metrics after 3 weeks of treatment, which did not improve further after 6 weeks of treatment. Pediatric compliance with NSI may be initially considered with skepticism, though with parental assistance, compliance is greater than 90%.[1158]

Reports on the efficacy of INCS such as fluticasone or mometasone are conflicting due a lack of proper clinical trials.[26] However, given the low systemic absorption, the low risk profile, and the favorable efficacy in adults with CRS, use of INCS is recommended as first line therapy. INCS is recommended both as a component of medical management and in post-operative treatment regimens, particularly in patients suspected to have IgE-mediated pathophysiologic processes.[26]

Scientific evidence supporting the use of systemic antibiotics in PCRS is limited. An empiric broad-spectrum treatment with culture-directed antibiotics for 21 days could however be recommended based on clinical practice observations and extrapolation from studies in pediatric ARS.[2349] Initial empiric treatment with amoxicillin/clavulanate, and second (cefuroxime) or third (cefdinir and cefixime) generation cephalosporins could be used as first-line antibiotics. In case of allergy to penicillin, cephalosporins and macrolides, or clindamycin, could alternatively be prescribed as second- or third-line antibiotics, respectively.

Systemic corticosteroids have demonstrated clinical efficacy in the management of PCRS as an adjunct to systemic antibiotics. Ozturk, *et al.* performed a double-blinded, randomized prospective trial of 48 children (age 6-17 years) who were treated with either amoxicillin/clavulanate and methylprednisolone or amoxicillin/clavulanate and placebo twice daily for 30 days. Both groups demonstrated significant improvement in symptom and CT scores. However, children who received corticosteroids had significantly greater improvement in symptom scores, CT scores, and duration of benefit. There were no treatment-related adverse events in either group.[2350] However, the potential for serious side effects with systemic corticosteroid use should reserve consideration of such therapy for disease recalcitrant to more conservative measures and as a possible adjuvant to surgical therapy. There is limited knowledge of the risks of using systemic corticosteroids in pediatric CRS. However, based on studies on pediatric asthma,[2351] a single short-term systemic corticosteroids course could be considered in pediatric patients suffering from CRS not responding to more conservative measures.[2351] Randomized prospective studies examining antihistamines, decongestants or bacterial lysates in the management of PCRS are lacking.

Contributing comorbid conditions, such as GERD, immunodeficiencies, PCD, and CF, may increase the complexity of PCRS management. Randomized prospective data and clinical consensus examining the efficacy of anti-reflux medication in the management of PCRS are lacking.[26,2341]

Surgical intervention should be considered after appropriate medical therapy has failed. While there is no precise definition of appropriate medical therapy, it should generally include a course of antibiotic therapy, INCS, nasal saline irrigation, and consideration of oral corticosteroids.[26]

Surgical treatment options may vary based on the patient's age, anatomy, extent of disease, and comorbid conditions. In younger children, adenoid disease may play a larger role in the development of CRS, both as an obstructive process and as a reservoir for bacterial growth.[2352] There is evidence that adenoidectomy alone is an effective treatment for PCRS in children up to age 6 years, and may have similar efficacy in some children up to age 12, though evidence is lacking beyond this age group.[2341] A 2008 meta-analysis of 9 studies (moderate evidence: level 2 in 5 studies and level 4 in 4 studies) found a clinical improvement, as judged by caregivers, in 70% of children aged 4-7 years with CRS after adenoidectomy.[2353] A 1999 prospective, non-randomized cohort study analyzed the success of adenoidectomy and ESS in children aged 2 to 14 years, where failure was defined as persistence of symptoms and need for additional procedure at 6 months postoperatively. Adenoidectomy had a 47% success rate, while ESS had a 77% success rate.[2354] A 2017 prospective interventional study in 66 children aged 4-12 years with refractory CRS showed improvement in QoL scores after adenoidectomy when compared to baseline in 88% of children using the SN-5 instrument.[2355] Because there is a significant overlap of symptoms between CRS and chronic adenoiditis, the diagnosis before surgery must rely on objective measures such as nasal endoscopy or CT scan. In children with CRS symptoms, a Lund-Mackay score of 5 or greater may be considered diagnostically "positive" for CRS with a high positive predictive value, whereas CRS symptoms and a CT score below that probably indicates isolated adenoiditis.[2345] Supporting this concept, a retrospective study found that in pediatric patients with Lund-Mackay scores greater than 6, the addition of maxillary sinus irrigation at the time of adenoidectomy improved clinical symptoms one year after the procedure.[2356]

Most data supporting ESS for PCRS are retrospective, and study subjects and design are heterogeneous. In a 2013 systematic review, Makary *et al.* reported success rates over 82% with a minor complication rate of 1.4%.[2357] Another systematic review and meta-analysis performed by Vlastarakos *et al.*, also in 2013, reported a surgical success from 71 to 100% for improvement of PCRS symptoms and QoL with a low incidence (0.6%) of major complications.[2358]

In the last decade, balloon sinus dilation (BSD) has been introduced as a surgical option. A recent multicenter prospective study reported a favorable safety profile of BSD in children. Sinus dilations were performed in 50 children and adolescents aged 2-21 years. No complications were reported.[2359] Most studies report cases that combined BSD with other surgical interventions such as adenoidectomy and/or ethmoidectomy,[2360-2362] and prospective randomized trials have not been performed. Hence, it is uncertain how much benefit is due to BSD alone.[2346] Finally, consensus exists that the use of CT imaging is recommended prior to ESS, and image guided navigation has a role in revision ESS or if distorting polyposis is present.[311,2341] Though a potential for therapeutic improvement is acknowledged, there is limited pediatric data regarding turbinoplasty or excision of obstructive concha bullosa. With respect to postoperative debridement, one study failed to show significant postoperative benefit.[2341]

Table XIII-7. Management of pediatric CRS

Study	Year	LOE	Study Design	Study groups	Clinical Endpoint	Conclusion
Fokkens[26]	2020	1	Systematic Review	N/A	N/A	Treatment evidence and recommended management

						algorithm provided.
Makary[2357]	2013	1	Systematic Review	11 studies (3 prospective) supporting the use of ESS in PCRS	ESS success and complication rate	ESS offers a surgical alternative in the treatment of CRS in children with an excellent safety profile.
Setzen[311]	2012	1	Systematic Review	N/A	Clinical Consensus Statement	CT imaging in PCRS is recommended in the setting of treatment failures and complications.
Brietzke[2353]	2008	1	Systematic Review and Meta-analysis	9 studies (6 cohort studies, 4 case series)	Effectiveness of adenoidectomy alone in management of medically refractory PCRS	Adenoidectomy should be considered first line therapy for medically refractory, uncomplicated pediatric RS.
Gallant[2311]	2018	2	Systematic Review	5 evaluable studies exploring the use of NSI in PCRS (2/5 retrospective)	No study met all inclusion criteria. Mainly due to their design and heterogeneous comparators	Higher LOE studies are necessary.
Ozturk[2350]	2011	2	RCT	48 children with CRS randomly assigned to either oral antibiotics and methyl-prednisolone or antibiotics and placebo	Mean change in symptom and CT scan scores after treatment	The addition of oral corticosteroids to oral antibiotics reduced clinical PCRS symptoms and CT findings.
Wei[1158]	2011	2	RCT	40 children with CRS randomized to once-daily irrigation with saline or saline/gentamicin	CT scan and SN-5 scores before and after treatment	High tolerance, compliance, and effectiveness of saline irrigation support its use as a first-line treatment for PCRS.
Ramadan[2354]	1999	3	Prospective, non-randomized,	61 children with refractory CRS treated by	Pre and postoperative symptoms	Higher success in PCRS patients undergoing ESS in

			cohort Study	ESS (n=31) or adenoidectomy (n=30)		comparison to adenoidectomy
Bettadahalli[2355]	2017	4	Prospective non-randomized, uncontrolled, interventional study	60 children with refractory PCRS before and after adenoidectomy	Rhinosinusitis symptom severity score, Sinus and Nasal Quality of Life Survey (SN-5), CT scan and nasal endoscopy	Adenoidectomy improves symptoms and QoL in refractory PCRS
Soler[2359]	2017	4	Prospective, multicenter, uncontrolled, non-randomized study	50 children at 4 centers with PCRS treated with BSD	Technical success and procedure complication rate, surgical revision rate and changes in disease-specific QoL.	BSD is a safe procedure for PCRS. It may be effective and improve QoL. 60% of patients had adjunctive procedures.
Brietzke[2341]	2014	4	Consensus Statement	N/A	N/A	Evidence based expert panel consensus in the diagnosis and management of PCRS.
Ramadan[2356]	2008	4	Retrospective Series	60 children with refractory PCRS treated with adenoidectomy alone (n=38) or adenoidectomy with maxillary sinus wash (n=22)	Pre and postoperative symptoms and CT score	For pediatric patients with Lund-Mackay scores greater than 6, the addition of maxillary sinus irrigation at the time of adenoidectomy was found to improve clinical symptoms of PCRS one year post procedure

XIII.B.5. Pediatric CRS: Complications

Literature for complications related to pediatric CRS is sparse with no identified systematic reviews related specifically to this topic. One systematic review of intracranial complications in combined pediatric RS (PARS and PCRS) identified risk factors for male gender and adolescent age without discerning between PARS and PCRS.[2318] Case reports and small case series of pediatric CRS highlight extra-cranial and intra-cranial complications which are similar to those of PARS, including orbital abscess, frontal bone chronic osteomyelitis (Pott's puffy tumor), mucocele, intracranial abscess, and cavernous sinus thrombosis.[39,2363-2365]

XIV. Special Considerations in Rhinosinusitis

XIV.A. Cystic Fibrosis (CF)

CF is a genetic disorder caused by autosomal recessive inheritance of mutations in the CFTR protein, leading to exocrine gland dysfunction.[2366] The resulting disruption in ion and water transport results in impairment of MCC and propensity for bacterial colonization.[2367] The incidence of CRSwNP and CRSsNP in CF patients has been reported at 90-100% and 36-58%, respectively.[2368-2370] The concept of the unified airway model, when applied to this population, suggests that the sinuses may act as a bacterial reservoir for transmitting disease to the lower airways.[2371] As pulmonary infection and inflammation have been shown to be the leading causes of both morbidity and mortality in CF, control of sinonasal disease has become a focus for improving pulmonary outcomes.[2372] In addition, as life expectancy for individuals with CF increases, factors such as QoL are taking on increasing importance.[2373]

Medical intervention, normally comprising long-term combinations of oral and topical treatment, remains the first step in managing CRS in CF patients. Consensus recommendations for medical treatment are lacking, as a 2019 Cochrane Review failed to identify any studies that met the inclusion criteria of randomized trials of medical interventions compared to each other or to placebo.[2374] Given the improving life expectancy for patients with CF, there is a growing need for sound clinical research that can guide our decisions for medical treatment of CRS in this population.

Nasal saline irrigation

Despite robust evidence for saline irrigations in the medical treatment of CRS in general,[1] there remains no conclusive evidence supporting their use for CRS related to CF. Hypertonic saline theoretically creates an osmotic gradient to improve MCC and is occasionally considered as a nasal irrigation due to reports of positive pulmonary outcomes in CF with nebulized inhalation.[2375] In addition, a 2016 Cochrane review showed improvement in disease-specific QoL with 2% nasal saline irrigation versus placebo in non-CF patients with CRS.[1048] However, a more recent double-blind crossover RCT compared nebulized hypertonic 6.0% saline to isotonic 0.9% saline in CF patients with CRS and failed to show any comparative benefit in SNOT-20 score at 1 month, while also resulting in increased nasal irritation.[2376]

Oral and topical antibiotics

While inhaled antibiotics have gained significant traction in the treatment of lower airway infections in CF, the treatment of sinonasal colonization of *Pseudomonas aeruginosa* has not been well studied, with only a single RCT showing QoL improvement with daily intranasal nebulized tobramycin in a cohort of six patients versus placebo.[1150] However, more robust data exists for the use of antibiotic therapy during the postoperative period in an effort to eradicate chronic sinonasal bacterial colonization.[2377,2378] While macrolides have shown promise in treating lower airway disease due to antibacterial and anti-inflammatory effects[2379], further studies are needed to reveal the utility of systemic antibiotics in treating CRS in CF patients.

Oral and topical steroids

Contrary to CRS patients without CF, there is a paucity of evidence for or against the use of topical corticosteroids in CF patients with CRS for CF. One double-blind RCT showed that topical betamethasone reduced the size of NPs, albeit without concomitant improvement in nasal symptoms.[2380] Nonetheless, a 2019 study reported that 88.6% of pediatric otolaryngologists advocate for use of INCS for CRS in CF[2381], which may be partly due to the low side effect profile.[1083] Comprehensive studies regarding the use of oral corticosteroids in the treatment of CRS in CF are also lacking.

Anti-inflammatory agents

While transient resolution of NP was observed with high-dose ibuprofen in a 2007 retrospective study, its adoption as a treatment option for NP in CF has been limited due to its side effect profile, findings of polyp recurrence, and the likelihood of requiring eventual endoscopic surgery despite treatment.[2382]

DNAse mucolytics (Dornase alfa)

Mucolytic agents such as Dornase alfa reduce the viscosity of sinonasal mucus by cleaving extracellular DNA known to accumulate in CF upper and lower airways due to extensive neutrophil degradation.[2383] A 2018 systematic review showed consistent improvement of sinonasal symptom scores with topical dornase alfa compared to topical saline alone.[1211] However, the drug's impact on pulmonary function and endoscopic scores was variable, leading the authors to suggest the need for larger studies.

CFTR modulators

Ivacaftor, a potentiator that prolongs the open time of the CFTR channel and increases the liquid component of respiratory mucus, has shown significant long-term improvements in pulmonary disease in certain CF patients with gating (G551D) or residual function mutations.[2384] Lumacaftor and tezacaftor, two additional CFTR modulators, are used in combination with ivacaftor to target additional mutations of CF. With the US FDA approval of triple combination (TC) CFTR therapy (elexacaftor-tezacaftor-ivacaftor) in October 2019, 90% of individuals with CF $\geq$ 12 years of age have clinical access to highly effective modulator therapy based on genotype.[2385]

With respect to CRS in CF, a 2019 study of ivacaftor analyzed multicenter prospective data originally collected in 2013. It showed improvements out to six months in the rhinologic, psychological, and sleep domains of the SNOT-20 outcomes tool, albeit without a control arm and in young patients with limited CRS severity.[2386] TC CFTR therapy, which targets the most common mutation in CF, F508del, is anticipated to lead to improvements in CF-CRS, beyond substantial pulmonary effects.[2387] Despite the substantial cost (USD$300,000 / year),[2388] CFTR modulators show substantial promise in the treatment of CRS in CF.

Surgical Treatment Recommendations

It has been reported that approximately 25-60% of patients with CF and CRS fail appropriate medical therapy and require surgical intervention.[2389,2390] Studies have consistently shown a benefit of ESS on QoL outcomes,[2391,2392] but have mixed results with respect to pulmonary function tests (PFTs), antibiotic use, and pulmonary exacerbations.[2393,2394] Additionally, no data exist regarding the outcomes of ESS in the expanding era of highly effective CFTR modulator therapy. In CF patients who undergo ESS following lung transplant, studies have shown no significant improvement in PFTs, but demonstrated a significant improvement in total pulmonary-related hospitalizations.[2395,2396]

With respect to surgical technique, sinus hypoplasia and anatomic variants can make complete ESS difficult, which is especially important in CF as inspissated secretions may be trapped in partially removed partitions or unopened cells. Therefore, careful pre-operative review of CT anatomy remains crucial.[2397] While extended surgical procedures such as endoscopic medial maxillectomy and Draf 3 procedures have shown favorable long-term sinonasal outcomes,[1984,2398] comparative studies are lacking, and therefore should be considered on a case by case basis based on the degree of disease and mechanism of failure in the case of revision ESS.

XIV.B. Chronic Granulomatous Diseases

Chronic granulomatous diseases (CGD) include granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis), eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome), and sarcoidosis. CGD produces hallmark perivascular or perilymphatic non-caseating granulomas. GPA and EGPA cause systemic, necrotizing, ANCA-associated vasculitis, while sarcoidosis produces a chronic inflammatory disease of uncertain etiology.

GPA can affect any organ system with classic manifestations of systemic illness, otitis media, subglottic stenosis, nodular infiltrates on chest radiograph, and renal disease. From the rhinologic perspective, sinonasal disease is the most common manifestation of GPA.[2399] Progressive ischemic necrosis of the nasal mucosa and internal structures can occur, resulting in epistaxis, crusting, septal perforation, and saddle nose deformity.[2399] Churg-Strauss syndrome is associated with both ANCA-positive testing and 4 of 6 of the following clinical findings: refractory CRSwNP, peripheral eosinophilia, asthma, neuropathy, pulmonary infiltrates and systemic vasculitis.[2400] It is important that rhinologic symptoms, such as nasal obstruction or epistaxis, tend to appear at an early stage in GPA and EGPA. Therefore, otorhinolaryngologists should maintain a high index of suspicion to not overlook these rare entities.[2400]

Sarcoidosis is a systemic non-caseating granulomatous inflammatory process, which is typified by nodular, infiltrative submucosal lesions in the nasal mucosa. However, patients may develop friable mucosa with nasal crusting and structural deformities similar to GPA.

Management of CGD in general includes systemic control of disease via immunosuppression, with individualized medical and/or surgical rhinologic care. Recently, anti-IL-5 monoclonal antibody therapy has proven to be useful in some settings.[2401] Medical therapy remains the cornerstone of management of sinonasal involvement in CGD, including INCS and saline irrigations. Surgery for mucocele formation, nasolacrimal stenosis, and CRS in general may be beneficial to control sequelae of GPA in appropriately selected patients,[2401] although persistent or recurrent disease is common.[2399] Systemic manifestations of both sarcoidosis and EGPA are managed with chemotherapeutic agents, oral corticosteroids +/- immune modulators. Similar to GPA, the literature supports use of medical management, while reserving surgical intervention for persistent rhinologic symptoms in select patients.[2400,2402-2405, 2406] Given the epithelial abnormalities present in CGD patients, patients should be counseled regarding suboptimal and/or delayed healing that can follow intranasal procedures.

XIV.C. Primary Ciliary Dyskinesia

Primary ciliary dyskinesia (PCD) is a rare, genetically heterogeneous disease.[2407] Prevalence of the disease is estimated to be approximately 1 in 20,000 individuals. Situs inversus is present in 50% of

patients. Dysfunction of motile cilia leads to oto-sino-pulmonary manifestations. Classic Kartagener's syndrome is comprised of situs inversus, CRS and bronchiectasis. Cardiovascular abnormalities and infertility are also commonly noted.

Symptoms of PCD are often non-specific. Evaluation for PCD is recommended when chronic wet cough and 6 of the following 7 predictive parameters are present: full-term gestation, neonatal chest symptoms, neonatal intensive care admittance, chronic rhinitis, ear symptoms, situs inversus and congenital cardiac defect.[2408] For patients with supportive clinical symptoms as mentioned above, the following results are confirmatory of a positive diagnosis of PCD: 1) hallmark ciliary ultrastructure defects assessed by transmission electron microscopy, and 2) non-ambiguous bi-allelic mutations in PCD-causing genes.[2409] For patients with compatible clinical symptoms of PCD, the following results make the diagnosis of PCD highly likely; 1) Very low nasal nitric oxide plus high-speed video microscopy analysis findings consistently suggestive of PCD on three occasions, and 2) Very low nasal nitric oxide plus high-speed video microscopy findings consistent with PCD following cell culture.[2409]

At present, treatment of PCD is not standardized, and there are no validated PCD-specific therapies.[2410] The PCD Foundation recommends 1) daily airway clearance, 2) daily nasal sinus lavage, 3) standard vaccinations, 4) Influenza, Pneumococcal and RSV vaccine, 5) cessation of smoking, and 6) prompt antibiotics therapy at the time of respiratory tract infection.[2411] Although the effectiveness of ESS is controversial, combined ESS and adjuvant therapy can decrease sinus bacteria, reduce pulmonary infections and improve QoL of PCD.[2412]

Diagnosis in the early stages is important to prevent progression of bronchiectasis and deterioration of lung function.[1] One recent study reports PCD affects lung function early in life, which emphasizes the importance of early standardized care for all patients.[2413]

XIV.D. Invasive Fungal Rhinosinusitis

Fungi are ubiquitous and contribute to the diverse microbiome of the paranasal sinuses.[2414] However, in immunocompromised states such as diabetes mellitus (DM), hematologic disorders, HIV/AIDS, and organ transplantation, immunological defenses are disrupted and hyphae may invade mucosa, vasculature or bone, thereby causing invasive fungal sinusitis (IFS).

Classification of IFS exists along a continuum determined by host factors and symptom duration. Acute invasive fungal rhinosinusitis (AIFS) is defined by histopathologic evidence of fungal invasion into tissue with less than four weeks of symptoms, whereas chronic invasive fungal sinusitis (CIFS) is defined by symptoms beyond this period.[1709,2415,24162] Further distinction is based on presence of non-caseating granulomas, as seen in chronic granulomatous invasive fungal sinusitis (GIFS). Multi-institutional studies and systematic reviews in adults[2417] and children[2418] represent the best evidence for AIFS. Studies of CIFS and GIFS are much more limited but recent multi-institutional studies have provided important insights into these rarer variants.

XIV.D.1. Acute Invasive Fungal Rhinosinusitis (AIFS)

AIFS is the most common[2419] and life-threatening form of IFS, with a mortality rate of 50-80% in affected adults and children,[2417,2418,2420,2421] although disease-specific mortality may be lower.[2422] Nearly all

patients with AIFS are immunosuppressed. In adults, poorly controlled DM is the prevailing comorbidity (47.8%), followed by hematologic disorders (39.8%);[2417] whereas, hematologic disorders accounted for 81.5% of cases in children.[2418]

The two most prevalent organisms responsible for AIFS are from the *Aspergillus* genus and from the Zygomycetes order, including *Mucor, Rhizopus and Rhinomucor*.[2423,2424] *Aspergillus* is prevalent in the environment and becomes invasive when host immune defenses are compromised.[2414] Zygomycetes demonstrates a predilection for diabetic patients due to its affinity for acidotic and high glucose environments.[2414] *Fusarium*, *Scedosporium*, *Pseudoallescherii boydi* and dematiaceous fungi may also cause AIFS, however these organisms are much less common. While variety exists in the offending organisms, their differential effect on survival outcome in AIFS remains unclear.[2417,2425]

The risk of mortality varies by underlying immunologic impairment. In a systematic review of 52 studies and over 800 patients, odds of mortality in AIFS was about half in patients with DM (OR: 0.492) compared to others.[2417] Similarly, in a population-based study of 979 patients who underwent surgery for AIFS, the odds of mortality in patients with DM were also significantly lower (OR: 0.53).[2426] The lower mortality risk is attributed to the reversible nature of hyperglycemia in DM, as compared to the less reversible state of neutropenia in hematologic disorders. Encouragingly, a recent multi-institutional study of 114 patients demonstrated decreased mortality in patients with hematologic disorders after initiation of granulocyte stimulation factor.[2423] While this shows promise for these patients, the practicality and long-term effects warrant further investigation.

The most common symptoms of AIFS are nonspecific and include facial swelling (64.5%), fever (62.9%), and nasal congestion (52.2%).[2417] As such, increased clinical suspicion and prompt diagnostic testing in the appropriate clinical context is essential.[2417,2427] Most cases of AIFS demonstrate some degree of mucoperiosteal thickening within the nasal cavity (early) or paranasal sinuses on CT, often unilateral.[2428,2429] MRI can be used adjunctively to assess extent of disease particularly when there is bone erosion and orbital or intracranial involvement is suspected. Nasal endoscopy is critical, and early findings may be subtle, such as edema with violaceous or pale mucosa and lack of sensation, with subsequent progression to eschar and necrosis due to ischemia and vascular thrombosis.

Rapid diagnosis is critical. Diagnosis is established with biopsy of suspected tissue, with the middle turbinate often a high-yield location.[2430] Some experts have advocated for the use of frozen section in order to speed the diagnosis even further, with one study demonstrating improved survival rates in immunocompromised patients with presumed AIFS.[2431]

The mainstays of treatment for AIFS are (1) timely surgical debridement, (2) initiation of intravenous antifungal therapy, and (3) reversal of the underlying immunodeficiency. Effective multidisciplinary care for patients with AIFS is paramount and should include a clear understanding of the goals of care. As demonstrated by several studies, sinus surgery improves survival in patients with AIFS.[2417,2428,2432] Turner *et al.* reported odds of mortality were increased in patients with intracranial involvement (OR: 1.892) and decreased in patients undergoing either endoscopic or open surgery (OR: 0.357, 0.486, respectively).[2417] The survival benefit from surgery may be attributable to prompt diagnosis, which may also have benefit in decreasing long-term morbidity,[2433] collection of cultures, removal of the fungal burden, and enhanced postoperative endoscopic surveillance; however, selection bias of patients able to tolerate surgery must be considered.

Antifungal therapy should be initiated immediately if the clinical suspicion for AIFS is high as delay has been linked to decreased survival.[2434] In the treatment of *Aspergillus,* IV and oral azole agents (*e.g.*, voriconazole, isavuconazole) are the first-line therapy,[2435,2436] whereas IV liposomal amphotericin remains the treatment of choice for Zygomycetes infections.[2417,2434] Isavuconzole or posaconazole, which are available orally, may also be effective in treating Zygomycetes with potentially fewer side effects,[2437] however, additional evidence is needed to support their first-line use. Additionally, posaconazole as primary prophylaxis in high-risk populations (*e.g.*, graft-versus-host-disease, acute myeloid leukemia, myelodysplastic syndrome) has been studied, however, their potential benefit must be weighed against risk of toxicities and selection for resistant infections.[2438]

XIV.D.2. Chronic Invasive Fungal Rhinosinusitis (CIFS)

CIFS, which represents a distinct clinical entity within the spectrum IFS, is defined by its more indolent course. A recent multi-institutional study found the mean time from onset of symptoms to diagnosis was approximately six months.[2439] In this condition, the host immune system is typically only mildly impaired and is able to mount a vigorous inflammatory response (*e.g.*, chronic corticosteroid use or DM without ketoacidosis).[2440] Histopathology typically demonstrates evidence of invasive *Aspergillus fumigatus* accompanied by extensive chronic inflammation, although Zygomycetes infections have also been reported.[2441] While surgical intervention is critical for diagnosis and postoperative surveillance, debridement may be more conservative as long-term antifungal treatments are effective to address residual disease.[2415,2439]

XIV.D.3. Granulomatous Invasive Fungal Rhinosinusitis (GIFS)

GIFS is similar to CIFS in chronicity of symptoms but distinct in histopathology and underlying host factors. This condition is seen in immunocompetent patients and is more prevalent in the Middle East, Northern Africa, and Asia.[1709,2441] The most common presenting symptom is unilateral proptosis.[2442] As in CIFS, conservative surgery as well as long-term antifungal treatments have been shown to be effective for complete resolution.[2443] In distinguishing CIFS from GIFS, careful histopathological evaluation and history of travel to or living in Northern Africa, Middle East and Asia may be helpful for diagnosis. Histopathology typically demonstrates evidence of invasive *Aspergillus flavus*[2441,2444] accompanied by fibrosis, mild inflammation and non-caseating granulomas.[2440] *Aspergillus fumigatus*, however, has been reported as the causative agent in some cases in North America.[2442,2443]

XV. Summary of Knowledge Gaps and Research Opportunities

XV.A. Rhinosinusitis: State of the Science

The breadth and quality of research into virtually all aspects of RS has advanced considerably in the past decade. The sheer scope of the ICAR-RS document is, itself, evidence of such progress. Across the disparate subjects of epidemiology, pathophysiology, management, and outcomes, the document offers aggregate evidence on over 180 individual topics, 16 of which are grade A. Interestingly, the number of individual studies cited appears to roughly double with each decline in evidence between grade A and C. This phenomenon suggests that there remains a need to redirect energies towards higher quality research and the knowledge gaps revealed throughout the document which are summarized here (Table XV-1). Further analysis of studies on CRS management reveal more than twice the number of grade A trials in CRSwNP than CRSsNP. While multiple explanations of this phenomenon may be posited, one stands out with important implications for future research opportunities. The presence of obvious phenotypic characteristics (*e.g.*, nasal polyps) facilitates patient recruitment into mechanistic, outcomes, and therapeutic studies at the expense of more ill-defined disease states. These patients are then more easily targeted by investigators and industry partners willing to perform large, expensive, high quality studies when quantitative therapeutic outcome metrics can be tied to this same phenotype. It is therefore evident that the identification of sensitive and specific biosignatures of all CRS subtypes has the potential to fundamentally transform RS research by overcoming the reliance on phenotype in any study. Preliminary work into AECRS,[1010,1751] CRS,[54,61] and CRSwNP[2445] endotypes have already demonstrated the feasibility of this approach. Further large scale multi-institutional studies to both identify and validate non-invasive biosignatures associated with the entire spectrum of the disease therefore represents one of the single greatest unmet needs in CRS research.

XV.B. Etiopathogenesis and the Treatable Trait

Among the CRS subtypes, the ICAR-RS document calls out a specific paucity of literature in the role of odontogenic infection in ARS, the contributions of viruses, allergy and immunodeficiency in RARS, and the relationship between allergic inflammation and nasal polyps. More generally, this compendium demonstrates that RS is a multifactorial spectrum of diseases resulting from complex host inflammatory and environmental interactions with significant inter-patient and geographic variability. These attributes are shared by other complex airway diseases leading to emergence of the concept of the "treatable trait."[2446] This idea seeks to identify individual characteristics which function both as biosignatures of disease and therapeutic targets. This approach has already entered the field of rhinology in the form of biologic therapies targeting specific cytokines implicated in the pathogenesis of type 2 disease. Studies reporting therapeutic efficacy in these approaches[56] validate the treatable trait concept in CRS. However, the disease phenotype appears to recur after withdrawal of agents targeting the inflammatory cytokine cascade suggesting these traits are secondary to the inciting event or events. The application of poly-omic and bioinformatic approaches to patients with CRS[2447-2450] has revealed a host of potential upstream novel targets whose role in disease development remains unknown. Furthermore, these targets may exist within previously unrecognized populations of epithelial progenitor cells.[2451] The mechanistic investigation of these targets and identification of potential etiopathological treatable traits remains a significant research opportunity.

XV.C. Pharmacologic Management and the Topical Paradox

ICAR-RS provides evidence for the primary pharmacologic management of RS within multiple disease subtypes as well as in the pre- and post-operative period. Indeed, some of the highest quality grade data within the entire document exist around the effective use of INCS for the treatment of adult ARS, pediatric ARS, CRSsNP, and CRSwNP. These results are generally consistent with the promise of topical treatments for sinonasal disease in the context of providing high local concentrations directly to the end target organ while avoiding systemic exposure and off-target toxicity. In contradistinction, the data for topical antibiotic use consistently fail to demonstrate clear benefit. This finding appears paradoxical, particularly in light of grade A evidence for the benefit of systemic antibiotics. There are likely multiple factors contributing to this result however, one generalizable concept is that the majority of off-label agents have not been specifically studied or formulated for a topical sinonasal application. As such local mucosal factors including mucosal residence time, proteolytic degradation, mucus penetration, cellular uptake and metabolization may play unforeseen roles in limiting clinical efficacy. Consequently, continued research into systems to both model local sinonasal drug delivery and develop formulations and/or carriers specifically designed to optimize topical delivery represent a significant need.

The risks and benefits of pharmacologic management of CRS, particularly within the context of antibiotic administration, are germane to the concept of "appropriate (maximal) medical therapy" or AMT. It has become increasingly clear that inappropriate systemic antibiotic use is associated with significant risks including allergic reaction, resistance, and microbiome disruption.[2452] Furthermore, nascent evidence has emerged that a delay in surgical therapy may, in some cases, result in reduced QoL, increased absenteeism,[2453] and reduced surgical benefit.[1917] As described in ICAR-RS, there remains a significant gap in the literature regarding how to define the composition, length, and response rate to AMT. As the concept of AMT continues to be widely employed as a relative prerequisite for interventional strategies with their own pros and cons, it is incumbent upon the field to continue to develop high grade evidence-based algorithms to help guide the application of AMT.

XV.D. Interventional Strategies in Upper Airway Disease

The general growth of rhinology as an interventional field has ushered in an array of technical innovations in devices and implants aimed towards improving patient outcomes with less invasive techniques. Examples of these include balloon dilation, cryoablation, and biodegradable steroid-eluting implants. These technologies each offer an opportunity to provide enhanced care to patients provided they are used in an evidence-based manner. While the potential benefits are apparent, these must further be weighed against risk, effect size, and alternatives. This information is best attained through well-designed, sham-controlled studies, using validated patient reported outcome measures and clinically relevant objective endpoints. Even in the context of established efficacy, new pharmacological and interventional strategies require further scrutiny using shared decision modeling, cost-effectiveness, cost-minimization, and cost-benefit analyses to establish both relative value and where they should fit into overall treatment algorithms. The application of rigorous trial designs addressing each of these variables, therefore, remains an important research opportunity for both existing and future interventional technologies.

XV.E. Next Generation Research Tools

Rhinology is a unique field in which complex inflammatory pathways involving multiple cell and tissue types exert their effects in an area easily amenable to epithelial and mucus sampling as well as direct application of therapeutics. In many ways these features have facilitated significant research progress despite the conspicuous paucity of animal models and disease specific immortalized cell lines. Consequently, the rhinology research endeavor is well positioned to take advantage of many of the astonishing recent advances in biomedical research tools. These include CRISPR-Cas9, single cell RNA sequencing, 3D printing, artificial intelligence/machine learning, pharmacogenomics, and many others. The upper airway also provides for the ability to model other immunologic and inflammatory systems throughout the body.[2454] Multidisciplinary collaboration will become ever more important to maximize these opportunities however, through the sharing of knowledge across and between fields, the future of rhinology knows no limits.

XV.F. COVID-19 and Rhinology

The COVID-19 pandemic has impacted the field of rhinology in direct and unexpected ways. Some of the earliest reports regarding the SARS-CoV-2 virus suggested significant infection rates among Otolaryngologists,[2455] particularly high nasal/nasopharyngeal viral loads in even asymptomatic patients,[2] and prolonged viral persistence in air.[2456] Later data emerged suggesting anosmia as an early and prevalent symptom of COVID-19.[3,115,2457-2459] Consequently, the COVID-19 pandemic has raised additional knowledge gaps including the pathogenesis of SARS-CoV-2 related anosmia, the aerosolization[123] and infectious transmission risk of common rhinologic procedures, and the impact of delay of elective rhinologic care on patient outcomes.

Table XV-1. Research needs

Category	Research Need
Diagnosis of CRS	Validation of biosignatures of discreet CRS endotypes
Treatable Traits	Discovery of biomarkers that directly respond to targeted therapeutics and may predict efficacy
Topical Therapeutics	Development of formulations specifically designed to optimize mucosal distribution, stability, and absorption
Appropriate Medical Therapy	Define composition, duration, and response rate to AMT, through well controlled clinical trials
Interventional Strategies	Execution of sham-controlled studies using validated PROMS, clinically relevant objective endpoints, cost-benefit analyses
COVID-19	SARS-CoV-2 anosmia pathogenesis, rhinologic aerosol generating procedure risk, and how to deliver elective rhinologic care during pandemic conditions.

XVI. CRS Management in the Context of COVID-19

Editors' Note: Coronavirus disease 2019 (COVID-19) is a rapidly emerging topic and new data are constantly becoming available. This section was completed in early September 2020.

The COVID-19 pandemic, caused by the virus SARS-CoV-2, has heightened awareness and necessitated modifications to the workup and management of sinonasal pathologies including CRS.

XVI.A. Risk of COVID-19 for a CRS Patient

The relative viral susceptibility of a CRS patient remains unclear but thus far, there is no evidence that CRS patients are at increased risk for infection. Nasal expression of the SARS-CoV-2 receptor, angiotensin-converting enzyme 2 (ACE2), does not appear to be increased in CRS subjects. Compared to healthy controls, one study found no difference in ACE2 expression in CRS patients with or without polyps,[2460] while others found decreased ACE2 expression in cases of nasal polyposis and eosinophilic inflammation.[2461-2463] On the other hand, neutrophilic inflammation driven by IFNγ is associated with upregulated ACE2 expression.[2461,2464] At this time, the correlation between ACE2 expression and susceptibility to infection remains theoretical. Clinically, CRS subjects, maintained on topical steroids and biological therapy against type 2 inflammation, have not demonstrated higher risks of infection.[2462]

XVI.B. Risk of COVID-19 for a Healthcare Provider Treating a CRS Patient

Given the high viral burden found on nasal mucosal surfaces,[2] the field of otolaryngology has carefully assessed the risks of viral transmission between patient and healthcare provider. Diagnostic endonasal procedures are considered high risk as they have been shown to produce significant airborne aerosols,[127,2465] can induce cough/sneeze, require unmasking, and occur within an enclosed space in close proximity to the patient. While their specific designation as an aerosol-generating procedure (AGP) remains controversial, these features have all been shown to be associated with infectious transmission in community-based epidemiologic studies.[130-134] Furthermore, given their potentially obstructive nasal pathology, CRS patients are at risk for false-negative viral PCR results from nasopharyngeal swabs.[2466] Utilizing a combination of nasal and oropharyngeal swabs during PCR screening has been suggested for these patients.[2467]

Initial anecdotal reports of healthcare-associated infections following rhinological procedures highlighted the potential for viral transmissibility during endoscopic endonasal surgery.[2468] An international registry of otolaryngologists reported 39 suspected healthcare-associated cases of COVID-19 despite wearing N95 masks.[2469] However, these cases were self-reported and at risk for sampling bias. To date, there has been no definitive evidence that healthcare workers and otolaryngologists are at higher risk for infection.[2470-2473] Regardless, otolaryngology and rhinology societies around the world have recommended that endonasal surgeries be considered high-risk procedures.[2474]

XVI.C. Sinonasal Symptomatology Related to COVID-19

Viruses including coronavirus are implicated in both acute and chronic RS, but their role in the pathophysiology of CRS is ambiguous.[2475] While some studies have reported a high rate of viral detection during CRS exacerbations,[1006] others have shown similarly high rates in non-CRS patients,[25] thus a direct association between CRS and viral infection remains unclear. Thus far, there have been no data that links SARS-CoV-2 to increased CRS exacerbations.

Notably, olfactory dysfunction, a cardinal symptom of CRS, has been highlighted as a prevalent symptom of COVID-19.[3,107-110] In these cases, olfactory dysfunction is acute and profound, often heralding other viral symptoms or as the sole manifestation of disease. Unlike anosmia found in CRS, COVID-19-associated olfactory loss presents with no radiographic evidence of olfactory cleft disease or mucosal thickening of the sinuses.[111,112]

Importantly, olfactory loss has high diagnostic value as the strongest symptomatic predictor of COVID-19 with potential for early disease screening.[107,113,114] The prevalence of olfactory dysfunction has varied widely between 15 to 96% based on self-reported and quantitatively measured data.[115-117] The ability to accurately recognize one's olfactory impairment is debated,[115,2476-2479] but self-reported olfactory assessment is valuable for initial screenings when psychophysical testing cannot be conducted.[2476] Clinical implications of olfactory dysfunction as a prognostic marker for the disease also remain controversial.[2480-2484] Recovery of function appears to be generally rapid with most patients improving or recovering function within 4 weeks but with 21-39% experiencing persistent smell loss.[3,117,2485-2487] Olfactory symptoms often persist despite non-detectable viral loads and resolution of all other symptoms.[2488]

In addition to olfactory dysfunction, other chemosensory modalities including taste and chemesthesis are subjectively reduced with COVID-19. However, it is unknown if the taste disturbances in COVID-19 patients are due to retronasal olfactory dysfunction, with conflicting results found through psychophysical tests of gustatory function.[2479,2485,2489]

Aside from chemosensory dysfunction, there have been few sinonasal symptoms associated with COVID-19. Patient-reported sinonasal symptom severity scores using SNOT-22 found no other symptoms as commonly and significantly impacted as olfactory dysfunction. In fact, nasal obstruction is an uncommon symptom of COVID-19 infection and the paucity of nasal congestion with olfactory dysfunction together may serve as predictors for COVID-19.[3,2490,2491]

XVI.D. Medical Treatment of CRS in the Setting of COVID-19 Pandemic

The COVID-19 pandemic has necessitated flexibility in our treatment algorithms for CRS as guided by patient preference and concerns for viral transmission.

Topical INCS are recommended and maintained even during SARS-CoV-2 infection.[118,119] There is no evidence that INCS are associated with increased infectivity. Some fear discontinuing INCS may not only worsen symptoms but increase viral shedding due to coughing and sneezing. High volume nasal steroids are particularly efficacious in the treatment of CRS without necessitating surgical intervention.[2492,2493] One randomized, controlled trial in CRSsNP patients without history of sinus surgery showed greater improvements in SNOT-22 and Lund-Kennedy scores after using mometasone nasal irrigations compared to mometasone nasal spray for 8 weeks.[2492] These results suggest there is a role for prolonged high volume nasal steroid irrigations in this pandemic environment for those concerned about proceeding

with surgery. The utility and appropriateness of oral steroids remains controversial in the context of COVID-19, as its effects on COVID-19 lung injury are debated,[120] though more recent studies have shown improvement in COVID-19 mortality rate.[121]

Preliminary data have suggested that low concentrations of povidone-iodine (PVP-1) at 0.45-1.0% may be considered as a topical therapy for CRS and reduction of viral spread,[2494-2497] with effective virucidal activity against SARS-CoV-2 *in vitro*.[2498] PVP-1 rinses were well tolerated in post-surgical CRS patients and achieved similar SNOT-20 and Lund-Kennedy scores compared to mupirocin rinses though with lower bacterial culture negativity rates.[2495] However, it is important to note that PVP-1 at higher concentrations (5-10%) have demonstrated ciliotoxicity *in vitro* and increase risk of iodine toxity.[2499] *In vitro* efficacy furthermore, may not guarantee clinical anti-viral protection as mucosal coverage by topical rinses may be incomplete and can diverge from that of inhaled, aerosolized particles.

Biologic therapy targeting type 2 inflammation may also be considered an option for recalcitrant cases of CRS unwilling or unable to undergo surgical therapy.[2462,2500] The European Academy of Allergy and Clinical Immunology (EEACI) has recommended that non-infected patients on biologics continue their therapy. However, in case of an active SARS-CoV-2 infection, the authors recommended biological treatment be stopped until clinical recovery and confirmed SARS-CoV-2 negativity.[2501]

XVI.E. Surgical Treatment of CRS in the Setting of COVID-19 Pandemic

The implications on viral transmissibility for AGPs remain controversial.[122-125,127,128] Both high-speed drill and bipolar electrocautery are considered aerosol-generating devices, and are often required in extended surgical approaches for recalcitrant CRS.[123,128] The use of constant suctioning during these procedures may help mitigate particle transmission.[122,125] Notably the microdebrider, with its in-line suction, was not a significant aerosol producer. [123,128] Other aerosol-generating in-office devices include bipolar RF ablation (coblation) and cryotherapy, both used for treatment of rhinitis.[128]

While acknowledging the risks of endonasal instrumentation and mitigating unnecessary exposure, the otolaryngology field has continued to utilize AGPs in patient treatment. Comprehensive pre-visit patient screening, SARS-CoV-2 PCR testing, environmental safety, and full PPE utilization are recommended as appropriate precautions.[129]

XVII. References

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