International Consensus Statement on Allergy and Rhinology: Rhinosinusitis

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Background: **The body of knowledge regarding rhinosinusitis (RS) continues to expand, with rapid growth in number of publications, yet substantial variability in the quality of those presentations. In an effort to both consolidate and critically appraise this information, rhinologic experts from around the world have produced the International Consensus Statement on Allergy and Rhinology: Rhinosinusitis (ICAR:RS).**

Methods: **Evidence-based reviews with recommendations (EBRRs) were developed for scores of topics, using previously reported methodology. Where existing evidence was insufficient for an EBRR, an evidence-based review (EBR) was produced. The sections were then synthesized and the entire manuscript was then reviewed by all authors for consensus.**

Results: **The resulting ICAR:RS document addresses multiple topics in RS, including acute RS (ARS), chronic RS (CRS) with and without nasal polyps (CRSwNP and CRSsNP), recurrent acute RS (RARS), acute exacerbation of CRS (AECRS), and pediatric RS.**

Conclusion: **As a critical review of the RS literature, ICAR:RS provides a thorough review of pathophysiology and evidence-based recommendations for medical and surgical treatment. It also demonstrates the significant gaps in our understanding of the pathophysiology and optimal management of RS. Too often the foundation upon which these recommendations are based is comprised of lower-level evidence. It is our hope that this summary of the evidence in RS will point out where additional research efforts may be directed.**

Key Words:
rhinosinusitis; chronic rhinosinusitis; acute rhinosinusitis; recurrent acute rhinosinusitis; evidence-based medicine; systematic review; endoscopic sinus surgery

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List of Abbreviations Used

AAOA	American Academy of Otolaryngic Allergy
AAO-HNS	American Academy of Otolaryngology–Head and Neck Surgery
ABRS	acute bacterial rhinosinusitis
AECRS	acute exacerbation of chronic rhinosinusitis
AERD	aspirin-exacerbated respiratory disease
AFRS	allergic fungal rhinosinusitis
AIFS	acute invasive fungal rhinosinusitis
AJC	apical junction complex
AMCase	acidic mammalian chitinase
AMT	appropriate medical therapy
AOAH	acetyl hydroxylase
AR	allergic rhinitis
ARS	acute rhinosinusitis
ASA	acetyl salicylic acid
AVRS	acute viral rhinosinusitis
BID	twice daily
C3	complement component 3
CBF	ciliary beat frequency
CF	cystic fibrosis
ChT	chitotriosidase
CIFS	chronic invasive fungal rhinosinusitis
CMS	Centers for Medicare & Medicaid Services
CMT	conventional medical treatment
COX	cyclooxygenase
CRP	C-reactive protein
CRSsNP	chronic rhinosinusitis without nasal polyps
CRSwNP	chronic rhinosinusitis with nasal polyps
CS	conventional septoplasty
CSF	cerebrospinal fluid
CSS	Chronic Sinusitis Survey

CT	computed tomography
CVID	common variable immunodeficiency
cysLT	cysteinyl leukotriene
DAMP	damage-associated molecular pattern
DBRCT	double-blind randomized controlled trial
DC	dendritic cells
DSS	Dead Sea salt
DTH	delayed-type hypersensitivity
EBM	evidence-based medicine
EBR	evidence-based review
EBRR	evidence-based review with recommendations
EC	epithelial cell
ECP	eosinophilic cationic protein
EDN	eosinophil-derived neurotoxin
EER	extraesophageal reflux
ELISA	enzyme-linked immunosorbent assay
EMRS	eosinophilic mucin rhinosinusitis
EPOS	European Position Paper on Rhinosinusitis and Nasal Polyps
ES	endoscopic septoplasty
ESR	erythrocyte sedimentation rate
ESS	endoscopic sinus surgery
FEV1	functional expiratory volume within 1 second
FISH	fluorescent in situ hybridization
GERD	gastroesophageal reflux disease
GI	gastrointestinal
GIFS	granulomatous invasive rhinosinusitis
GOSS	Global Osteitis Scoring Scale
HBD	human beta defensin
HLA	human leukocyte antigen
HU	Hounsfield unit
ICAR:RS	International Consensus Statement on Allergy and Rhinology: Rhinosinusitis
IFS	invasive fungal rhinosinusitis
Ig	immunoglobulin
IGS	image-guided surgery
IHC	immunohistochemistry
IL	interleukin
ILC	innate lymphoid cells
INCS	intranasal corticosteroid spray
IV	intravenous
IVIG	intravenous immunoglobulin
LL-37	cathelicidin
LM	Lund-Mackay score
LOE	level of evidence
LT	leukotriene
MAD	mucosal atomization device
MBL	mannose-binding lectin
MCC	mucociliary clearance
MGO	methylglyoxal
MIF	migration inhibition factor
MMA	middle meatal antrostomy
MMP	matrix metalloproteinase
MMT	maximal medical therapy
MPRO	myeloperoxidase
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
mRNA	messenger RNA
MT	middle turbinate
NLR	nucleotide-binding oligomerization domain-like receptor
NO	nitric oxide
NOD	nucleotide-binding oligomerization domain
NP	nasal polyp
NPx	nasopharynx
NS	normal saline
NSAID	nonsteroidal anti-inflammatory drug
NSD	nasal septal deviation
OMC	ostiomeatal complex
PAMP	pathogen associated molecular pattern
PARE	pharyngeal acid reflux event
PCD	primary ciliary dyskinesia
PCR	polymerase chain reaction
PCRS	pediatric chronic rhinosinusitis
P	prostaglandin
PID	primary immunodeficiency
PLUNC	palate, lung, and nasal epithelium clone protein
PND	postnasal drip
PNIF	peak nasal inspiratory flow
PPI	proton pump inhibitor
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRR	pattern recognition receptors
PSQI	Pittsburg Sleep Quality Index
QID	4 times daily
QoL	quality of life
qRT-PCR	quantitative real-time polymerase chain reaction
RAGE	receptor for advanced glycation end products
RARS	recurrent acute rhinosinusitis
R-CRS	refractory chronic rhinosinusitis
RCT	randomized controlled trial
RQLQ	Rhinoconjunctivitis Quality of Life Questionnaire
RS	rhinosinusitis
RSDI	Rhinosinusitis Disability Index
RSI	Rhinosinusitis Symptom Inventory
RSOM	Rhinosinusitis Outcome Measure
RT-PCR	real-time polymerase chain reaction
SE	Staphylococcal enterotoxins
SF	Short Form Health Survey
SNOT	Sino-Nasal Outcome Test
SNP	single-nucleotide polymorphism
SP	surface protein
SPECT	single proton emission CT
TFF	trefoil factor family
TGF	transforming growth factor
TID	3 times daily
TLR	Toll-like receptor
TNF	tumor necrosis factor
TP-1	thymostimulin
TRE	target registration error
TSLP	thymic stromal lymphopoietin

TSST	toxic shock syndrome toxin
UES	upper esophageal sphincter
URI	upper respiratory infection
FDA	U.S. Food and Drug Administration
VAS	visual analog scale
VD_3	vitamin D

Appendix

I. Introduction

The body of knowledge about rhinosinusitis (RS) continues to expand. A search of the PubMed database using the search terms "sinusitis" or "rhinosinusitis" demonstrates that between 2000 and 2014, 12,847 articles were published on the subject. Further, this search shows that the annual number of publications on RS has continued to grow (Fig. I-1). Besides the daunting number of articles on the topic of RS, there is considerable variation in the quality of these publications.

The practice of evidence-based medicine (EBM) requires a thorough knowledge of the "best external evidence" (Fig. I-2). The sheer number and the varying quality of publications make it increasingly difficult for the clinician to practice EBM in caring for patients with RS.

This International Consensus statement on Allergy and Rhinology: Rhinosinusitis (ICAR:RS) has been developed in order to summarize that best external evidence. The authors' goal was to assemble and critically appraise all available evidence on the diagnosis, pathophysiology, and management of the various forms of RS. We employed a structured review of the evidence by utilizing over 100 authors from around the world, using a stepwise anonymous writing and iterative review process for each of over 140 topics. This methodology has produced a robust review of current evidence and treatment recommendations based upon the best available evidence.

The methodology we employed seeks to rely principally on higher-level published evidence and to diminish the impact of expert opinion such as that which may be seen in a literature review or proceedings of a consensus panel. At the same time, ICAR:RS has limitations. It is neither a meta-analysis nor a clinical practice guideline (CPG). Much of the RS literature does not lend itself well to meta-analysis because there are limited numbers of studies with variable methodologies for any given topic. Although ICAR:RS provides evidence-based care recommendations, ICAR:RS should not itself be confused with a CPG. CPGs require strong evidence as well as additional steps of critical review by many stakeholders, including medical specialty societies and patient advocates.

Importantly, although there has been a large and increasing number of publications on RS, 2 important caveats should be noted. First, as the number of RS publications has increased, the proportion of all publications annually has held steady at 0.10% throughout the last 15 years (Fig. I-1). Second, review of this ICAR:RS document will reveal that the vast majority of "best external evidence" on RS is relatively weak. As a rhinology community, we should reflect upon this ICAR:RS document for gaps in high-level evidence and, where possible, dedicate ourselves to filling those gaps.

This document as a compendium of recommendations has limitations. This ICAR:RS document does not represent a "cookbook" for providing care for the RS patient. The practice of 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 (Fig. I-2).[1] RS is a set of highly variable conditions, with different etiologies and a wide breadth of recommended treatments. For example, acute RS differs from acute exacerbation of chronic RS (AECRS), which in turn differs from chronic RS (CRS). Even within CRS, patients with and without nasal polyps (CRSwNP and CRSsNP, respectively) have significant differences in pathophysiology and recommended treatments. Applying the diagnostic and treatment recommendations for 1 condition to the others would be erroneous.

In addition to recognizing variability among subsets of RS, the clinician must also recognize the tremendous variability within a subset of RS, especially CRS. CRS patients can be mildly symptomatic or highly symptomatic; they may have limited findings on endoscopy or computed tomography (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 1 patient is just like another—and to apply the findings in this document under such an assumption—is not consistent with the practice of EBM.

The recommendations offered in this document should be interpreted in context of the robustness of the evidence upon which they are based. Although the recommendations

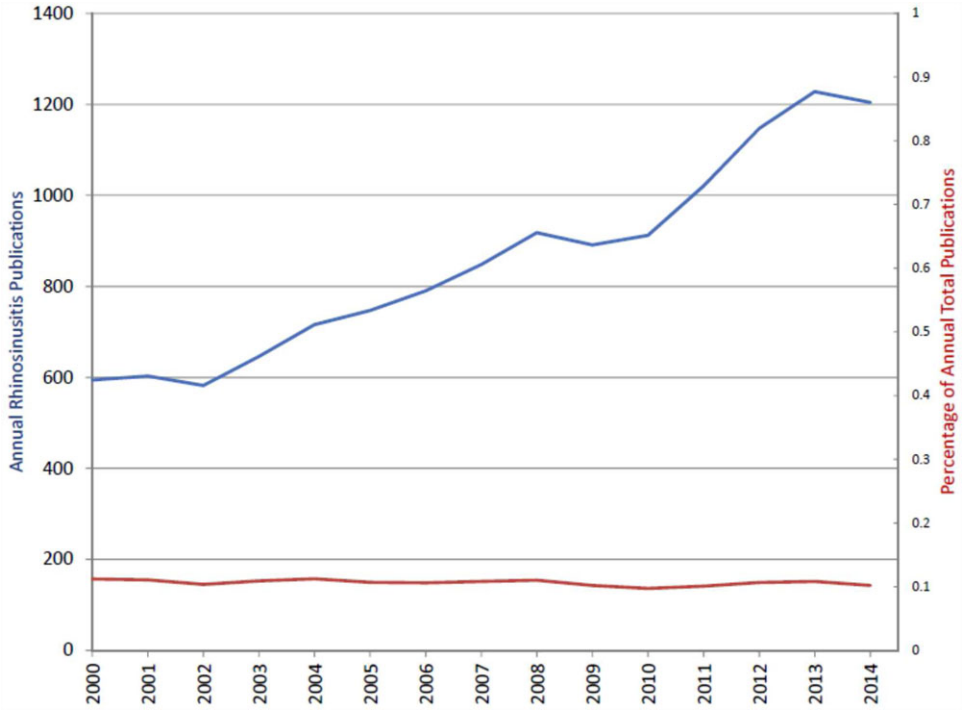

FIGURE I-1. Results of a PubMed search for the terms "sinusitis" or "rhinosinusitis" by year on the left axis. The right axis shows the sinusitis and rhinosinusitis articles as a percentage of the total number of articles listed for that year.

in this document are based on the best available evidence, they do not define standard of care nor do they define medical necessity. Healthcare 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.

Last, 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. It is our hope that this summary will guide all who care for RS patients, equipping them to provide our patients with the best possible outcome.

II. Methods

II.A. Topic Development

This document was developed and written so as to have the maximal reliance on published evidence. The authors adapted the method of writing an evidence-based review with recommendations (EBRR), as described by Rudmik and Smith in 2011.[2] The subject of RS was initially divided into 144 topics. Each topic was then assigned to a senior author who is a recognized expert in the field of rhinology, and specifically in RS. Some of the topics had no significant evidence and were assigned as literature reviews. Some 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. Many had evidence to inform recommendations and were assigned as EBRRs.

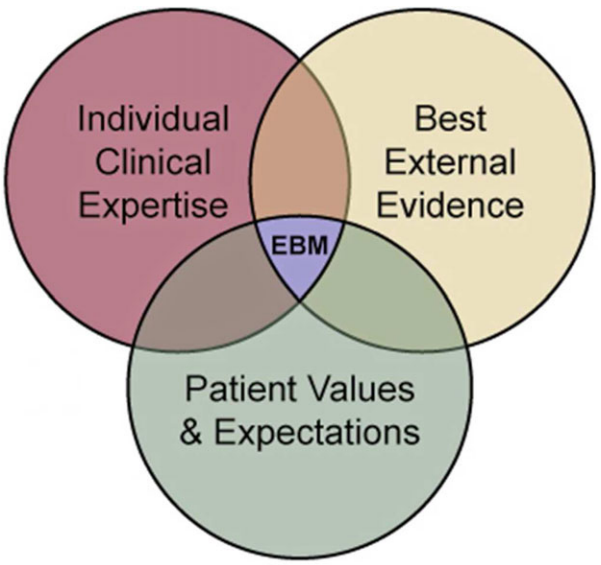

FIGURE I-2. The practice of EBM. Adapted from: Armstrong EC. Harnessing new technologies while preserving basic values. *Fam Syst Health.* 2003;21:351-355. EBM = evidence-based medicine.

To provide the content for each topic, a systematic review of the literature for each topic using Ovid MEDLINE® (1947 to July 2014), EMBASE (1974 to July 2014), and Cochrane Review databases was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standardized guidelines.[3] The search began by identifying any previously published systematic reviews or guidelines pertaining to the assigned topic.

TABLE II-1. 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

Because 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.[3] One major exception to the search window was made for the Clinical Practice Guidelines of the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS).[4] These guidelines were updated during preparation of the manuscript and were heavily referenced throughout the document. The updated 2015 version was therefore used.

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 1a to 5).[5] 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 II-1).[6]

After providing an aggregate grade of evidence for each EBRR topic (ie, A to D), 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 II-2).

After the development of the initial topic EBRR, the manuscript underwent a 2-stage online iterative review process using 2 independent reviewers. The purpose of these steps was to evaluate the completeness of the identified literature and ensure the recommendations were appropriate. The topic content was reviewed by another expert on that topic, and all changes were agreed upon by both reviewer and initial authors. The topic content was then reviewed by a second reviewer and changes were agreed upon by the initial authors and the first reviewer. Figures II-1 and II-2 show flowcharts of the topic development and EBRR iterative review processes.

II.B. ICAR:RS Statement Development

After the completion of all topics, the principal editors (R.R.O., T.T.K., and P.H.H.) compiled them into 1 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 the authors regarding the literature and final recommendations.

III. Rhinosinusitis Definitions

III.A. RS Definitions: Acute Rhinosinusitis

Acute rhinosinusitis (ARS) in adults may be defined as sinonasal inflammation lasting less than 4 weeks associated with the sudden onset of symptoms.[4,7–9] This definition is largely based on expert opinion and consensus. Several task forces and consensus groups have all agreed that an acute episode may last up to 4 weeks, though this does not seem to be based on any objective evidence.[4,7–11] Adult symptoms must include nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior) and facial pain/pressure or reduction/loss of smell. ARS in children may be defined as sinonasal inflammation associated with the sudden onset of 2 or more of the following symptoms: nasal blockage/obstruction/congestion, discolored nasal drainage, or a cough that may occur during the day or night.[7]

For both adults and children, inquiry should be made about symptoms suggestive of allergy (eg, sneezing, watery rhinorrhea, nasal and ocular pruritus, and watery eyes) in order to help differentiate acute viral or bacterial RS from allergic rhinitis (AR).

The consensus groups have all agreed that in acute viral RS nasal symptoms are generally present for fewer than 10 days. The most recent guidelines from the AAO-HNS included data on the duration of typical viral symptoms in support of the commonly accepted time frames used to differentiate acute viral RS from acute bacterial RS.[4]

The EPOS 2012 statement describes a process referred to as "acute postviral rhinosinusitis," which seems to be based on expert opinion and is defined as a worsening of symptoms after about 5 days, or persistent symptoms after 10 days, but with symptom duration of fewer than 12 weeks.[7] This process is not recognized as a separate entity by the 2015 AAO-HNS guidelines.[4]

These 2 most recent guidelines also differ slightly on how ARS is diagnosed. Both agree that discolored discharge (with unilateral predominance) and purulent secretions in the nasal passage, moderate to severe local pain, and prolonged symptoms and/or deterioration of condition after initial improvement are key for the diagnosis.[4,7] The EPOS statement includes an elevated erythrocyte sedimentation rate and/or C-reactive protein (CRP) and fever as diagnostic criteria.[7] The AAO-HNS guidelines cite the low sensitivity and specificity of fever as a rationale for not including fever as a diagnostic criterion.[4]

III.B. RS Definitions: CRS

CRS in adults is defined as sinonasal inflammation persisting for more than 12 weeks.[7–9] This definition is

TABLE II-2. AAP-defined strategy for recommendation development[6]

Evidence quality	Preponderance of benefit over harm	Balance of benefit and harm	Preponderance of harm over benefit
A. Well-designed RCTs	Strong recommendation	Option	Strong recommendation against
B. RCTs with minor limitations; overwhelmingly consistent evidence from observational studies	Recommendation	Option	Strong recommendation against
C. Observational studies (case control and cohort design)	Recommendation	Option	Recommendation against
D. Expert opinion, case reports, reasoning from first principles	Option	No recommendation	Recommendation against

AAP = American Academy of Pediatrics.

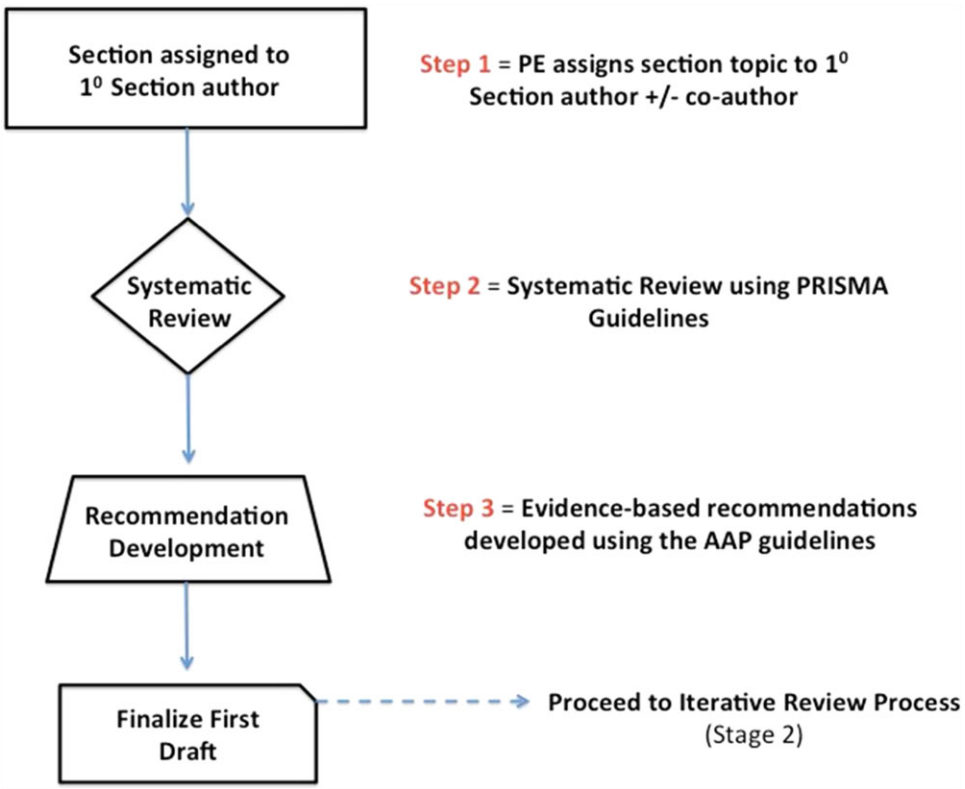

FIGURE II-1. Topic development. PE = principal editor; 1^0 = primary.

based on consensus and has been relatively consistent over the past 25 years. The most recent guidelines agree that CRS in adults is characterized by nasal obstruction/congestion/blockage, nasal drainage (mucopurulent) that may drain anteriorly or posteriorly, facial pain/pressure/fullness, and decreased or loss of sense of smell.[4,7] Symptoms alone have a high sensitivity but an unacceptably low specificity, which is why the symptoms must be accompanied by objective findings including positive nasal endoscopy (purulence, polyps, or edema) or positive imaging findings consisting of inflammation or mucosal changes within the sinuses.[4,7]

CRS in children is defined and diagnosed similarly to CRS in adults, with the difference being cough is a much more significant symptom than is decreased sense of smell.[7] Interestingly, this definition too is essentially based on consensus but does have some data supporting headache, nasal obstruction, postnasal drainage/rhinorrhea, and cough as the 4 most common symptoms identified in children with sinusitis.[12]

For both adults and children, CRS with nasal polyps (CRSwNP) is diagnosed when nasal polyps (NPs) can be visualized in the nose and/or middle meati, in the context of appropriate symptoms.[4,7] Unilateral polyps

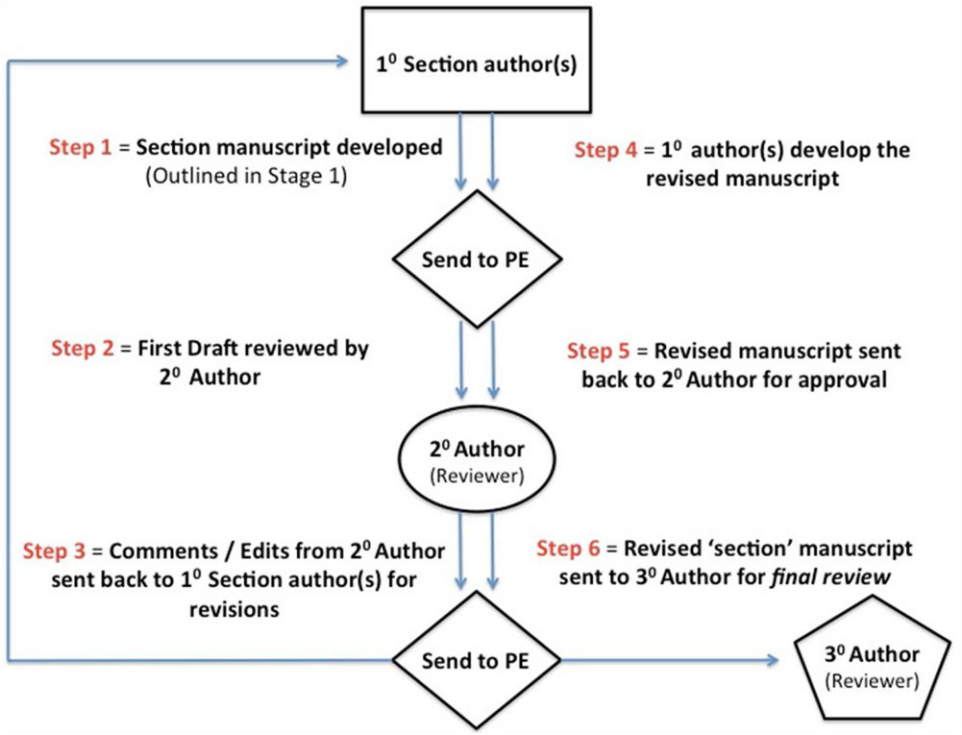

FIGURE II-2. Topic EBRR iterative review process. 1^0 = primary; 2^0 = secondary; 3^0 = tertiary; EBRR = evidence-based review with recommendations; PE = principal editor.

may require further investigation to exclude neoplastic pathologies.

III.B.1. CRS Definition: Disease or Syndrome?

In view of the different clinical phenotypes and inflammatory endotypes of CRS, it can be considered an umbrella term covering several inflammatory disease states of the sinonasal cavities. On the basis of clinical and/or radiologic examination, CRS is generally divided into CRSsNP and CRSwNP. Apart from these 2 major clinical phenotypes, other phenotypes relate to the variety of presenting symptoms in CRS patients and the presence or absence of concomitant bronchial disease.[4,7] It is not surprising to find different phenotypes of the disease, given the multitude of underlying etiologic factors.

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 the recent attempt to define endotypes of disease. CRS has been classified into different inflammatory clusters, such as T helper 1 (Th1)-driven or neutrophilic inflammation, and T helper 2 (Th2)-driven or eosinophilic inflammation.[13] Several specific inflammatory mediators have been associated with CRS, and the beneficial effects of novel treatments with biologics like anti–interleukin 5 (IL-5), anti–immunoglobulin E (IgE), and others support their importance. We should, however, realize that mixed inflammatory clusters are likely common and important in these patients; this would help explain the limited beneficial effects of targeting 1 inflammatory mediator such as IgE or IL-5 in isolation.

Taken together, CRS represents a condition with different phenotypes and endotypes, which we are only starting to better understand. In a single CRS patient, pinpointing the different etiologic factors responsible for the development of the disease remains the challenge for the future.

III.C. RS Definitions: Recurrent Acute Rhinosinusitis

Recurrent acute rhinosinusitis (RARS) has been defined as 4 episodes per year of ARS with distinct symptom-free intervals between episodes.[4,7,8,14] Each episode must meet the criteria listed in Section III.A for ARS. The number of episodes required for the diagnosis of RARS has varied between consensus statements, but the 2007 guidelines in Rosenfeld et al.[15] addressed this number. Citing the published literature, they reported that the average adult gets between 1.4 and 2.3 viral upper respiratory infections (URIs) per year. They felt that setting the number of acute bacterial rhinosinusitis (ABRS) episodes at 4 for RARS decreased the chances of misdiagnosis.

Only a few cohort studies have examined the clinical course of this group of patients. Patients with RARS tend not to be treated surgically, and when they are, they undergo less extensive surgery than CRS patients.[16,17] Postoperatively they require fewer long-term medications. This

may possibly be due to a relatively higher number of sinonasal anatomic variants in this patient group.[18]

III.D. RS Definitions: AECRS

AECRS is defined in a patient in whom a previous diagnosis of CRS exists, and a sudden worsening of symptoms occurs, with a return to baseline symptoms following treatment.[8,11] A more stringent definition has not been proposed to this point nor have more precise diagnostic criteria been put forward. The concept for AECRS was based on a similar disease pattern in otitis media (personal communication with Donald Lanza, MD). Although the literature on this condition is limited, potential diagnostic criteria are proposed in Section IX.C.

III.E. RS Definitions: Subacute RS

Although absent from recent guidelines, subacute RS has been a term used to describe clinical presentations that fall between the time frames of ARS and CRS (symptoms of 4 to 12 weeks' duration). To date, there have been very few clinical reports on which to base the delineation of these patients as a distinct clinical entity; reports that do make that distinction define the process based on consensus. The term has been used at least since 1975, and Lanza and Kennedy[11] recommended reintroducing the term although there was no formal definition provided by the U.S. Food and Drug Administration (FDA) for disease lasting 4 to 12 weeks.[12] It is likely that patients who fall into this group either have slow-to-resolve ARS or an early presentation of evolving CRS. Use of this definition or classification should be limited until a better understanding of this condition is achieved.

III.F. RS Definitions: Sinusitis or RS?

In 1996, the Task Force on Rhinosinusitis sponsored by the AAO-HNS reached a consensus regarding specific diagnostic criteria and working definitions to describe RS.[19] The Task Force agreed to replace the word "sinusitis" with the more descriptive term "rhinosinusitis" to emphasize the close relationship between the nose and paranasal sinuses, the similarities in both morphology and physiology between the mucosal lining of the 2, and the fact that the 2 conditions often exist simultaneously in the same patient, even when 1 might be the predominant feature of the presentation.

One of the key arguments used to support the development of this terminology is that rhinitis not only occurs concomitantly with "sinusitis" but often heralds its onset.[19] Furthermore, nasal obstruction and drainage, which are 2 of the key features of sinusitis, are closely related to symptoms of rhinitis.[20] Since the Task Force reached a consensus regarding the use of the term "rhinosinusitis," several multidisciplinary position papers have supported the notion that "sinusitis" is almost always accompanied by rhinitis.[9,19–22] However, there are very few studies that have examined objective evidence to support the use of this terminology.

A key study providing evidence regarding this relationship was conducted by Gwaltney et al.[23] The authors evaluated computed tomography (CT) data from 31 patients with an acute rhinovirus infection and detected simultaneous involvement of both the nasal cavity and the paranasal sinuses. Specifically, thickening of the walls of the nasal passages, engorgement of the inferior turbinates, obstruction of the ethmoid infundibulum, and abnormalities of the maxillary, sphenoid, and frontal sinuses were found in 77%, 87%, 39%, and 32%, respectively. The radiographic abnormalities resolved after 2 weeks without any antibiotic therapy in 79% of the patients.

Two studies have evaluated for the presence of inflammation in the nasal cavity in patients with CRS. Bhattacharyya[24] identified inflammatory cells in the nasal septal mucosa in patients with CRS. A more recent study conducted by Van Crombruggen et al.[25] evaluated the presence of inflammatory mediators in the ethmoidal mucosa or polyp tissue from patients with CRSsNP and those with CRSwNP, respectively, and compared them to inferior turbinate nasal mucosal tissue from the same patients and to inferior turbinates from healthy controls. In both CRSwNP and CRSsNP, inflammatory mediator levels were increased in both sinus and nasal mucosa, compared to healthy control tissues.

Although limited published experimental evidence exists supporting the term "rhinosinusitis," it has clearly been accepted by several multidisciplinary, international expert groups, and it is physiologically logical and clinically evident.

IV. The Burden of RS

IV.A. Societal Burden of RS

IV.A.1. RS Societal Burden: Direct Costs

RS (both acute and chronic forms) affects approximately 12% to 15.2% of the adult population in the United States, annually.[26,27] This annual prevalence exceeds that of other common respiratory conditions such as hay fever (8.9%), acute asthma (3.8%), and chronic bronchitis (4.8%).[26] The direct costs of managing ARS and CRS exceed US$11 billion per year.[4] These figures, however, do not distinguish between ARS and CRS; further stratification is presented in the next sections.

IV.A.1.a. Societal Direct Costs: ARS. Direct cost estimates attributable to the diagnosis and treatment of ARS are sparse in the literature. The disease burden of ARS 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.[28] ARS is the fifth most common

diagnosis associated with antibiotic therapy.[4] In 1 of the few prospective, observational studies on ARS, Scandinavian researchers determined the direct costs of 1 episode of ARS at €266 (about US$300).[29]

IV.A.1.b. Societal Direct Costs: CRS. The direct costs of CRS include the costs for both 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 US$921 to US$1220 per patient-year.[30,31] These data may, however, represent a bias toward more severely diseased patient populations and also rely on some extrapolation of costs.

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.[32] identified 4460 patients undergoing endoscopic sinus surgery (ESS). The healthcare costs for CRS in the year leading up to ESS (therefore, the medically refractory group) were US$2449, US$1789 of which were attributable to facility and physicians' charges. Costs related to the management of CRS are not limited to medical management only; economic studies have demonstrated the cost of ESS to range from US$3500 per case (in Canada) to US$7700 per case (in the United States).[32,33] The presence or absence of polyps also influences direct medical costs in CRS. Patients with recurrent polyps after prior surgery demonstrated higher direct medical costs per year (US$866) than non-polyp patients (US$570) or primary polyp patients (US$565).[34]

Finally, population-based assessments have determined incremental costs of CRS relative to those without CRS. Bhattacharyya[35] determined significantly increased *incremental* healthcare utilization costs of US$772 for total healthcare expenses, US$346 for office-based expenditures, and US$397 in prescription expenditures for CRS in a nationally representative healthcare economics database ($p \leq 0.01$ vs those adults without CRS). From an international perspective, also utilizing a national healthcare insurance database, Chung et al.,[36] found that Taiwanese patients with CRS diagnoses incurred significantly higher outpatient costs (US$953 vs US$665; $p < 0.001$) and total healthcare costs (US$1318 vs US$946; $p < 0.001$) than comparison subjects without CRS. Although less commonly studied, recent claims-based data indicate an annual direct cost of treatment attributable to RARS of US$1091 per patient-year.[37] The overall direct cost burden of CRS in the United States has been estimated at US$8.6 billion per year.[35]

IV.A.2. RS Societal Burden: Indirect Costs

In contrast to direct healthcare costs, 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. home life). In a nationally based household study, among the 15.2% of those reporting acute or chronic RS annually, 5.7 workdays were missed vs 3.7 for those without ($p < 0.001$).[26] This translates into 61.2 million potential workdays missed per year among adults in the United States and an estimated work productivity loss of US$3.79 billion per year.[26,38] Data for presenteeism and other forms of lost productivity due to RS as a whole are currently lacking, but data for subtypes of RS are available.

IV.A.2.a. Societal Indirect Costs: ARS. Data for the indirect costs of ARS are somewhat limited, with most data coming from control arms of interventional studies for ARS. Recently, Spanish investigators found the indirect cost of an ARS episode to range from €224 to €439 (about US$250 to US$490) depending on treatment intervention.[39] If patients are assumed to be absent from work during the symptomatic days of an ARS episode, the indirect costs increase to US$747 to US$820, depending on whether antibiotic treatment is offered.[38]

IV.A.2.b. Societal Indirect Costs: CRS. The overall 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.[40] This figure includes both nonrefractory and refractory patients and directly compares those with and without CRS diagnoses. European investigators found 57% of CRS patients (n = 207) reported absenteeism from work due to CRS.[41] In patients with relatively limited CRS but planning balloon dilatation (n = 56), Stankiewicz et al.[42] found substantial proportions of patients reporting absenteeism (6.5%), presenteeism (36.2%), and productivity loss (38.3%) via a validated work-specific survey. In a multi-institutional study from tertiary-level rhinology clinics, likely representing a cohort of the most severely diseased refractory patients (n = 55), Rudmik et al.[43] found mean annual rates of absenteeism of 24.6 days per year and presenteeism of 38.8 days per year, with an overall annual productivity cost of US$10,077 per patient. Although caution must be exercised when extrapolating these figures to the general CRS population, it is clear that CRS imparts significant indirect costs.

The indirect costs of CRS are not only work-related. Stankiewicz et al.[42] identified a 40.0% rate of impairment of activity with CRS. In a nationally representative sample, Bhattacharyya[40] determined activity limitations of 13.3%, work limitations of 12.0%, social limitations of 9.0%, and cognitive limitations 6.0% with CRS.

IV.A.2.c. Societal Indirect Costs: 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 data are available for indirect costs for this RS subtype, investigators found an average of 4.4 workdays missed per year specifically due to RARS.[44] Economic studies of RARS have identified absenteeism and presenteeism rates of 1.7 and 0.66 days per acute episode, respectively.[45]

IV.B. Individual Burden of RS

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. Description of individual sinonasal symptoms and overall burden of disease is often done using individual symptoms scales or sinus-specific quality-of-life (QoL) instruments. However, the impact of CRS often extends beyond the sinonasal region and can have profound effects on functional well-being and general health-related QoL. Several 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 disease states. 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 = dead, 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.[46] Similar studies have been performed showing severe impairment in general QoL and well-being using the Short-Form 36 (SF-36) and Euroqol 5 Dimension (EQD-5) questionnaires.[47–49] When responses of CRS patients are examined in detail, the most common extrasinus disease manifestations include fatigue and bodily pain, sleep dysfunction, and depression.

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.[50] The baseline median prevalence of fatigue was 54%, ranging from 11% to 73% across studies. Another systemic review with meta-analysis examined bodily pain in 11 studies with 1019 patients.[51] 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% confidence interval [CI], 0.59 to 0.95) for fatigue and 0.55 (95% CI, 0.45 to 0.64) for bodily pain.

Poor sleep quality is a frequent complaint of patients with CRS but this dysfunction has only recently been explored in depth. Using the Pittsburgh Sleep Quality Index (PSQI), subjective sleep quality was assessed in a multi-institutional cohort of 268 patients with CRS.[52] The PSQI is a self-reported questionnaire (range, 0 to 21, with higher scores indicating worse sleep) measuring sleep quality and disturbance over the preceding 1-month period, with high internal consistency, reliability, and construct validity. The mean PSQI score in this group was 9.4, with 75% reporting "poor" sleep based on accepted cutoffs (ie, abnormal is >5). In this group, PSQI scores significantly correlated with sinus-specific QoL scores on both the 22-item Sino-Nasal Outcome Test (SNOT-22) and Rhinosinusitis Disability Index (RSDI) instruments ($r = 0.55$ and $r = 0.53$, respectively).[53,54] A recent contemporary review examined potential mechanisms of sleep dysfunction in CRS, including 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.[55]

Another prominent factor that impacts overall QoL and well-being in patients with CRS is the presence of depression. Studies have reported prevalence rates for depression in CRS ranging from 9% to 26%.[56–61] The wide range likely reflects differences in patient populations and diagnostic accuracy for depression (ie, patient-report, physician diagnosis, validated questionnaire). Regardless, the frequency of depression in patients with CRS is above population norms of between 5% and 10%.[62] The comorbid presence of depression is associated with worse sinus-specific and general QoL compared to CRS patients who are not depressed.[58,59,61] 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.[60] A number of studies have examined the impact of depression on outcomes after sinus surgery.[56,58,59,61] 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. However, patients with depression do appear to have a similar degree of overall improvement compared to those without depression; they just start and end with worse QoL. Further studies are required to understand whether depression is simply a comorbid disease commonly found alongside CRS or whether the presence of CRS contributes to depression.

IV.C. Measurement of Disease Severity

Current clinical evaluation of subjects with CRS involves evaluation of disease-specific QoL, clinical history, physical examination often including endoscopic exam, and radiographic evaluation with CT. Clinicians synthesize these data to both establish the diagnosis of CRS as well as to decide on a potential medical or surgical intervention. A key measure of success is outcome from the patient's perspective, measured by QoL. Endoscopic and radiologic improvements matter little if the patient does not feel better, especially for a QoL condition like CRS. Despite the broad use of CT and endoscopy to confirm diagnosis and

tailor treatment, neither endoscopic nor radiographic findings have been shown to correlate strongly with preintervention and postintervention QoL outcomes. However, refinements of current measures and potential development of novel measures of CRS may someday improve outcome prediction and clinical decision-making.

Endoscopic exams can be performed in both a preoperative and postoperative setting, and multiple efforts have been undertaken to standardize these exams.[63–68] A variety of scoring systems exist, but fundamentally each system comprises a weighted composite of some combination of the available endoscopic variables: extent and location of mucosal inflammation, presence and character of discharge, presence of scar, presence of crust, and middle turbinate (MT) position. Investigation of the test-retest reliability and content validity of several of these scales has been investigated. Unfortunately, at best, endoscopic scoring systems only weakly correlate with current QoL[64,67] and postoperative gains in QoL.[69] Although there is room for refinement of endoscopic scoring, endoscopic exams likely provide only a portion of the data required to accurately predict symptomatology.

CT of the sinuses has been a mainstay of clinical outcomes research,[70] yet several studies have shown that this method of scoring does not correlate well with contemporaneous measures of QoL.[71–74] However, there is conflicting evidence on the ability of CT severity to predict QoL gains postintervention, with some studies showing correlations[71,75] but more studies showing that CT stage is not an independent predictor of outcome.[71,76,77] Among currently available radiographic scoring systems, there is simply binary data; eg, presence or absence of inflammation. However, there is likely missing information in this scheme. CT scans do provide important information on anatomy, location of disease, extent of disease, and presence of osteoneogenesis. Some have tried to identify predictive data from CT scans, and have noted that presence of osteoneogenesis on CT is associated with diminished QoL gains after surgery,[78] and also that intrasinus quantity and density of opacification may correlate with QoL measures.[79]

Although both endoscopic and radiographic measures may be further refined in the future to better correlate with QoL measures and outcomes, it seems clear that they are not measuring exactly the same constructs, and failure to identify a high level of correlation with symptoms does not imply that the measure is not useful. Future research might identify other factors that predict outcome, such as measures of immune response and regulation and the status of the microbiome.

V. ARS

V.A. ARS: Incidence/Prevalence

The reported incidence of ARS is significantly affected by how ARS is defined. For this consensus statement, ARS is defined as the symptomatic inflammation of the paranasal sinuses and nasal cavity lasting less than 4 weeks. Although viral, bacterial, or fungal pathogens can cause ARS, the majority of cases begin when a viral URI involves the nasal cavity and paranasal sinuses.

It is estimated that adults will experience between 1 and 3 episodes of viral ARS per year and 12% of the adult population will be diagnosed with RS.[27,80–83] Furthermore, ARS accounts for 2% to 10% of primary care and otolaryngology visits.[84,85] Data from the United States often fail to differentiate between the various types of RS to a degree that renders it challenging to provide an accurate estimate of ARS prevalence.[86] However, 1 prospective study estimated ARS incidence at 9%.[87]

The current literature shows that a broad range of epidemiologic methods have been used to assess the prevalence of RS. Estimation of disease prevalence based on review of medical records only covers patients who sought and received medical attention, and may thus reflect a biased selection strategy. These methods almost certainly result in underestimation because they do not capture episodes of disease for which patients did not seek care. The use of household visits sought to eliminate sampling bias by including patients who may not have had access to medical care, thus encompassing a truly representative population.[27] These data represent the best available estimates of ARS prevalence currently available.

V.B. ARS: Pathophysiology

Important in the defense of the sinonasal tract are sneezing to remove large particles, mucus to trap smaller particles, and ciliary transport to propel mucus to the gut for degradation. Sinus health also involves identification of foreign particles and mounting the appropriate response through the innate and adaptive immune systems.[88] It is the downstream effects of these defensive responses that we perceive as the symptoms of ARS.

The immune response within the sinonasal cavity is multifaceted, complex, and interrelated. Allergic, viral, bacterial, and fungal insults as well as environmental irritants are implicated in causing ARS. Resulting mucosal swelling causes sinus ostial obstruction, exacerbating ARS. Also, nose blowing has been hypothesized to seed pathogen-bearing mucus into the sinuses, and thereby serves as another mechanism of sinus infection.[89] As traditionally defined, allergy involves a systemic IgE-mediated response to local antigen exposure. Although data correlating allergy and ARS are weak, changes at the cellular receptor level suggest a relationship. For example, intercellular adhesion molecule 1 (ICAM-1) is a receptor for rhinovirus and is upregulated in patients with AR.[90] This suggests a possible mutually-reinforcing relationship among allergic and infectious immune insults. Environmental exposure to smoking[91,92] and air pollution[86,93,94] have also been linked to ARS, though mechanisms remain unclear.

Several anatomic abnormalities have been suggested to predispose to ARS. These include recirculation

TABLE V-1. Anatomic variants as risk factors for RS*

	ARS		Mixed group		CRS		
Pathology	Effect	No effect	Effect	No effect	Effect	No effect	Effect size
Concha bullosa	S[16]	S[17] (+ trend)	S[99],S[100],M[101]	S[102],M[103]		S[104],M[105],S[106],S[107]	Mild effect if large
Intralamellar cell				S[99]			None
Paradoxical middle turbinate		S[16]		S[102],S[99],S[100]		S[106], S[107]	None
Infraorbital ethmoid	S[17]	S[16]	M[97]	S[99]		S[106], S[107]	>3 mm may have effect
Septal deviation		S[17] (+ trend)	R[108],S[100],M[101]	S[102]		R[109],S[106],S[107]	Small effect with increasing angle
Accessory ostium	S[16]						Effect noted
Infundibulum stenosis	S[17]	S[16]					Possible effect
Uncinate bullosa				S[99]		S[106]	None

*When the classification of RS is separated into acute, chronic, or a mixed distribution, anatomical variants have greater impact on ARS than CRS. Superscripted numbers are reference citations.
S = study with confirmed symptoms of RS in addition to CT evidence of inflammation; M = study that only identified mucosal thickening and did not confirm cases had symptoms of RS; R = well-performed systematic review.

phenomenon, conchae bullosa, and nasal septal deviations (NSDs).[95] Periapical infections of maxillary molars can lead to direct inoculation of the overlying sinus cavity, although dental causes of ARS are rare and more commonly seen in CRS.[96] The evidence addressing the relative contribution of several factors is explored in greater detail in the next sections.

V.B.1.a. ARS Pathophysiology Contributing Factors: Anatomic Variants. Because radiographic imaging is not indicated for uncomplicated cases of ARS,[15] there is no direct research to determine anatomic causes of ARS. Instead, inferences are made from studies of complex cases including RARS, complications of ARS, and patients with AECRS.

Anatomical anomalies that have the potential to cause sinusitis include stenosis of the infundibulum, recirculation phenomenon, anomalies of the uncinate and MT, infraorbital ethmoid cells (Haller cells), and NSDs.[95] A 97-patient case-control study by Jain et al.[16] examined patients with clinical symptoms of CRS and either CT evidence of pansinusitis or isolated maxillary/ostiomeatal complex (OMC) disease (classified as "limited sinusitis"). Both groups were compared to normal controls. The premise of that study was that, if anatomical anomalies truly caused obstructive RS, patients with limited sinusitis should have a higher incidence of pathologic anatomic variants relative to patients with pansinusitis or controls. The authors searched for concha bullosa, infraorbital ethmoid cells, lateralized uncinate processes, accessory ostium, and paradoxical MTs in both groups. They found that only the presence of a concha bullosa and accessory ostium were significantly related to those cases associated with obstructive pathology ("limited disease").

Another study, by Alkire and Bhattacharyya,[17] compared 36 patients meeting strict criteria for RARS to 42 contemporaneous control patients, searching for causative anatomical anomalies. The presence of infraorbital ethmoid cells (39.9% vs 11.9%, $p = 0.006$) and a narrowed infundibulum (0.591 mm vs 0.823 mm, $p < 0.001$) were identified as potential causative factors. Additionally, the authors noted a trend that did not achieve statistical significance for increased presence of concha bullosa and septal spurs in cases of RARS.

When the literature is collectively considered by sorting studies according to ARS vs CRS, a few findings emerge (Table V-1). CRS appears unrelated to anatomic variation and is more likely inflammatory in nature. ARS appears to be related to several anatomical anomalies: concha bullosa, infraorbital ethmoid cells greater than 3 mm in size,[97] accessory ostia in the common drainage pathway,[98] and stenosis of the infundibulum.[16]

Non–OMC-related causes of ARS include oroantral fistula and dental infections. One retrospective case series showed that a periapical abscess of a maxillary tooth has a 9.75 odds ratio ($p < 0.001$) of causing substantial reactive mucosal thickening on cone beam CT.[110] Additionally, another study showed that periodontal disease with tooth roots emerging into the antrum and oroantral fistulas can cause the symptoms and signs of ARS.[96]

In summary, the evidence for an association between ARS and anatomic variants is weak and largely inferred from studies on RARS, CRS, and mixed groups of RS (Table V-2).

- Aggregate Grade of Evidence: C (Level 4: 16 studies).

V.B.1.b. ARS Pathophysiology Contributing Factors: Allergy. AR and ARS have been proposed to interact. To reach conclusions on the relationship between these diseases, we should consider the available epidemiologic

TABLE V-2. Evidence for anatomic variants and ARS

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Jain[16]	2013	4	Diagnostic case-control	1. Maxillary/OMC inflammation (limited); 2. Pansinusitis; 3. Normal (control)	CT evidence of sinus disease	Limited disease showed increased concha bullosa and accessory ostium
Shanbhag[110]	2013	4	Retrospective case series	CT with maxillary sinusitis	1. Fluid filling sinus (by thirds); 2. Mucosal thickening	Oroantral fistula, periodontal disease and projected root or abscess predict maxillary sinusitis
Azila[106]	2011	4	Diagnostic case-control	1. CRS symptoms; 2. Normal	CT evidence of sinus disease	No effect of concha bullosa, paradoxical MT, Infraorbital ethmoid cell, NSD, or uncinate bullosa
Cho[102]	2011	4	Diagnostic case-control	1. CRS symptoms; 2. Normal	CT evidence of sinus disease	No effect of NSD, concha bullosa, or paradoxical MT
Alkire[17]	2010	4	Diagnostic case-control	1. RARS symptoms; 2. Normal	CT evidence of sinus disease	RARS associated with Infraorbital ethmoid cell and smaller infundibular width
Bomeli[96]	2009	4	Retrospective case series	CT with mucosal thickening	1. Periapical tooth lucencies; 2. Periodontal disease	Periapical lucencies increase presence of sinus inflammation by 9.75 times (odds ratio)
Caughey[101]	2005	4	Diagnostic case-control	1. CT evidence of mucosal thickening; 2. Normal CT	CT evidence of sinus disease	Concha bullosa, NSD, and infraorbital ethmoid cell increases risk of sinus disease
Kieff[107]	2004	4	Diagnostic case-control	1. Ipsilateral maxillary CRS; 2. Contralateral normal side	CT evidence of sinus disease	No effect from concha bullosa, Infraorbital ethmoid cell, NSD or paradoxical middle turbinate
Stallman[103]	2004	4	Diagnostic case-control	1. CT with mucosal disease with concha bullosa; 2. CT with mucosal disease without concha bullosa	CT evidence of sinus disease	In cases of mucosal thickening, no increased chance of concha bullosa
Stackpole[97]	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
Lam[104]	1996	4	Diagnostic case-control	CRS with concha bullosa	CT evidence of sinus disease	No evidence that concha bullosa has effect on CRS
Nadas[105]	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
Bolger[99]	1991	4	Diagnostic case-control	1. CRS symptoms; 2. Normal	CT evidence of sinus disease	Concha bullosa showed association with CRS; infraorbital ethmoid cell showed no association
Calhoun[100]	1991	4	Diagnostic case-control	1. Any sinus symptoms; 2. No sinus symptoms	CT evidence of sinus disease	Concha bullosa and NSD increased risk of sinus disease. Paradoxical MT showed no effect

TABLE V-3. Evidence for allergy and ARS

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Baroody[115]	2008	1b	DB 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
Rantala[120]	2013	2a	Cross-sectional (n = 1008)	Atopic and nonatopic adults age 21–63 years	Upper and lower respiratory tract infections	Individuals with atopic disease had higher risk of developing URIs including RS
Chen[114]	2001	2a	Questionnaire (n = 8723)	Children in Taiwan	Rhinosinusitis	Children reporting allergic more likely to have RS
Holzmann[113]	2001	2b	Retrospective review (n = 102)	Children with orbital complications of ARS	Prevalence of AR	Orbital complications more common in allergy season
Frerichs[121]	2014	3a	Systematic review	Allergic and nonallergic patients	Prolonged course (>4 weeks) of RS	No significant increase in prolonged RS
Naclerio[116]	1997	3a	Observational (n = 10)	Allergic subjects at peak of season	Sinus CT abnormality	60% had CT abnormalities
Savolainen[112]	1989	3b	Case control (n = 224)	Acute maxillary sinusitis with and without allergy	ARS	Prevalence of AR 25% and 16.5% in non-AR patients

DB = double-blind.

evidence, plausible mechanisms that may explain their interaction, relevant human and animal studies, and whether treatment of AR changes disease expression in ARS.

The estimated prevalence of AR is about 20%, whereas over 50% of the U.S. population has evidence of IgE sensitization, demonstrating that a positive skin test does not necessarily indicate nasal allergic disease.[111] Thus, positive skin tests in ARS patients are not proof of a relationship between AR and ARS because they only indicate sensitization. Conversely, local nasal allergic reactions can occur without evidence of systemic IgE sensitization. Thus, even the absence of a positive allergy test does not rule out a role for AR in ARS.

Many, but not all, studies support an association between AR and ARS. Savolainen[112] found the incidence of allergy to be 25% in a group of 224 patients with acute maxillary sinusitis, which was significantly greater than the 16% incidence in a control group. Holzmann et al.[113] reported an increased prevalence of AR in children who had orbital complications of ARS, and also reported that these complications occurred more commonly during pollinating seasons. In a study involving 8723 children, Chen et al.[114] found the prevalence of RS to be significantly higher in children with AR than in children without allergies. Importantly, having AR did not predict a prolonged course of ARS.

Studies suggest that allergic inflammation may lead to inflammation in the sinuses. On a pathologic basis, nasal challenge with allergens in allergic individuals leads to an influx of eosinophils into the maxillary sinus.[115] Similarly, the majority of subjects with ragweed-sensitive AR (60%) had sinus mucosal abnormalities on CT imaging during the peak of ragweed season, yet resolution of symptoms after treatment did not correlate with radiologic imaging.[116] Furthermore, individuals with ragweed AR had significantly more eosinophils in the maxillary sinus during the ragweed season compared to outside the ragweed season.[117] These studies suggest that AR could affect the inflammation in the sinuses.

Because of the challenges of human studies, a mouse model was developed to address the influence of AR on ARS.[118,119] Mice with ongoing nasal allergic reaction (but not mice with lower airway reaction or sensitization alone) had a worsened episode of ARS, and this effect could be transferred by Th cells. These studies suggest that local allergic inflammation plays an important role in the expression of ARS.

Currently, there are no definitive data that show that medical treatment or immunotherapy prevents the development of ARS. There are no studies demonstrating that treatment for seasonal or perennial rhinitis reduces the incidence of ARS during allergen-exposed periods. The limited frequency of ARS occurring during seasonal AR makes the prospect of a definitive immunotherapy study whose outcome is the development of ARS highly unlikely.

In summary, observational studies provide a modest LOE supporting a relationship between AR and ARS. This is further supported by evidence from a mouse model of ARS induction in allergen-sensitized, allergen-exposed mice. There is some evidence that AR increases the likelihood of orbital complications of ARS but no evidence that AR prolongs the duration of ARS (Table V-3).

- Aggregate Grade of Evidence: C (Level 1b:1 study; Level 2a:2 studies; Level 2b:1 study; Level 3a:2 studies; Level 3b:1 study).

TABLE V-4. Evidence for viruses and ARS

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Gwaltney[134]	1992	2b	Prospective (n = 343)	Intranasal viral inoculation	Development of sinusitis symptoms	94% of patients became infected
van den Broek[132]	2014	3b	Systematic review (n = 265)	Clinically diagnosed ARS	Positive culture	Presence of purulence is not diagnostic for ABRS
Autio[124]	2014	4	Observation case series (n = 50)	Clinically diagnosed ARS	Viral and bacterial detection early phase (2–3 days) and late phase (9–10 days)	Total 84% viral detection;56% early-phase bacterial detection; 40% late-phase bacterial detection
Lu[122]	2013	4	Observation case series (n = 596)	Patients presenting with common cold	Presence/absence of virus	38.8% positive virus detection rate
Rawlings[128]	2013	4	Observation case-control (n = 88 controls, n = 70 common cold)	Patients presenting with common cold	Presence/absence of bacterial pathogens	Positive bacterial culture 5 times more likely in patients with the common cold
Gutierrez[131]	2012	4	Observation case series (n = 10,048 H1N1; n = 31 common cold)	Patients presenting with H1N1 virus and common cold	Presence/absence of ABRS	0.55% of patients with H1N1 developed an ABRS
Han[129]	2011	4	Observation case-control, (n = 8 controls; n = 70 common cold)	Patients presenting with common cold <8 days	Presence/absence of bacterial pathogens	Bacterial pathogens more prevalent in patients with the common cold vs controls (31% vs 8%)
Makela[123]	1998	4	Observation case series (n = 200)	Patients presenting with common cold	Presence/absence of virus or bacteria	69% positive detection rate for virus. 3.5% positive for bacteria
Puhakka[136]	1998	4	Observation case series (n = 197)	Patients presenting with common cold	Presence/absence of virus and/or bacteria days 1, 7, and 21	Virus found early in patients presenting with the common cold (day 7); no significant increase in bacteria was found
Gwaltney[23]	1994	4	Observation case series (n = 90 with common cold)	Patients presenting with common cold	Presence/absence of rhinovirus	27% of patients found to have rhinovirus

V.B.1.c. ARS Pathophysiology Contributing Factors: Septal Deviation. The role of NSD in ARS is not well studied. One systematic review has examined the role of NSD in RS in general.[108] The studies included in this review largely failed to separate ARS from CRS, so that a definitive statement regarding NSD as a contributing factor for ARS cannot be made. The review did, however, show an increasing risk of RS in general with increasing angle of NSD. Despite these findings, additional research must be performed before NSD can be defined as a risk for development of ARS. Clearly the role of septoplasty in reducing the risk of ARS is unknown.

- Aggregate Grade of Evidence: not applicable.

V.B.1.d. ARS Pathophysiology Contributing Factors: Viruses. ARS is commonly associated with an antecedent acute viral RS (AVRS). Although the recovery of viral agents from the nose in the setting of ARS has ranged from 27% to 84%, this may reflect the variability and limitations of the specific techniques used.[23,122–124] Inoculation of rhinovirus in humans produced greater than a 90% infection rate with up to 74% displaying ARS symptoms.[125,126] It has been hypothesized that a preceding AVRS may be associated with subsequent ABRS by inhibition of mucociliary clearance (MCC) and blockade of sinus ostia due to local swelling. However, the LOE that supports this assumption is lacking (Table V-4).

CT imaging in patients with AVRS demonstrates occlusion of the maxillary sinus infundibulum 77% of the time,[23] and experimentally-induced RS with rhinovirus has been associated with symptoms of the common cold and corresponding reduced MCC.[127] This led to investigations that examined bacterial pathogens in the infundibulum and sinuses during wellness and suspected AVRS. These studies found that patients with the common cold had higher levels of bacteria in the nasal cavity and OMC compared to well patients.[128,129] It should be noted that the authors made the assumption that those patients who presented

with the common cold truly had an AVRS. Therefore, it is unclear if viral inflammation directly led to subsequent increased bacterial loads. Interestingly, current literature suggests that only 0.5% to 2.2% of AVRS becomes complicated by bacterial RS.[130] Similarly, the risk of developing a bacterial upper respiratory tract infection after a positive H1N1 influenza virus culture was demonstrated to be a meager 0.55% from 46.4% of patients who presented with AVRS.[131] However, time course was not specified and study data were retrospectively collected, suggesting limited causality.

One of the reasons we have a limited understanding of how AVRS progresses to an ABRS is the inability to clinically distinguish between the 2 entities. Current evidence suggests that symptoms alone such as purulent nasal discharge, fever, or facial pain cannot distinguish between viral or bacterial infection.[132,133] For these reasons, studies that directly sample the sinuses during an infection are needed. Autio et al.[124] found that up to 84% of patients presenting with ABRS had viral nucleic acid detected during the early phase of the disease (days 2 to 3), and a coinfection with bacteria (56%) during the viral infection was found to correlate with worse disease scores.

Current clinical practice guidelines recommend that the presence of bacterial infection is more likely with duration of symptoms greater than 10 days. This is based on the probability of confirming a bacterial infection by sinus aspiration (60%) following 10 days of symptoms[134] in addition to the completion of the natural time course for a spontaneous rhinovirus infection.[135] It is important to understand that a bacterial infection could potentially occur at any time during the illness.

- Aggregate Grade of Evidence: C (Level 2b: 1 study; Level 3b: 1 study; Level 4: 8 studies).

V.B.1.e. ARS Pathophysiology Contributing Factors: Odontogenic Infections. The adult maxillary sinus expands toward the maxillary alveolar ridge during development. This process allows the maxillary tooth roots to reach and even penetrate through the floor of the maxillary sinus. The close anatomic proximity of the root apices of the teeth to the maxillary sinus is most likely responsible for the development of odontogenic RS in patients with maxillary dental pathology.[137]

Odontogenic RS is considered in those patients with unilateral ARS or CRS, and/or with uncontrolled unilateral disease despite medical or surgical treatment. Further, the microbiology of odontogenic sinusitis differs in that anaerobic microorganisms are more commonly prevalent.[138]

Historically, the prevalence of RS of odontogenic origin has been quoted to be 10% to 15%.[139] A more recent study by Bomeli et al.[96] evaluated the frequency of acute maxillary RS and found that oroantral fistulas to be the only independent predictor of RS. Periodontal disease, projecting tooth roots, and apical abscess were not independent predictors, but there were interaction effects: the presence of periodontal disease along with either a projecting tooth root or an abscess were predictive of RS using regression analysis.

It is believed that the most common causes of odontogenic RS include those processes that violate the mucosal membrane, such as dental abscesses, periodontal disease, secondary infections caused by intraantral foreign bodies, and sinus perforations during tooth extraction. Although there is scarce evidence in the literature pointing to complications between a dental source and ARS, several case reports were identified suggesting an association, including dislodged bone grafts or implants blocking the maxillary ostium[140,141]; however, it should be noted that ARS was not defined in these reports. Further, more robust data showing an association between periapical abscesses and RS was found in aspirates between both the periapical abscess and the maxillary sinus. The authors demonstrated a concordance in the microbiological findings between the periapical abscess and the maxillary sinus flora, suggesting extension from the odontogenic source.[138]

It has been hypothesized that endosseous implant placement which projects into the maxillary sinus may also be a nidus for infection resulting in acute maxillary sinusitis,[142,143] although some authors refute this concept.[144] 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.[145]

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 (Table V-5).

- Aggregate Grade of Evidence: C (Level 4: 6 studies).

V.C. ARS: Diagnosis

ARS is defined in Section III.A. The diagnosis of ARS is clinical and based on multiple symptoms, including nasal congestion or blockage, drainage or postnasal drip (PND), facial pressure/pain, and reduction in the sense of smell.[147–151] ARS may also be associated with regional upper airway symptoms such as sore throat, hoarseness, and cough, as well as nonspecific systemic complaints such as malaise, fatigue, and low-grade fever.[147,152] Nasal endoscopy and radiographic imaging are not required for diagnosis in uncomplicated cases. Anterior rhinoscopy is recommended and may reveal evidence of inflammation, mucosal edema, and discharge.[149] Elevations in erythrocyte sedimentation rate (ESR) and CRP may be associated with ARS, but are not required for diagnosis.[153]

- Aggregate Grade of Evidence: C (Level 2a: 2 studies; Level 2b: 2 studies; Level 3b: 1 study; Level 4b: 1 study; Table V-6).

TABLE V-5. Evidence for odontogenic source of ARS

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Abi Najm[145]	2013	4	Observation case series (n = 70)	Patients with dental implants	Maxillary sinus imaging	Implant penetration is not associated with odontogenic sinusitis
Tabrizi[144]	2012	4	Observation case series (n = 18)	Patients with dental implants	Maxillary sinus imaging	No increased risk
Bomeli[96]	2009	4	Observation case series (n = 124)	Acute maxillary sinusitis patients	Maxillary sinus imaging	Odontogenic infections predictive of opacification in 17% to 86%
Jung[143]	2007	4	Observation case series (n = 23)	Patients with dental implants	Maxillary sinus imaging	Implant projection of 4 mm associated with mucosal thickening
Abrahams[146]	1996	4	Observation case series (n = 84)	Patients presenting with periodontal disease	Maxillary sinus imaging	38% positive detection rate for maxillary opacification
Regev[142]	1995	4	Observation case series (n = 8)	Patients with dental implants	Presence/absence of maxillary sinusitis symptoms	Maxillary sinusitis associated with implants

TABLE V-6. Evidence for diagnosis of ARS

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Lindbaek[150]	2002	2a	Systematic review	1.ABRS; 2.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[153]	1995	2a	Prospective cohort study	Acute maxillary sinusitis	ESR, CRP association with acute maxillary sinusitis	Elevations in ESR and CRP significantly associated with acute maxillary sinusitis
Shaikh[147]	2013	2b	Validating cohort study	1. ARS; 2. URI	Symptom prevalence	Mild symptoms, absence of green discharge or disturbed sleep more likely viral
Berg[152]	1988	2b	Validating cohort study	1. Maxillary empyema; 2. No maxillary empyema	Association between sinus symptoms and empyema	High reliability of local pain, purulent rhinorrhea, especially when unilateral, with maxillary sinus empyema
Klossek[148]	2011	3b	Cross-sectional survey	ARS	Symptom prevalence	Most common symptoms were nasal obstruction, pain, rhinorrhea, and headache
Hueston[149]	1998	4b	Retrospective case series	1. ARS; 2. URI	Association between symptoms and ARS diagnosis	Sinus tenderness, pressure, postnasal drainage, and discolored nasal discharge were highly associated with ARS diagnosis

V.C.1. ARS Diagnosis: Differentiating Viral from Bacterial ARS

ABRS is frequently a complication of a viral URI, and the symptoms associated with these conditions overlap greatly.[132,133] Duration is a key factor distinguishing 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.[4,132,154,155]

The ability to determine whether bacterial infection is present in ARS is challenging in the primary care setting, particularly without endoscopy or imaging.[133] Clinical factors associated with ABRS include purulent discharge,[4]

localized unilateral pain,[156] and a period of worsening after an initial milder phase of illness.[147] Nasopharyngeal cultures are not necessary for ABRS diagnosis, but can help with antibiotic guidance in the primary care setting.

Fokkens et al.[7] suggest assuming bacterial ARS if diagnostic criteria for ARS are met and at least 2 of the following criteria are additionally present: (1) the disease lasts longer than 7 to 10 days or worsens again after initial improvement (double sickening); (2) symptoms, particularly pain over teeth and maxilla, are severe (7 to 10 cm on a visual analog scale [VAS]); (3) purulent secretions on rhinoscopy; (4) increased ESR or elevated CRP; and (5) fever >38°C. In contrast, Rosenfeld et al.[4] point out there are no data to support symptom severity or purulence as differentiators of bacterial vs viral ARS and recommended relying principally on time course.

The evidence related to differentiating acute viral from acute bacterial RS is variable and is summarized in Table V-7.

- Aggregate Grade of Evidence: B (Level 1a: 1 study; Level 1b: 3 studies; Level 2a: 2 studies; Level 2b: 4 studies).

V.C.2. ARS Diagnosis: Differential Diagnosis

The differential diagnosis of ARS includes AR, dental disease, chronic fatigue syndrome, and facial pain syndromes.[164,165] Accurate diagnosis is most often possible solely on clinical grounds, but additional testing may be required for symptoms that are persistent or severe.

AR is another condition with symptoms similar to ARS, which can mainly be differentiated from ARS on the basis of a prior history of allergy and atopy, as well as exacerbation with exposure to allergens.[112] If current pollen counts and skin-prick tests in a patient with symptoms suggestive of AR yield consistent results, AR is assumed.[166] The presence of itchy and watery eyes is common in AR but rare in ARS. Conversely, ARS symptoms of mucopurulent discharge, pain, and anosmia are uncommon in AR.

Dental disease can present with sinus pain, sometimes in the absence of toothache or fever.[96] Diagnostic criteria for ARS are usually not met, because nasal congestion, hypersecretion, and/or hyposmia are absent. The lack of other typical ARS-associated symptoms makes the diagnosis of ARS less likely, and dental evaluation by a specialist with appropriate imaging will provide clarification.

Headaches and midfacial pain syndromes are frequently in the differential diagnoses of RS.[167] The most common primary headache syndromes are tension-type headache, atypical facial pain, migraine, paroxysmal hemicrania, cluster headache, and midfacial segment pain.[168,169] Usually the chronic course and pattern of these symptoms make differentiation from ARS easy, but some headache syndromes may be episodic and, with the exception of cluster headaches, nasal symptoms are frequently absent. Ocular pain syndromes, particularly glaucoma, may also mimic ARS.[170] Orofacial pain syndromes including temporomandibular disorders have been extensively reviewed in recent years.[171,172]

In summary, the differential diagnosis of ARS includes AR, headache or facial pain syndrome, and dental conditions. Although diagnosis is most often possible solely on clinical grounds, additional testing may be helpful to differentiate ARS from other entities with overlapping symptoms.

V.D. ARS: Management

V.D.1. ARS Management: Antibiotics

As noted in Section V.C.1, differentiating viral from bacterial ARS can be challenging, and is often based on time course. Once the clinical suspicion of ABRS exists, the next controversial decision point is determining whether to prescribe antibiotics.

Although antibiotics have traditionally been prescribed for ABRS, this practice has recently been questioned. There is substantial evidence that ARS has a high spontaneous resolution rate and the adverse events and costs from adding antibiotics may outweigh any potential benefits. Four recent systematic reviews of RCTs have compared the efficacy of antibiotics to that of placebo for ABRS.[173–176] The reviews found that antibiotics conferred a benefit, but it was small; cure rates at 7 to 15 days improved from 86% with placebo to 91% with antibiotics. This effect was sufficiently small that the number needed to treat with antibiotics to show improvement in 1 individual ranged between 11 and 15. Moreover, the rate of adverse events was higher in those treated with antibiotics, with the number needed to treat before harm was seen being 8.1 (Table V-8).

In making the decision to prescribe or withhold antibiotics for ABRS, clinicians must practice sound EBM, which includes taking into account the patient's expectations and the clinician's individual experience. Nonetheless, educating patients on the small benefit of antibiotics relative to the risk of adverse events may create a more sound shared decision-making process. As 1 option to address patients' concerns about the inconvenience, expense, and delay in treatment for those who fail an initial period of "watchful waiting," Rosenfeld et al.[4] recommend the use of "wait and see" or "safety net" prescriptions. These prescriptions can be given at the initial visit with instructions on when to fill them, typically if there is no improvement after 7 days or worsening at any time.

If the decision is made to prescribe an antibiotic, next the clinician is faced with choosing which one. Many different antimicrobial agents are indicated for acute bacterial sinus infections, yet none has been found to have clearly superior clinical outcomes compared to the others. Multiple systematic reviews,[173,175] reviews with recommendations,[7,177] and CPGs[4,178] have thoroughly reviewed the scores of comparisons of differing antibiotics, differing dosages, and differing durations of therapy. The consensus of all of these analyses is that amoxicillin, either alone or with clavulanate, is the first antibiotic of choice in treating suspected

TABLE V-7. Evidence for diagnosis of acute bacterial RS

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Young[157]	2003	1a	RCT	1. Augmentin; 2. 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 laboratory tests
Smith[158]	2015	1b	Systematic review	1. Radiographic evidence; 2. 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
Lacroix[156]	2002	1b	Validating cohort study	1. Rhinosinusitis; 2. URI	Discolored discharge, facial pain, radiograph compared to NPx culture	Discolored drainage, facial pain, radiological maxillary sinusitis were associated with positive culture
Engels[159]	2000	1b	Meta-analysis	Positive or negative maxillary sinus cultures	Symptoms, radiographs, ultrasound	Ultrasound was least predictive due to variability
Hauer[133]	2014	2a	Systematic review	ABRS and ARS	Fever, facial pain	Cannot distinguish viral from bacterial based on fever or facial pain
van den Broek[132]	2014	2a	Systematic review	1. RS; 2. URI	Symptom duration, purulent rhinorrhea	Cannot distinguish viral from bacterial based on symptom duration or purulent rhinorrhea
Lee[160]	2013	2b	Validating cohort study	1. NPx culture; 2. MM culture	Concordance between culture locations	Good concordance for the culture sites makes them a viable diagnostic tool
Berger[161]	2011	2b	Prospective cohort	1. ABRS; 2. No ABRS	Correlation of fiber-optic endoscopy, radiography with ABRS diagnosis	Fiber-optic endoscopy is valuable for diagnosis of ABRS
Hansen[162]	2009	2b	Validating cohort study	Positive or negative maxillary sinus cultures	Symptoms, blood laboratory tests	Elevated ESR and CRP were sensitive but not specific for positive bacterial cultures
Savolainen[163]	1997	2b	Validating cohort study	Positive or negative maxillary sinus cultures	ESR, CRP, WBC count	None of the blood tests were sensitive indicators of ABRS

MM = middle meatal; WBC = white blood cell.

ABRS. Second-line drugs for those who have failed amoxicillin/amoxicillin-clavulanate or who are allergic to amoxicillin may include trimethoprim-sulfamethoxazole, doxycycline, or a respiratory fluoroquinolone. Duration of therapy is typically recommended as 10 days or less, with shorter courses favoring fewer adverse events and higher patient compliance.[4,7]

High-dose (4 g/day) amoxicillin-clavulanate appears to have greater efficacy of reducing nasopharyngeal carriage of pneumococcus compared to lower dose (1.5 g/day). One study reported that of 27 pneumococcal isolates, 6 (only 1 in the high-dose arm) had intermediate to high resistant organisms, whereas none of the other isolated bacterial species were resistant.[179] Another study reported clinical resolution using amoxicillin-clavulanate in approximately 88% of culture-proven ARS, including an 88% to 97% response in penicillin-resistant pneumococcus-positive and beta-lactamase–positive infections.[180]

Resistance of common bacteria in ARS is an increasing concern. Middle meatal swabs from a mixed adult/pediatric group showed penicillin-resistant pneumococcus in 72%, and ampicillin-resistant *Haemophilus influenzae* and *Moraxella catarrhalis* in 60% and 58.3%, respectively.[181]

The choice of whether to include clavulanate has differed among recent reviews and clinical practice guidelines. Chow et al.[178] recommend amoxicillin-clavulanate for all treatments, whereas Rosenfeld et al.,[4] Fokkens et al.,[7] and Desrosiers et al.[177] all consider it an option, and encourage its addition when penicillin resistance is more likely, when

TABLE V-8. Evidence for antibiotic therapy in ARS

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Ahovuo-Saloranta[173]	2014	1a	Systematic review of RCTs and meta-analysis	1. Antibiotic vs placebo for ARS; 2. Differing classes of antibiotics	1. Clinical symptoms; 2. Radiologic outcome	There is moderate evidence that antibiotics provide a small benefit
Lemiengre[174]	2012	1a	Systematic review of RCTs	Antibiotic vs placebo for ARS	1. Symptom resolution; 2. Adverse events	"There is no place for antibiotics" in uncomplicated ARS
Falagas[175]	2008	1a	Meta-analysis of RCTs	1. Short-term therapy (up to 7 days) for ARS; 2. Longer-term therapy for ARS	Improvement of symptoms	There is no difference seen between short-term and long-term courses of antibiotics
Young[176]	2008	1a	Meta-analysis of RCTs	Antibiotics vs placebo for ARS	Symptom resolution	15 patients need to be treated before 1 patient benefits from antibiotics

the clinical course is more severe, or when comorbidities are present.

Adverse events must also be taken into account. A Cochrane review[173] showed dropout rates from adverse effects were small in both antibiotic and placebo patients (1.5% and 1%, respectively), but highest in the amoxicillin-clavulanate subgroup (3.4%). Also, overall adverse effects were greater in amoxicillin-treated patients than placebo (31% vs 22%).

Direct costs of both amoxicillin and amoxicillin-clavulanate are similar and low given the availability of both drugs as generics. Indirect costs are also expected to be similar given similar side-effect profiles, and the results of a trial demonstrating no significant difference between amoxicillin and placebo with regard to missed work days or in the inability to do nonwork activities (Table V-9).[173,182]

- Aggregate Grade of Evidence: A for choosing whether to prescribe antibiotics (Level 1a: 4) B for amoxicillin vs amoxicillin-clavulanate (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.
- Cost: Low to moderate.
- Benefits-Harm Assessment: Benefit of treatment over placebo is small.
- Value Judgments: Improvement in patient symptoms is limited with risk of adverse events. Patient preference may be strong and education regarding benefit-harm balance may be necessary.
- Policy Level: Antibiotic use in suspected ABRS: Option. If an antibiotic is chosen, amoxicillin-clavulanate vs amoxicillin: Option.
- Intervention: Withholding antibiotics with close follow-up is an option in suspected ABRS. If an antibiotic is chosen, both amoxicillin and amoxicillin-clavulanate are options for treatment of uncomplicated ARS. Consider amoxicillin-clavulanate for potentially complicated infection or when resistant organisms are suspected.

V.D.2. ARS Management: Corticosteroids

ARS develops as a result of structural, infectious, and inflammatory processes. Intranasal corticosteroid sprays (INCSs), due to their anti-inflammatory and possible decongestant properties, have been investigated as possible adjuvant therapies to limit transcription of proinflammatory factors, stabilize phospholipid membranes, and inhibit IgE-induced release of histamine, all with the effect of reducing mucosal swelling.[186,187] Numerous studies have reported varied efficacy of intranasal or systemic corticosteroids to reduce ARS symptom severity and duration, and Cochrane review meta-analyses have reviewed trials of both modalities to provide a assessment on the role of corticosteroids in the management of ARS.

V.D.2.a. ARS Management: INCSs. INCSs offer anti-inflammatory benefits and potential decongestant action with negligible systemic bioavailability vs oral corticosteroids.[186] Randomized, placebo-controlled blinded trials have evaluated the role of various INCSs in managing the duration and severity of ARS symptoms, as adjuvant therapies to antibiotic-based regimens, and more recently as monotherapies.[188,189] The latest INCS trials have used either fluticasone propionate 110 μg daily or twice daily or mometasone furoate 200 μg daily or twice daily to reduce daily impact of major ARS symptoms.[188,189] Although an early trial using budesonide demonstrated only minimal improvement with INCS,[186] results from subsequent trials suggest modest but significant improvements

TABLE V-9. Evidence for amoxicillin vs amoxicillin-clavulanate in ARS

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Garbutt[182]	2001	1b	RCT in pediatric patients	1. Amoxicillin; 2. Amoxicillin-clavulanate; 3. Placebo	Telephone interviews at 3 to 60 days	Day 14 improvement rate was similar between groups. Similar relapse/recurrence rates
Wald[183]	1986	1b	RCT in pediatric patients	1. Amoxicillin; 2. Amoxicillin-clavulanate; 3. Placebo	Telephone questionnaire at 1 to 10 days	Both antibiotics were superior to placebo at days 3 and 10
Anon[180]	2006	2b	Cohort study	Amoxicillin-clavulanate	Bacterial eradication or no clinical evidence of infection	Success in 87.8%
Brook[179]	2005	2b	Cohort study	Amoxicillin-clavulanate with 2 different amoxicillin doses (4 g/day vs 1.5 g/day)	Bacteria isolated by NPx swab pretherapy and posttherapy	Bacteria were isolated by pretherapy and posttherapy
Olwoch[184]	2010	4	Case series	Patients with complicated sinusitis treated with antibiotics and surgery	Bacterial isolates and resistance	Pneumococcal prevalence low (2.6%); penicillin resistance high (64.3%)
Brook[185]	2008	4	Retrospective series without control	Culture data from 2 different time periods	Prevalence of *Staphylococcus aureus* and MRSA	Prevalence of MRSA was greater in the latter time period
Huang[181]	2004	4	Case series	Middle meatal discharge cultured during ARS episode	Prevalence of antibiotic resistance	First-line penicillin class resistance in 58% to 72% for common pathogens

MRSA = methicillin-resistant *Staphylococcus aureus*.

in symptom control with hastened onset of relief, when pairing INCS with antibiotics.[188–194] A Cochrane review meta-analysis, which included 1943 participants from 4 studies, arrived at a similar conclusion: symptoms in patients receiving INCS, particularly higher-dose treatments, were more likely to resolve or improve than in placebo-treated patients.[187] However, these effects were admittedly modest, requiring INCS treatment of 100 patients to provide 7 patients with complete or marked symptom relief.[187]

With infrequent adverse events and limited systemic uptake, INCS use in ARS is a recommendation with grade A aggregate quality of evidence. Additional studies comparing ideal INCS formulation, dose, and timing will provide important insight into tailoring INCS treatment in ARS (Table V-10).

V.D.2.a. ARS Management: Systemic Corticosteroids. Although the majority of trials have focused on the role of INCSs in ARS, a few trials have evaluated the implications of systemic corticosteroids as adjuvant therapy to antibiotics. Each of the 3 studies used different corticosteroid formulations in varying dosing and duration regimens, thus preventing direct comparison of results.[195–197] Studies by Gehanno et al.[197] and Ratau et al.[196] offered early support for the use of systemic corticosteroids, specifically methylprednisolone and betamethasone, for management of ARS-associated symptoms, particularly facial pain. However, Venekamp et al.[195] provide the most recent study, which is also the most scientifically rigorous and the only study performed without confounding adjuvant antibiotics. They failed to find significant symptomatic improvement in patients taking prednisolone who had been diagnosed clinically with ARS.[195] A Cochrane review meta-analysis, which included the Venekamp et al. study,[195] failed to find significant evidence to support systemic corticosteroids in ARS, despite reviewing trial results from 1193 participants.[198] Interestingly, only 3 of the 5 studies included in the Cochrane review used objective measures to diagnose ARS, the other 2 relied only on a clinical diagnosis.

Given the lack of consensus, systemic corticosteroids in cases of uncomplicated ARS are not recommended, with a grade B aggregate quality of evidence (Table V-11).

- Aggregate Grade of Evidence: A (Level 1a: 7 studies; Level 1b: 11 studies [8 for INCS, 3 for systemic corticosteroids]).
- Benefit: INCS improved patient symptoms as monotherapy or adjuvant to antibiotics in severe cases, and hastened recovery; systemic minimal benefit.
- Harm: Minimal harm with rare mild adverse events.
- Cost: Low for both interventions.
- Benefits-Harm Assessment: Benefit of treatment over placebo small, but tangible; minimal harm with INCS, greater risk for prolonged systemic corticosteroids.
- Value Judgments: INCS improved patient symptoms with low risk for adverse event.
- Policy Level: Use of INCS: Strong recommendation. Use of systemic corticosteroid: No recommendation.

TABLE V-10. Evidence for intranasal corticosteroids in ARS

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
van Loon[199]	2013	1a	Systematic review (n = 539)	INCS review in RARS	Time to clinical cure (duration of symptoms)	INCS not recommended as monotherapy in RARS
Zalmanovici[187]	2013	1a	Analysis of 4 RCTs (n = 1943)	1. INCS; 2. Placebo	Resolution of symptoms, adverse events, rates of relapse, etc.	INCS improved resolution of symptoms; higher doses may have stronger effect on improvement
Fokkens[7]	2012	1a	Systematic review	ARS patients		Recommended in moderate ARS as monotherapy or severe ARS as an adjunct to antibiotics
Hayward[200]	2012	1a	Systemic review (n = 2495)	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[201]	2008	1a	Systemic review	ARS patients		Effective as adjunct or as monotherapy to reduce symptoms
Scadding[202]	2008	1a	Systematic review	BSACI guidelines		INCS with antibiotics hastens resolution of symptoms
Keith[189]	2012	1b	RCT (n = 737)	1. Fluticasone 110 μg BID (n = 240); 2. Fluticasone 110 μg daily (n = 252); 3. Placebo (n = 245)	Symptom improvement	Both doses of INCS reduced symptoms. Neither dose showed differences in time to improvement or SNOT-20
Meltzer[188]	2012	1b	RCT (n = 967)	1. Mometasone 200 μg BID (n = 233); 2. Mometasone 200 μg daily (n = 240); 3. Amoxicillin 500 mg TID (n = 248); 4. Placebo (n = 246)	Minimal-symptom days and minimal-congestion days	High-dose INCS had more minimal-symptom days
Bachert[194]	2007	1b	RCT (n = 981)	1. Mometasone 200 μg BID (n = 243) + placebo antibiotic; 2. Mometasone 200 μg daily (n = 235) + placebo antibiotic; 3. Amoxicillin 500 mg TID (n = 251) + placebo INCS; 4. Placebo INCS + placebo antibiotics (n = 252)	SNOT-20	200-μg BID regimen had clinically significant improvement in SNOT-20 vs placebo
Williamson[186]	2007	1b	RCT (n = 240)	1. Amoxicillin 500 mg TID + budesonide 200 μg daily (n = 53); 2. Amoxicillin 500 mg TID + placebo INCS daily (n = 60); 3. Budesonide 200 μg daily + placebo antibiotic (n = 64); 4. Placebo antibiotic + placebo INCS (n = 63)	Improvement in Total Symptom Severity Score by >4 points, as assessed in symptom diary	No synergistic effect between INCS and antibiotics. Milder cases benefited from the INCS whereas more severe cases did not
Meltzer[191]	2005	1b	RCT (n = 981)	1. Mometasone 200 μg BID (n = 243) + placebo antibiotic; 2. Mometasone 200 μg daily (n = 235) + placebo antibiotic; 3. Amoxicillin 500 mg TID (n = 251) + placebo INCS; 4. Placebo INCS + placebo antibiotics (n = 252)	Change symptoms diary	INCS BID was significantly better than all other groups; no difference between INCS daily and placebo

(*Continued*)

TABLE V-10. Continued

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Nayak[190]	2002	1b	RCT (n = 967)	Amoxicillin/clavulanate 875 mg BID plus: 1. Mometasone 400 μg BID (n = 324); 2. Mometasone 200 μg (n = 318); 3. Placebo INCS (n = 325)	Change from baseline symptoms and CT normalization	High-dose and low-dose INCS improved symptoms with no significant change in CT score
Dolor[192]	2001	1b	RCT (n = 95)	1. Fluticasone propionate 200 μg daily (n = 47); 2. Placebo INCS (n = 48)	1. Symptoms improved at 10–56 days); 2. Time to success; 3. Number of ARS recurrences	INCS patients have higher rates of "clinical success," shorter time to success (6 vs 9 days); and trend toward fewer recurrences
Meltzer[193]	2000	1b	RCT (n = 407)	1. Mometasone furoate 400 μg BID + amoxicillin/clavulanate 875 mg BID (n = 200); 2. Placebo INCS + amoxicillin/clavulanate 875 mg BID (n = 207)	Symptom improvement	Congestion, facial pain, and headache significantly improved with INCS. No difference in purulent rhinorrhea, PND, or cough

BSACI = British Society for Allergy and Clinical Immunology; NNT = number needed to treat.

TABLE V-11. Evidence for systemic corticosteroids in ARS

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Venekamp[198]	2014	1a	Meta-analysis of 5 RCTs (n = 1193)	1. Systemic corticosteroid; 2. 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[195]	2012	1b	RCT (n = 185)	1. Prednisolone 30 mg daily (n = 93); 2. Placebo (n = 92)	Resolution of facial pain/ pressure and other symptoms	No differences seen in any outcomes.
Gehanno[197]	2000	1b	RCT (n = 417)	Amoxicillin/clavulanate 500 mg TID plus: 1. Methylprednisolone 8 mg 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[196]	2004	2b	RCT (n = 42)	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 treatment

- Intervention: INCS should be trialed as monotherapy in moderate or as adjuvant to antibiotic therapy in severe cases of ARS. Systemic corticosteroids may be useful in palliation when predominant symptoms are facial pain or headaches, otherwise no tangible benefit.

V.D.3. ARS Management: Other Treatments

Decongestants are recommended by physicians in ARS with the presumed benefit of reducing nasal congestion and hence improving patient symptoms. There is minimal evidence regarding the use of decongestants in adult ARS. Inanli et al.[203] performed an RCT looking at this topic. The primary outcome measure in this study was saccharin transit time. This was demonstrated to be slower initially in those with ARS and faster with the use of oxymetazoline and hypertonic saline. Ultimately, however, no significant difference between treatment groups and controls was observed at the conclusion of the study. Wilkund et al.,[204] performed a double-blind RCT on patients with acute maxillary sinusitis. They examined oxymetazoline or an oral antihistamine against a placebo. The outcome measures were patient reported symptoms and radiology. Neither treatment was shown to have significant benefit over placebo at the study conclusion.

Several systematic reviews on this topic have been published.[7,15,205] None have found sufficient evidence to allow a recommendation to be made (Table V-12).

- Aggregate Grade of Evidence: not applicable.

Antihistamines. Antihistamines are prescribed in ARS on the basis that they reduce nasal secretions. Systematic

TABLE V-12. Evidence for decongestants in ARS

Study	Year	LOE	Study Design	Study groups	Clinical endpoint	Conclusions
Fokkens[7]	2012	1a	Systemic review			Sufficient data lacking to recommend
Rosenfeld[15]	2007	1a	Systematic review			No evidence for efficacy in ABRS
Inanli[203]	2002	1b	RCT	ARS patients treated with amoxicillin/ clavulanate and: 1. No treatment; 2. INCS; 3. Oxymetazoline; 4. Hypertonic saline irrigation; 5. Normal saline irrigation	Saccharin transit times	Oxymetazoline was associated with faster times than no treatment
Wiklund[204]	1994	1b	DBRCT	Patients with acute maxillary sinusitis treated with phenoxymethylpenicillin and: 1. Oxymetazoline and an oral antihistamine; 2. Placebo	Clinical examination through 28 days; conventional sinus X-ray; VAS entries in patient diary	No difference between groups
Leung[212]	2008	5	Expert opinion			No evidence

reviews have looked at their efficacy in the treatment of adult ARS.[7,177] No evidence to support their use in this setting was demonstrated. A review of the literature was unable to identify any studies upon which to make recommendations.

- Aggregate Grade of Evidence: not applicable.

Nasal Saline Irrigation. Saline has long been used in the treatment of ARS. Multiple studies have shown it to improve saccharin transit times in normal patients and those with ARS.[203,206–208] Limited evidence also exists to suggest it improves symptoms and QoL for patients with ARS.[15,209]

A number of systematic reviews and clinical guidelines on the subject of saline irrigation in ARS have been published and have found an overall benefit in symptom reduction (Table V-13).[4,7,155] Although the studies individually do not provide a compelling case for the use of saline in ARS, taken together they can be interpreted as demonstrating a likely benefit in terms of nasal function and patient symptoms with minimal likely harms.

- Aggregate Grade of Evidence: A (Level 1a: 3 studies; Level 1b: 4 studies; Level 2b: 1 study).
- Benefit: Possible nasal symptom improvement. Improved nasal saccharin transit times.
- Harm: Occasional patient discomfort.
- Cost: Minimal.
- Benefits-Harm Assessment: Benefit likely to outweigh harm.
- Value Judgments: None.
- Policy Level: Option.
- Intervention: Use of saline may benefit patients in terms of improved symptoms and is unlikely to lead to significant harm.

Other Interventions. Although commonly prescribed by practitioners for ARS, no identifiable evidence for or against the use of ipratropium bromide and mucolytics in this condition was found.

A number of herbal interventions for ARS have been published in the literature (Table V-14). Although extract of *Pelargonium sidoides*[210] and cineole[211] 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.

V.E. ARS: Complications

Complications of ARS are classified into orbital, osseous, and intracranial,[216] though some unusual complications have also been described.[217–221] Sinus disease is the underlying cause of about 10% of intracranial suppuration,[222,223]and is associated with 10% to 90% of periorbital infections.[224] In large epidemiological studies, the overall incidence of complications ranged from 3 per million individuals per year in the Netherlands,[225] to 2.7 to 4.3 per million children per year in the United States (intracranial),[226] to 2.5 per million of population per year in France.[227] In almost all studies males are significantly more frequently affected than females[225–227] and ARS was more often the precipitating factor in children, whereas CRS with or without nasal polyposis was more important in adults.[228,229] The most common complications were orbital, appearing at least twice as often as intracranial, with osseous being the least common.[225,228,230] There was a clear seasonal pattern of complications, mirroring the incidence of URIs.[226] Although orbital complications tend to occur primarily in small children, intracranial

TABLE V-13. Evidence for nasal saline irrigation in ARS

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Fokkens[7]	2012	1a	Systemic review			Most studies indicate reduction of symptoms
Rosenfeld[15]	2007	1a	Systematic review			Saline improves QoL and reduces symptoms and pain medication use
Slavin[155]	2005	1a	Systematic review			Hypertonic saline improves MCC
Hauptman[206]	2007	1b	DBRCT	Patients with "RS": 1. Hypertonic saline; 2. Normal saline	SNOT-20; acoustic rhinometry; saccharin transit time	Improved MCC with either solution. Buffered physiologic saline improved acoustic rhinometry
Wabnitz[213]	2005	1b	RCT blinded	8 healthy volunteers; 0.9% or 3% saline	Collected ciliated cells and CBF calculated	Hypertonic saline increases CBF at 5 minutes but not maintained at 60 minutes
Inanli[203]	2002	1b	RCT	1. No treatment; 2. INCS; 3. Oxymetazoline; 4. Hypertonic saline irrigation; 5. Normal saline irrigation	Saccharin transit times	Hypertonic saline was associated with improved MCC
Adam[214]	1998	1b	RCT blinded	Adults with common cold or ABRS in primary care setting: 1. Hypertonic saline; 2. Normal saline	Nasal symptom score on day 3 and "day of well-being"	No difference in outcomes between treatments. No difference between ABRS and cold groups
Rabago[209]	2002	2b	Lower-quality randomized trial (not blinded or placebo-controlled)	Patients with ARS and CRS: 1. Hypertonic saline irrigation daily; 2. "Their usual treatment"	QoL questionnaires	Improved sinus-related QoL with irrigation; improved symptom severity

TABLE V-14. Evidence for herbal treatments in ARS

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Guo[215]	2006	1a	Systematic review of RCTs			Some evidence for benefit with bromelain and Sinupret® in ARS
Bachert[210]	2009	1b	Multicenter prospective DBRCT	1. *Pelargonium sidoides* drops; 2. Placebo	Sinus severity score. Radiologic changes; SNOT-20, activity level, ability to work	Every result was statistically significant in favor of *Pelargonium sidoides*
Tesche[211]	2008	2b	DBRCT; no placebo control	Patients with ARS and viral RS randomized to: 1. Cineole; 2. Combination of 5 different components	Clinical and endoscopic assessment	Cineole was more effective

complications can occur at any age, with predilection for the second and third decade of life.[225,231]

V.E.1. ARS Complications: Orbital Complications

Chandler et al.'s[232] classification of orbital complications included preseptal cellulitis, orbital cellulitis, subperiosteal abscess, orbital abscess, and cavernous sinus thrombosis. However, the orbital septum is the anterior limit of the orbit, hence "preseptal cellulitis" could be considered as an eyelid, rather than an orbital, infection.[233,234] Cavernous sinus thrombosis[228] is an intracranial complication and not necessarily the end stage of orbital infection, so it will be discussed in Section V.E.2.[235]

Typical signs of orbital cellulitis include conjunctival edema (chemosis), a protruding eyeball (proptosis), ocular pain and tenderness, and restricted and painful movement of the extraocular muscles.[228,236,237] In most series, high fever and raised leucocyte count as well as an increased number of immature neutrophils in peripheral blood were

strongly associated with (subperiosteal or intraorbital) abscess formation.[238]

A subperiosteal abscess forms between the periorbita and the sinuses and is extraconal (located outside the extraocular muscles). The clinical features of a subperiosteal abscess are similar to orbital cellulitis; however, as a consequence of extraocular muscle involvement, the globe may become fixed (ophthalmoplegia) and visual acuity may be impaired.

An orbital abscess is intraconal (contained within the space defined by the extraocular muscles) and generally results from diagnostic delay or immunosuppression of the patient[239] with a frequency of between 13%[229] and 8.3%[240] in pediatric studies of orbital complications. The predictive accuracy of a clinical diagnosis has been found to be 82% and the accuracy of CT to be 91%.[241] If a concomitant intracranial complication is suspected or in cases of uncertainty, magenetic resonance imaging (MRI) can provide valuable additional information.[229,241–244]

Management is with intravenous (IV) antibiotics and drainage of subperiosteal or intraorbital abscess. Evidence of an abscess on the CT scan or absence of clinical improvement after 24 to 48 hours of IV antibiotics are indications for orbital exploration and drainage,[229] as well as drainage of the paranasal sinuses.[245] In small children with subperiosteal abscesses, there have been a number of studies showing good outcomes with IV antibiotics alone and no surgical drainage in selected cases. [246–249]

V.E.2. ARS Complications: Intracranial Complications

These complications include epidural or subdural abscesses, brain abscess, meningitis, cerebritis, superior sagittal and cavernous sinus thrombosis, and isolated oculomotor or abducens nerve palsy.[222,226–228,231,250–252]

The clinical presentation of these complications can be nonspecific, characterized simply by high fever with severe, intractable headache, or even be silent.[228,253] The majority, however, present with more specific signs and symptoms that suggest intracranial involvement, such as nausea and vomiting, neck stiffness, and altered mental state.[227,228,254–256] Intracranial abscesses are often heralded by signs of increased intracranial pressure, meningeal irritation, and focal neurologic deficits, including third, sixth, or seventh cranial nerve palsies.[228,254,257] Although an intracranial abscess can be relatively asymptomatic, subtle affective and behavioral changes often occur, showing altered neurologic function, altered consciousness, gait instability, and severe, progressive headache.[252,258]

A CT scan is essential for diagnosis because it allows an accurate definition of bone involvement. MRI utilization is increasing, being more sensitive than CT,[259] as well as having an additional value in cavernous sinus thrombosis.[227,256] Magnetic resonance angiography (MRA) may be useful in cavernous sinus thrombosis as well.[260] Moreover, if meningitis is suspected, a lumbar puncture could be useful[256] after imaging excludes an abscess.

High-dose IV antibiotic therapy with burr hole abscess drainage, craniotomy, or image-guided aspiration as needed, are usually required for successful treatment.[261,262] There is evidence that combined drainage of the paranasal sinuses can be performed endoscopically.[259,263] Pathogens most commonly involved in the pathogenesis of intracranial complications are *Streptococcus* and *Staphylococcus* species and anaerobes.[222,261]

Cavernous sinus thrombosis may present as bilateral lid drop, exophthalmos, ophthalmic nerve neuralgia, retroocular headache, complete ophthalmoplegia, papilledema, and/or signs of meningeal irritation associated with spiking fevers.[264] The cornerstone of diagnosis is MR venogram, demonstrating absence of venous flow in the affected cavernous sinus. The use of anticoagulants in these patients remains controversial.[264,265] Corticosteroids may help to reduce inflammation and are likely to be helpful, administered with concomitant antibiotics. Drainage of the offending sinus (almost always the sphenoid) is indicated.

V.E.3. ARS Complications: Osseous Complications

Sinus infection can also extend to the bone producing osteomyelitis, especially the frontal bones. On the anterior wall of the frontal sinus it presents clinically with "doughy" edema of the skin over the frontal bone producing a mass (Pott's puffy tumor) whereas from the posterior wall spread occurs directly or via thrombophlebitis of the valveless diploic veins leading to meningitis, epidural abscess, or brain abscess.[264] Therapy includes a combination of broad-spectrum, IV antibiotic administration, surgical debridement of sequestered bone, and (endoscopic or open) drainage of the frontal sinus.[264]

VI. RARS

VI.A. RARS: Incidence/Prevalence

The annual incidence of recurrent RARS was obtained from MarketScan Commercial Claims and Encounters database (2003-2008) and was estimated to be 0.035% (3.5/10,000 per year).[37]

VI.B.1. RARS: Physiologic Contributing Factors

Similar to ARS, several factors predispose an individual to developing RARS and include viral infection, AR, environmental factors, and immunologic deficiency. Few authors specifically delineate RARS as a separate entity and much of what follows is extrapolated from studies on ARS and/or CRS.

Viral infections are a common cause of RARS and commonly precede bacterial infections. Although the average adult experiences 2 to 3 URIs a year, these URIs typically resolve spontaneously. Between 0.5% and 2% of individuals with URIs develop ABRS.[130,266] Viruses including

rhinovirus, adenovirus, influenza, and parainfluenza are the most commonly associated with URIs.[267] Rhinovirus is the predominant cause of the common cold and has been found within the respiratory epithelium in patients with ARS.[268] It has been shown that 50% of these patients possessed rhinovirus in mucosal biopsies.[269]

There has been some debate about the influence allergy has on the development of RARS. Although a number of studies provide evidence that allergy is a predisposing factor, others have disputed this. Similar to viral infections, the inflammation and obstruction associated with allergic disorders cause mucosal edema, ostial obstruction, and retained sinus secretions. As a result, the sinus environment becomes conducive to bacterial overgrowth.[266,270,271] Not only is there a reported increased coexistence of AR in 25% to 31% of adults with acute maxillary sinusitis compared to healthy controls, there is also an association between AR and abnormal sinus CT scans.[112,272] In an attempt to understand a potential effect that AR has on a patient's innate immunity, 1 study found higher levels of eosinophil-derived neurotoxin (EDN) and decreased levels of lysozyme in the nasal fluids of patients with AR with RARS compared to patients with AR alone or control patients.[273] It was suggested that the alteration in antimicrobial peptides and proteins predisposes patients to recurrent infections. In contrast, another study of innate immunity found that Toll-like receptor 9 (TLR9) expression in sinonasal epithelial cells was significantly increased in patients with AR and RARS compared to the AR-only group. Indeed, rather than a TLR9 defect increasing susceptibility to recurrent RS, there was actually an upregulation, perhaps in response to repeated antimicrobial insults.[274]

Another predisposing factor for the development of RARS is immunodeficiency.[275,276] The majority of primary immune deficiencies (PIDs) associated with RARS are humoral in nature and include Ig deficiency and common variable immunodeficiency (CVID).[277–279] Additionally, other types of immune deficiencies such as human immunodeficiency virus–acquired immunodeficiency syndrome (HIV-AIDS), ataxia telangiectasia, Wiskott-Aldrich syndrome, and C3 deficiency may also present with recurrent RS.[275] One significant limitation in evaluating the role of immunodeficiency in RARS is that many studies do not discriminate RARS from CRS.

In conclusion, there is a paucity of information regarding predisposing factors for RARS. As a result, there is some controversy on its etiology. Although limited, the available data suggest that viral infections, allergy, and certain immunodeficiencies can predispose patients to develop RARS (Table VI-1).

- Aggregate Grade of Evidence: C (Level 2a: 1 study; Level 2b: 8 studies; Level 2c: 1 study; Level 3b: 3 studies; Level 4: 4 studies).
- Benefit: Ability to identify predisposing factors for the development of RARS, which may allow a more tailored and targeted therapeutic approach.
- Harm: Falsely identifying conditions that may not have a significant association with the development of RARS.
- Cost: Cost associated with allergy and immune testing.
- Benefits-Harm Assessment: Preponderance of benefit over harm.
- Value Judgments: Identifying predisposing factors for RARS will allow for a more targeted therapeutic approach and improve outcomes.
- Policy Level: Recommendation
- Intervention: Consider viral, allergic, and immunodeficiency as a cause for RARS.

VI.B.2. RARS: Anatomic Contributing Factors

The literature that evaluates the impact of anatomic variants on RS is largely composed of radiographic studies that evaluate CT scans for anatomic variants in patients with and without RS. Most of these studies have small numbers of patients and usually combine all forms of RS or mucosal thickening and do not specifically examine a specific type of RS such as RARS. However, there is 1 study that did assess RARS with regard to sinonasal anatomic variants (Table VI-2). This was a small, retrospective radiographic study comparing adult RARS patients to control patients without RS,[17] with 36 RARS patients and 42 patients in the control group. In the study, the RARS group had a mean Lund-Mackay (LM) score of 2.25, whereas the control group had a mean LM score of 1.27. 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 insufficiently powered.

- Aggregate Grade of Evidence: not applicable.

VI.C. RARS: Diagnosis

Correct diagnosis of RARS necessitates that there be a complete resolution of the signs and symptoms of ARS between episodes of recurrence. Diagnosis of this condition can therefore be challenging because patients may present with longstanding, episodic histories of common RS symptoms such as sinus pain, pressure, congestion, and PND without an abnormal CT or abnormal endoscopic exam between acute episodes. The clinician is therefore mandated to take a detailed history so the recurrent pattern of ARS can be identified and the diagnosis of RARS clinched.

There is evidence to support that due to the lack of characterization of this particular form of RS, a significant burden of cost is incurred by the healthcare system.[37] Bhattacharyya et al.[37] demonstrated that in a population with RARS, only 2.4% of patients received a nasal endoscopy over the course of the first year and only 9.2% after 3 years from the onset of RARS. As for imaging exams, only 40% had received at least 1 CT scan after 4 years of the onset of symptoms. It is important to point

TABLE VI-1. Evidence for physiologic contributing factors for RARS

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Wise[276]	2007	2a	Systematic review of cohort studies	Patients with recurrent or chronic RS	Impact of CF, sarcoidosis, AFRS, and aspirin sensitivity	Recommended treatment of comorbidities accordingly
Kirtsreesakul[270]	2004	2a	Systematic review of cohort studies	Systematic review of the literature regarding AR and RS		RS and AR share common feature. The mechanisms explaining how AR leads to RS remain unclear
Melvin[274]	2010	2b	Prospective cohort study	1. 8 AR (AR) patients; 2. 13 AR + RARS patients	TLR9 expression in sinonasal epithelial cells	AR+RARS had a significant increase in TLR9 expression compared with that of AR-only patients
Edwards[278]	2004	2b	Individual retrospective cohort	127 IgA-deficient patients referred to an immunology clinic	Relationship between vaccination and recurrent infections	There was no relationship between recurring infections and pneumococcal vaccine responses
Kalfa[273]	2004	2b	Prospective cohort study	1. 15 patients with PAR with recurrent RS; 2. 16 patients with PAR alone; 3. 16 controls	1. Lysozyme levels; 2. EDN levels; 3. Lactoferrin levels; 4. HBD-2 levels	Decreased lysozyme and increased EDN levels in PAR+RS patients. No differences in lactoferrin and HBD-2 levels
Chee[275]	2001	2b	Retrospective cohort study	1. 79 patients with RARS	1. Results of immunological evaluation for atopy; 2. Ig levels	40% of patients were anergic. Low IgG was found in 18%, low IgA in 17%, and low IgM in 5.%. CVID was diagnosed in 9.9%
Savolainen[112]	1989	3b	Case-control	1. 224 young adults with acute maxillary sinusitis; 2. Age-matched controls	Occurrence of allergy in the 2 groups	Higher occurrence of allergy in the sinusitis group
Carr[277]	2011	3b	Individual case-control study	129 patients with CRS who underwent ESS	Prevaccination and postvaccination IgG and IgA titers for *Streptococcus pneumoniae*	72% had low baseline anti-pneumococcal titers; 11.6% had an inadequate response to the vaccine
Ramadan[272]	1999	3b	Retrospective case-control	42 patients with RS who underwent CT scan and RAST testing	CT sinus findings in patients with and without allergies	Allergic patients had higher Lund-Mackay scores than nonallergic patients
Pitkaranta[269]	2001	4	Prospective case series	14 adult patients with ARS	Detection of HRV in maxillary sinus tissue	HRV RNA was detected inside the epithelial cells of the maxillary sinus in 50% of patients with ARS
Pitkaranta[268]	1997	4	Prospective case series	20 adults diagnosed with acute community-acquired RS	Detection of HRV and/or HCV. Bacterial cultures	HRV infection was found in 40% and HCV in 15% of patients with ARS
Gwaltney[23]	1994	4	Prospective case series	110 patients with self-diagnosis of URI for 48 to 96 hours	Viral cultures	Rhinovirus was detected in 27% of patients
Turner[280]	1992	4	Prospective case series	19 adults exposed to rhinovirus	MRI abnormalities of the paranasal sinuses	33% showed sinus MRI abnormalities that are reversible without antimicrobial therapy

HCV = human coronavirus; HRV = human rhinovirus; PAR = perennial AR; RAST = radioallergosorbent test.

TABLE VI-2. Evidence for anatomic contributing factors for RARS

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Alkire[17]	2010	3b	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

out that the delay and inappropriate use of diagnostic tools for RARS yielded a direct healthcare cost of approximately US$1000 per year per patient. This amount is similar to the one usually presented for CRS patients. Taken into perspective, it highlights the importance of early and appropriate diagnosis of RARS.

Because a complete resolution in between episodes must be achieved, and is part of the diagnostic criteria, the separation of RARS from CRS remains difficult. There are even proposals that patients with RARS may represent a distinct phenotype, representing a separate disease entity altogether.[18]

Although the diagnostic evaluation of these patients is clinical, it is important to evaluate for CT findings of anatomic obstruction in RARS, and to assess for allergy that may be the instigating factor for RARS.[17] It may also be important to recommend that patients return for clinical evaluation during an acute episode for documentation, sinus culture (often most accurately obtained via nasal endoscopy), and evaluation of the ARS episodes, so that a proper diagnosis can be made and appropriate treatment initiated early. It is highly desirable to obtain microbiological evidence of bacterial infection during an episode to help confirm the diagnosis.[44] Evaluation may include CT imaging to aid objective assessment.

VI.D. RARS: Management

VI.D.1. RARS Management: INCS

A total of 3 studies were identified with the primary objective of assessing the effect of INCSs on symptom outcomes of patients with RARS (Table VI-3). All study designs were double-blinded RCTs (DBRCTs). All studies reported improvement in symptoms in the treatment groups. In addition, a recent systematic review by van Loon et al.[199] summarized the impact of INCS use on symptom relief in patients with RARS. Dolor et al.[192] demonstrated significant improvement in median days to clinical success (6 in treatment group vs 9 in placebo group; $p = 0.01$) with intranasal fluticasone. Meltzer et al.[193] demonstrated that mometasone resulted in improvement of total symptom scores and specific symptoms of headache, congestion, and facial pain. One major limitation of the available data is that none of the studies defined RARS according to the commonly accepted definition of 4 or more episodes per year with absence of intervening symptoms. This may limit applicability to RARS patients, and is considered a limitation of the RCTs. Dolor et al.[192] included a heterogeneous population of patients with a history of RARS or chronic rhinitis, whereas Qvarnberg et al.[281] included a small ($n = 40$), heterogeneous population of patients with recurrent acute maxillary RS (defined as 2 episodes per year for 2 years) and CRS. The study by Meltzer et al.[193] included only patients with RARS, defined as at least 2 episodes per year for 2 years. Another limitation of all studies was inclusion of additional therapeutic agents in addition to INCSs. All studies included antibiotic therapy, and 1 included nasal decongestant therapy. Finally, INCSs were used in these studies during periods of acute exacerbation, and thus efficacy as a preventative therapeutic measure in this population is unknown. No serious side effects were reported from INCS use.

- Aggregate Grade of Evidence: B (Level 2b: 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, and facial pain.
- Harm: Mild irritation.
- 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.
- Policy Level: Option.
- Intervention: Option for use of INCS spray for acute exacerbations of RARS.

VI.D.2. RARS Management: Antibiotics

Although the symptom burden in RARS is similar to CRS, antibiotic utilization is higher.[44] RARS patients average 4 courses of antibiotics per year.[282] Current guidelines on adult RS do not provide recommendations regarding antibiotic use in RARS.[4] A recent, exhaustive systematic review investigated the effectiveness of short-course antibiotics on the severity and duration of symptoms and recurrences in patients with RARS, and failed to identify any placebo-controlled studies.[282] 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. After careful examination of the methodology of this exhaustive review, and with no available data subsequent to this, it is not possible to provide additional recommendations for the use of antibiotics in RARS different from recommendations for treating ABRS.

TABLE VI-3. Evidence for INCS in the management of RARS

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Dolor[192]	2001	2b	DBRCT	10-day cefuroxime, 3-day xylometazoline, and: 1. 21-day INCS; 2. 21-day placebo	Symptoms; QoL scores (SNOT-20 and SF-12)	INCS with xylometazoline and cefuroxime improves clinical success rates and accelerates recovery
Meltzer[193]	2000	2b	DBRCT	21 days amoxicillin clavulanate and: 1. 21 days of INCS; 2. placebo	Symptoms	INCS produced a more rapid and greater relief of specific individual and overall symptoms
Qvarnberg[281]	1992	2b	DBRCT	Erythromycin for 7 days plus: 1. Budesonide for 3 months; 2. Placebo	Symptoms	Budesonide group had greater reduction in facial pain and sensitivity

TABLE VI-4. Evidence for ESS in the management of RARS

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Levine[285]	2013	3b	Case-control	Balloon dilation in RARS and CRS	SNOT-20, RSI	Mean improvement in SNOT-20 and RSI scores in RARS group comparable to the CRS group
Bhandarkar[284]	2011	3b	Case-control	ESS in RARS and CRS	Antibiotic utilization	61.2% reduction in antibiotic utilization in RARS patients
Poetker[18]	2008	3b	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[283]	2006	4	Case series	ESS in RARS	RSI	Significant decrease in RSI scores. Decreased antihistamine use, workdays missed, and acute episodes

VI.D.2. RARS Management: ESS

A total of 3 studies were identified looking at patient outcomes after ESS in patients with RARS (Table VI-4). Two looked at patient-based QoL scores and objective measures, whereas a third study looked specifically at antibiotic utilization following ESS. All 3 studies used standardized inclusion criteria and disease definitions for RARS as defined by the Rhinosinusitis Task Force criteria.[15]

Bhattacharyya[283] reported on 19 patients undergoing ESS for RARS with a mean follow-up of 19 months. Significant improvement was noted for this cohort in Rhinosinusitis Symptom Inventory (RSI) domains, antihistamine use, number of workdays missed, and number of acute infectious episodes. However, declines in weeks of antibiotic use and number of antibiotic courses were not significant. Poetker et al.[18] reported outcomes after ESS in 22 patients with RARS. Their cohort was matched to CRSsNP patients. Fourteen patients were available for postoperative follow-up at a mean of 30 weeks. Their RARS cohort showed significant improvement in the RSDI and Chronic Sinusitis Survey (CSS) total and symptom domains, and patients used significantly fewer sinus medications postoperatively as measured by the CSS. A third study looked at antibiotic utilization following ESS in patients with CRS and RARS.[284] Patients with RARS (n = 21) reported a 61.2% reduction in the average time on antibiotics postoperatively. Through direct comparison to the CRS group, the reduction in antibiotic utilization was shown to not be significantly different between these patient cohorts (RARS vs CRS).

Two studies involving balloon dilation in RARS patients were identified. Levine et al.[285] reported results using the transantral/canine fossa puncture technique for balloon dilation of the maxillary sinus ostium in the office setting. They reported significant mean improvement in the SNOT-20 and RSI scores at 1 year in the RARS cohort of 17 patients. Mean number of antibiotic courses, sinus-related physician visits, and number of acute sinus infections were decreased. Patient use of INCSs, patient use of antihistamines, and workdays missed were not found to change significantly in the RARS group. In another study, 9 patients with RARS were treated as part of a larger cohort using an office-based multi-sinus balloon dilation

tool/technique.[286] Unfortunately, outcomes data specific to this small RARS group were not provided.

Limitations with these studies include small sample sizes and the inherent difficulties in studying RARS related to accurate diagnosis. These patients represent a small subgroup of RS patients and do not necessarily adhere to strict postoperative long-term follow-up. The fluctuating disease pattern, both subjective and objective, also introduces significant problems in studying this population.

- Aggregate Grade of Evidence: C (Level 3b: 3 studies; Level 4: 1 study).
- Benefit: Postoperative improvement in patient symptoms. May reduce postoperative antibiotic utilization, number of acute episodes, and missed workdays. Results appear comparable to CRS cohorts.
- Harm: Surgery is associated with potential complications.
- Cost: Significant costs are associated with ESS.
- Benefits-Harm Assessment: Balance of benefit and harm.
- Value Judgments: Properly selected patients with RARS may benefit both symptomatically and medically from ESS. This option should be assessed and utilized cautiously, however, because data remains limited.
- Policy Level: Option.
- Intervention: ESS is an option for properly selected patients with RARS.

VII. CRSsNP

This discussion of CRSsNP pertains to adults with this condition only. Pediatric RS is discussed in Section XII.

VII.A. CRSsNP: Incidence/Prevalence

Based on an analysis of the Medical Expenditure Panel Survey (MEPS) for 2007 encompassing 225.1 million Americans, Bhattacharyya[35,287] estimated the prevalence of CRS (with or without polyps) to be 4.9% ± 0.2% (490/10,000). In contrast to this prevalence data of CRS overall, Tan et al.[288] examined the incidence of CRSsNP. They used electronic health records from 307,381 adults who received care from the Geisinger Clinic primary care from 2007 through 2009 and found the incidence of CRSsNP to be 105 (± 7.0) cases per 10,000 person-years.

VII.B. CRSsNP: Comorbid Asthma

CRS and asthma are both common manifestations of an inflammatory process within the contiguous upper and lower airway system. Although the etiology and pathogenic mechanisms underlying the development and progress of these 2 conditions are not fully known, it is clear that the upper and lower airways are influenced by common risk factors.[7] Both CRS and asthma are multifactorial diseases caused by multiple interactions between genetic background, environmental factors, and the specific host reaction of the airway mucosa. Eosinophilia and airway remodeling are 2 major histological hallmarks that suggest the same pathologic disease process.[289–292]

Epidemiological and clinical studies have consistently shown that CRS and asthma frequently coexist in the same patient. In a recent random sample survey study with over 52,000 adults aged 18 to 75 years in 12 European countries, the prevalence of self-reported current asthma (5.1-16.8%) was found to be strongly associated with CRS appropriate symptoms (adjusted OR, 3.47; 95% CI, 3.20 to 3.76) in all ages, in both men and women, irrespective of smoking behavior.[293] The reported incidence of asthma varies from 2% to 38% in patients with CRS,[294–299] 2% to 66% in CRSwNP,[289,294–314] and 68% to 91% in refractory CRSwNP.[290,299] Among these reports, the prevalence of asthma in patients with CRSsNP or CRSwNP appears to be lower in Asians than whites. In patients with CRS, the coexistence of asthma is associated with a higher incidence of CRSwNP (47%) than CRSsNP (22%)[315] Asthma is often underdiagnosed in CRS patients and is more common in patients who subsequently are diagnosed with CRS.[288,295,306,315,316]

CRS has been postulated as a risk factor for the development and severity of asthma. Asthma severity may have a significant correlation with the presentation of CRS.[317] In a survey study, the prevalence of CRS was found to be 36.7% in patients with well-characterized asthma, and there was a significant correlation between the severity of the asthma and sinus CT scan abnormalities.[318]

Treatments for CRS or asthma could potentially alleviate the coexisting condition. Both CRSsNP and CRSwNP, when suboptimally controlled, worsen the course of lower airway disease. For example, asthmatic patients resistant to drug therapy need frequently revision surgeries because of their CRS recurrences, but their asthma symptoms and pulmonary function improve after both medical and surgical treatments.[314] In a retrospective database analysis of 9105 CRS patients who had undergone ESS in 2008 (in the United States), asthma was found to be associated with an increased total number of surgeries, increased rate of inpatient admissions, increased number of outpatient visits, and increased drug utilization when compared to patients with CRS without asthma.[298,315]

Summary of evidence for CRSsNP and asthma (Table VII-1).

Statement (Grade of evidence)

- CRS and asthma frequently coexist in the same patient (A)
- Asthma is underdiagnosed in CRS patients (C)
- The etiology and pathogenic mechanisms underlying the development and progress of these 2 diseases largely overlap (C)
- Treatments for CRSsNP or asthma could potentially alleviate the coexisting condition (B).

VII.C.1. CRSsNP: Pathophysiology

VII.C.1.a. CRSsNP Pathophysiology Contributing Factors: Allergy. It is commonly accepted that the pathophysiology of CRS is persistent inflammation and the cause of this inflammation varies from patient to patient.

TABLE VII-1. Evidence for CRSsNP and asthma as a comorbidity

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Jarvis[293]	2012	1a	Population-based survey	Adults from 19 centers in 12 European countries	Self-reported current CRS and asthma	Asthma is associated with CRS
Ragab[319]	2006	1b	Randomized, prospective study with 1-year follow-up	35 patients with CRSwNP; 55 patients with CRSsNP; 43 patients with CRS and asthma	Objective sinonasal assessments; lung function test	Treatment of CRS, medical or surgical, benefits concomitant asthma
Klossek[307]	2005	1b	Population-based random sample survey	French population (adults, aged ≥18 years)	Presence of NP and asthma	The number of asthmatic subjects was significantly higher among NP (26.1%) than controls (6%)
Benninger[298]	2014	2b	Retrospective cohort study	8329 adult patients with CRS after ESS; 776 pediatric patients with CRS after ESS	Medical history of respiratory comorbidities	CRS patients with asthma (20.7%) received significantly more healthcare for CRS than patients without asthma
Ponikau[290]	2003	3a	Prospective study	22 patients with refractory CRS; 4 healthy controls	Medical history	Asthma was found in 11 patients with CRS (68.29%)
Tanaka[295]	2014	4	Case series study	170 patients with CRSwNP after ESS; 40 patients with CRSsNP after ESS	Asthma history; lung function test	13% of CRSwNP and 20% of CRSwNP had obstructive lung dysfunction yet no history of asthma
Batra[299]	2013	4	Cross-sectional (case series) study	CRSwNP: 109; CRSsNP: 116	Medical history; sinus CT scan assessment; serum IgE measurements	High prevalence of NP, asthma (48.4%), inhalant allergy, aspirin sensitivity is found in patients with refractory CRS
Fan[294]	2012	4	Case series study	309 patients with CRSwNP; 42 patients with CRSsNP	Questionnaire; lung function test; oral aspirin challenge	AERD was found 0.57% in Chinese patients with CRS; 2.3% had asthma
Matsuno[318]	2008	4	Case series study	188 asthmatic patients (survey): among them, 104 patients had had sinus CT performed	Clinical findings; CT scan abnormalities	Asthma is closely related to RS; onset age of asthma is important when considering AR frequency
Staikūniene[296]	2008	4	Case series study	84 patients with CRSwNP; 37 patients with CRSsNP; 23 healthy controls	Nasal endoscopy; sinus CT scan; absolute eosinophil count; allergy testing; asthma history	CRS associated with NPs and asthma is the most severe form of unified respiratory tract disease
Seybt[315]	2007	4	Retrospective clinical date review study	34 patients with CRS with asthma; 111 patients with CRS without asthma	Medical history; CRS symptoms; need for surgical treatment	CRS patients with asthma did require significantly more revision sinus procedures overall
Dunlop[320]	1999	4	Case series study with a 1-year follow-up	50 asthmatic patients with either CRSwNP or CRSsNP	Overall asthma control; peak flow measurements; medication requirements	Aggressive management of sinonasal pathology can improve asthma status

However, there are no controlled studies of the role of allergy in the pathophysiology of CRSsNP. Nor are there any controlled trials of treatment options which show that the treatment of allergy alters the course of CRSsNP. There are no studies to show how treating CRS affects the outcome of AR patients and vice versa, and few studies have compared patients with CRS with allergy to those patients with CRS without allergy. The majority of studies are epidemiologic and these provide our current state of knowledge about this relationship.

In CRSsNP the vast majority of patients show a Th1-skewed inflammatory response whereas in the CRSwNP group it is rather heterogeneous and often shows Th-2 type inflammation.[321] Data from a 12-country European study of 52,000 adults showed a strong association of asthma with CRS, and this association with asthma was stronger in those reporting both CRS and AR (adjusted OR, 11.85; 95% CI, 10.57 to 13.17).[293] Because the pathophysiology of CRSsNP is in many ways still unclear, it is difficult to evaluate the role of allergies in this type of CRS when there are no controlled studies published.[7]

In 2014, Wilson et al.[322] reviewed the role of allergy in CRSwNP and CRSsNP. They considered only studies that delineated the presence of polyps or not, so that studies examining "CRS" alone were excluded. 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 in CRSsNP. Four of these studies (1 small level 1b, 3 level 3b) supported an association, whereas 5 (all level 3b) 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 LOE did not support a strong recommendation either for or against this practice.

- Aggregate Grade of Evidence: D (Conflicting epidemiologic data [1 small level 1b, 7 level 3b, 1 level 4], expert opinion, and reasoning from first principles).
- Benefit: Management theoretically reduces triggers and could potentially modify symptoms of 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.
- Cost: Moderate direct costs for testing and treatment; some tests and therapies require significant patient time (eg, 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.

VII.C.1.b. CRSsNP Pathophysiology Contributing Factors: 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 (ECM).[323] Using "quorum sensing" molecules, the bacteria communicate density status and begin to form a biofilm once an appropriate microbe concentration has been reached.[324] The protection of the biofilm renders the bacteria or fungus much more resistant to external insults, including host defenses. The organisms themselves also undergo a phenotypic change[325] to require less oxygen and nutrients, which confers additional resistance to conventional antimicrobials.[326] Microbes that would normally be vulnerable to typically effective antibiotics are up to 1000 times more resistant in the biofilm state.[327] Antibody action, phagocytosis, and complement binding can be equally unsuccessful in this setting.[324]

Biofilms in vivo can often be difficult to detect and culture. Reliance on conventional media results in an "enrichment bias" in which the organisms with the fastest growth rates are overrepresented.[328] Identification of a biofilm-forming pathogen in diseased mucosa therefore requires special techniques to obtain an accurate result.[329] Biosensor molecular detection and fluorescent in situ hybridization (FISH) have both proven to be effective.[330,331] Interestingly, a study comparing FISH to culture technique showed very little overlap in the identities and relative quantities of bacteria detected.[331]

The precise relationship between biofilm formation and CRS pathogenesis is poorly understood. However, biofilm presence in the sinonasal tract is correlated with concurrent CRS,[332] and outcomes after ESS are worse in patients who have biofilm colonization.[333] Specifically, endpoints of postoperative symptoms, ongoing inflammation, and recurrent infections were all increased in biofilm-positive surgery patients.[323,334–337] Biofilm formation in CRS may also be associated with increased need for surgical intervention. Although around 20% of patients with CRS show biofilm formation,[323] up to 50% of CRS surgical candidates are biofilm-positive.[334] Importantly, biofilms can also be found in control patients without CRS, showing that they are neither necessary nor sufficient to cause the pathology.[338]

Treatment of biofilm-positive CRS is difficult, and therapeutic strategies are far from fully elucidated. 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-fold to 1000-fold increase in dosing to achieve an effect.[339,340] Topical therapy may be a more effective approach. Mupirocin has been shown to reduce biofilm mass,[340] but it is unclear if there is a maintained effect after antibiotic application has ceased.[341] Macrolides inhibit quorum sensing in *Pseudomonas aeruginosa*, and these may become a useful therapeutic strategy for treating biofilm-associated CRS.[334] Furosemide, which acts as a cation channel blocker, also reduces biofilm size.[342] Corticosteroids have shown some effect against *Staphylococcus aureus* biofilm formation specifically.[343]

Other less conventional treatments have been attempted with varying degrees of success. Detergent agents have

appreciable biofilm-disrupting effects, but currently are not in use because of several side effects, including ciliary toxicity.[344–347] Photodynamic therapy is a new and promising treatment that shows tremendous biofilm reductions in vitro, and preliminary tissue studies have not shown deleterious side effects.[348,349] Last, low-frequency ultrasound treatments also seem effective in reducing biofilms, also without observed side effects.[350]

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.[351] Detection of these molecules allows the host to mount an innate defensive response before the bacteria reach the density required for biofilm formation.[352] One of these bitter taste receptors, T2R38, is activated by AHLs and has downstream effects of increased MCC and bactericidal nitric oxide (NO) production. CRS patients with a nonfunctional mutation in the T2R38 gene are at a higher risk for needing surgical intervention for their disease.[353] Bitter-taste testing for the presence of T2R38 could potentially predict CRS severity or necessary treatment,[354] and bitter compounds themselves could serve as therapeutic agents that activate the host immune response against biofilm formation in CRS.[355]

VII.C.1.c. CRS Pathophysiology Contributing Factors: Fungus.

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

The potential pathogenic role for fungus as a trigger of CRS first emerged in 1983 following a report by Katzenstein et al.[356] A key observation of this study was the presence of noninvasive *Aspergillus* species within eosinophilic mucin recovered from patients with CRS. Subsequent reports of phenotypically similar patients eventually led to the disease entity "allergic fungal rhinosinusitis" (AFRS).[357–359] Given its histopathologic similarity to allergic bronchopulmonary aspergillosis, AFRS was originally thought to represent a clinical manifestation of IgE-mediated response to fungus within the nose and sinuses.[360] When Ponikau et al.[361] later found that eosinophils and fungi could be recovered from essentially all patients with CRS, a broader role for noninvasive fungi in the pathogenesis of CRS with and without polyposis was considered.

A number of recent studies illustrate potential mechanisms through which fungi might induce inflammatory responses within the nose. One such example is that of fungal proteases capable of binding to protease-activated receptors on host vessels, leukocytes, and epithelial cells. These proteases trigger release of mediators responsible for damage of host tissue.[362–364] Further, *Alternaria* can directly activate eosinophils leading to production of IL-8 and surface expression of eosinophil receptors key to cellular adhesion.[365]

Immunologic responses to fungi have been observed in patients with CRS. Production of cathelicidins and defensins, 2 key antimicrobial peptides associated with mucosal innate immunity, is upregulated in CRS without eosinophilic mucin in the presence of *Aspergillus fumigatus* and *Alternaria tenuis*.[366] Pulmonary surfactant protein (SP-D), another important mechanism of innate immunity expressed within respiratory mucosa, serves an important role in the immune response to *Aspergillus fumigatus* in the lung. SP-D is noted to be absent in patients with CRS with eosinophilic mucin and fungal allergy.[367]

Systematic IgE-mediated allergy to fungus is axiomatic to the diagnosis of AFRS and has been felt to represent a key component in the pathophysiology of that disease.[360] In attempting to expand the role of fungus to all types of CRS, other types of reactions must be considered. Non–IgE-mediated adaptive responses to fungi in CRS have been identified. Shin et al.[368] showed that peripheral blood monocytes from patients with CRS cultured in the presence of *Alternaria* extract produced significantly more IL-5 and interferon γ (IFN-γ) as compared to healthy controls, suggesting that fungi can induce a specific peripheral blood monocyte Th2 cytokine profile. This response was independent of IgE sensitivity to fungi. Orlandi et al.,[369] however, replicated the methods of Shin et al.[368] and had opposing results. They found that IL-5 levels correlated strongly with fungal-specific IgE, but did not correlate with fungal-specific IgG as described by Shin et al.[368] In a study performed by Pant et al.,[370] IgG1 and IgG3 isotypes to fungi were identified in CRS patients with eosinophilic mucin. The effect was independent of IgE sensitivity to fungus.

Despite the interesting laboratory findings regarding immunologic reactions to fungus, the clinical evidence is not as supportive of an etiologic role. Fungal spores are ubiquitous and continuously presented to the nasal respiratory mucosa.[371] *Aspergillus*, *Cladosporium*, *Candida*, *Aureobasidium*, and *Alternaria* are most frequently recovered from both CRS patients and normal controls.[372,373] 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. Although some studies have shown increased fungal loads in some CRS patients compared to controls,[374,375] others have revealed no difference in either prevalence rates of fungus or number of different fungi recovered.[361,376]

Numerous studies, including multiple RCTs, have examined the role of antifungal treatment in CRS and none have shown a clinically meaningful improvement.[377–381] Although not directly addressing fungus as an etiologic factor, these clinical studies cast significant doubt on the role of fungus in the etiology of CRS.

Despite the well-recognized coexistence of fungus with CRS, its role as a direct cause in the pathophysiology remains uncertain.

- Aggregate Grade of Evidence: C (Level 3: 8 studies; Level 4: 2 studies; Table VII-2)

TABLE VII-2. Evidence for CRS and fungus as a contributing pathogenic factor

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Porter[374]	2014	3	Case-control study	1. CRSsNP (n = 21); 2. CRSwNP (n = 37); 3. AFRS (n = 26); 4. Controls (n = 15)	Positive fungal culture of sinus lavage	Fungal cultures were more frequently positive in CRSwNP and AFRS patients compared to CRSsNP and controls
Orlandi[369]	2009	3	Case-control study	1. CRS (n = 10); 2. Controls (n = 7)	1. Cytokine production following fungal exposure; 2. 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
Murr[373]	2006	3	Case-control study	1. CRS (n = 37); 2. Controls (n = 37)	1. Fungal recovery on QPCR; 2. 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[372]	2005	3	Case-control study	1. CRS (n = 82); 2. 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[370]	2005	3	Case-control study	1. Eosinophilic mucin CRS; 2. AFRS; 3. AFRS-like; 4. Nonallergic fungal eosinophilic RS; 5. Nonallergic, nonfungal eosinophilic RS; 6. AR with fungal allergy; 7. 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[376]	2004	3	Case-control study	1. CRS (n = 19); 2. 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[368]	2004	3	Case-control study	1. CRS (n = 18); 2. controls (n = 15)	1. Cytokine production following exposure to fungi; 2. 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
Ponikau[361]	1999	3	Case-control study	1. CRS (n = 210); 2. controls (n = 14)	Fungal culture results	96% of CRS patients had positive fungal cultures; 100% of controls had positive fungal cultures
Tosun[382]	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
Taylor[383]	2002	4	Case series	CRS patients	Presence of chitin	All specimens were positive for chitin

IFN = interferon; QPCR = quantitative PCR.

VII.C.1.d. CRS Pathophysiology Contributing Factors: Osteitis. *Because of limited data, CRSwNP and CRSsNP are combined in this analysis.*

Osteitis may play a role in the pathogenesis of CRS, particularly in patients with recalcitrant disease.[384–387] Notably, some have questioned whether the changes seen are truly inflammatory and have suggested the term "neo-osteogenesis" may be more appropriate.[388] Animal and human studies examining histopathologic changes of paranasal sinus mucosa and bone support its role in CRS.[389–398] Early studies by Kennedy et al.[391] described the histomorphometry and histology of the ethmoid bone to better understand the pathogenesis of disease. Ethmoid bones harvested from patients with and without CRS were labeled with tetracycline and found to have significant activity by histologic evaluation (new bone formation, fibrosis, and inflammatory cell presence). Similar histopathologic results were obtained by other investigators.[390,392] Lee et al.[392] found an increased incidence of osteitis according to pathologic features in patients with CRS undergoing a revision sinus surgery (58%) compared to those with CRS undergoing primary surgery (6.7%), but did not differentiate between CRSsNP and CRSwNP patients. The estimated prevalence of osteitis in CRS patients based on radiographic criteria or histopathology is 32.5% to 79%,[399,400] which underscores the potential clinical impact of this finding.

Although there is no standard diagnostic test for osteitis, CT is currently the modality of choice.[384–386,401,402] CT imaging offers availability, good bony detail, and excellent sensitivity and specificity for detecting mucosal abnormalities and thickening.[401] Single photon emission CT (SPECT) has been suggested as another modality, but is costly, not readily available, and exposes the patient to larger doses of radiation.[401,402] A variety of grading systems using CT imaging have also been proposed, including the Kennedy Osteitis Score, Global Osteitis Scoring Scale (GOSS), scoring based upon Hounsfield units (HU), thickness of bony partitions, as well as systematic examinations of separate reference points in the sinuses.[387,389,392,403,404] As with diagnostic testing for osteitis, these grading systems have not been standardized.

Mounting evidence indicates that osteitis is a contributor to disease progression and indicator of worse clinical outcomes when compared to CRS without osteitis. Giacchi et al.[390] found a strong correlation between higher LM CT staging and the presence of osteitis. Importantly, pathologic change may precede radiographic findings because only 67% of patients with pathologic evidence of osteitis had corresponding changes noted on CT imaging.[392] Telmesani and Al-Shawarby[398] found that in CRSwNP patients, the presence of osteitis was correlated with an increase in disease recurrence rate. Osteitis may also predict QoL measurements or response to surgical intervention. Saylam et al.[400] showed markedly worse subjective scores for patients with osteitis (as determined by higher SPECT scan) compared to a non-osteitis cohort. Bhandarkar et al.[78] found no difference on Rhinosinusitis Outcome Measure (RSOM), RSDI, or CSS in patients with and without osteitis. Nonetheless, fewer patients with osteitis achieved improvement from ESS after controlling for baseline disease-specific factors. Of note, previous surgery has been associated with worsened osteitis scores in several studies, suggesting osteitis may be a marker of more severe disease and/or possibly a reaction to previous surgery.[386,399,401,402]

The causality and relationship of bacterial biofilms, mucosal pathology, and bacterial infection is not well understood in relationship to osteitis. Bacterial infection of the bone is an unlikely cause of osteitis in CRS patients. Wood et al.[405] noted small colonies of bacteria within the bone of both CRSsNP and CRSwNP patients and normal controls. Bacterial microcolonies were found in 1 CRSsNP and 2 CRSwNP cases, as well as in 2 of 6 control cases. [405] Dong et al.[406] demonstrated that 85% of CRS patients with mucosa with bacterial biofilms had some form of osteitis present. Additionally, the histopathologic grade, GOSS score, and HU value in patients with bacterial biofilms were greater than those without biofilms. Snidvongs et al.[407] evaluated the association of osteitis with systemic eosinophilic markers of eosinophilic CRSwNP, a more severe disease subgroup of CRS patients likely to have polyposis, and found a significant correlation between tissue and serum eosinophilia to osteitis.

In conclusion, osteitic bone is recognized as a manifestation of inflammatory changes in paranasal sinus bone that may play a role in refractory CRS. Additional high-level evidence is needed to determine a cause and effect relationship between osteitis and both CRSsNP and CRSwNP.

- Aggregate Grade of Evidence: C (Level 1b: 1 study; Level 2b: 5 studies; Level 3a: 5 studies; Level 3b: 13 studies; Table VII-3).

VII.C.1.e. CRS Pathophysiology Contributing Factors: Reflux. *Because of limited data, CRSwNP and CRSsNP are combined in this analysis.*

Laryngopharyngeal reflux (LPR) is theorized to contribute to the pathophysiology of CRS in 3 possible ways: direct gastric acid exposure to the nasal cavity and paranasal sinuses causing mucosal inflammation and impaired MCC[408]; a vagal-mediated response in the nasal mucosa from esophageal stimulation[409]; and *Helicobacter pylori* infection.[410]

Ulualp et al.[411] demonstrated more pharyngeal acid reflux events in patients with medically refractory CRS (7/11, 64%) vs healthy controls (2/11, 18%). Pincus et al.[412] reported that 25 of 30 patients with refractory CRS had positive pH studies, and 14 of 15 positive pH study patients treated with proton pump inhibitors (PPIs) had improvement of their RS symptoms after 1 month. DiBaise et al.[413] found modest improvement in CRS symptoms in 67% of 18 medically and surgically refractory CRS patients after

TABLE VII-3. Evidence for CRS and osteitis as a contributing pathogenic factor

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Saylam[400]	2009	2b	Prospective cohort study	CRS patients with and without osteitis	SPECT scores, subjective evaluation of treatment and prognosis	Poorer subjective scores of patients with higher SPECT scores, presence of osteitis
Sethi[385]	2015	3a	Systematic review of literature	CRS patients		Osteitis has been found to correlate with mucosal eosinophilia. Only a suggested association exists of CRS and osteitis
Bhandarkar[401]	2013	3a	Systematic review of literature	CRS patients		Osteitis is associated with worse treatment outcomes and with worse disease
Georgalas[402]	2013	3a	Systematic review of literature	CRS patients		Correlation between radiologic severity and extent osteitis exists. No correlation between clinical severity and osteitis
Videler[386]	2011	3a	Systematic review of literature	CRS patients		CT is recommended for identification of osteitis. No evidence of bacteria in paranasal sinus bone. Surgery may incite osteitis
Chiu[384]	2005	3a	Systematic review of literature	CRS patients		The cause of bone remodeling is unknown
Dong[406]	2014	3b	Prospective cohort study	84 CRS patients undergoing ESS and 22 control patients	Tissue samples: biofilm volume, biofilm score, histopathologic bony grade, GOSS, and HU value	The rate of osteitis in CRS was higher by CT and by histopathologic grading. Biofilms were associated with osteitis
Wood[405]	2012	3b	Prospective case control	CRSsNP (n = 8); CRSwNP (n = 8); controls (n = 6)	Presence of bacteria and immune cells in bone removed during ESS or skull base surgery	Bacteria colonies and immune cells in bone were identified in similar number of CRS and controls
Georgalas[403]	2010	3b	Prospective, case control	CRS (n = 102) and controls (n = 68) undergoing sinus CTs	GOSS, LM grading scale	Osteitis was more common in CRS. Strong correlation between previous surgery and osteitis
Telmesani[398]	2010	3b	Prospective case control	CRSwNP (n = 82, divided into primary vs revision surgery	Histopathologic examination of ethmoid bone and mucosa. Disease recurrence	Higher risk of osteitis with worse mucosal pathology and revisions surgery. Osteitis predicted higher recurrence
Cho[399]	2008	3b	Retrospective case control	CRS patients having primary ESS (n = 25); CRS patients having revision ESS (n = 15); controls (n = 25)	Ethmoid NBF; HU; LM scores; bone thickness on CT	NBF higher in revision cases and higher LM scores. CRS groups had increased bone thickness
Giacchi[390]	2001	3b	Prospective case control	CRS patients with ESS (n = 20); controls having CSF leak repair (n = 5)	Ethmoid mucosa and bone evaluated by pathology for mucosal and bone changes	Bone resorption and osteoneogenesis noted in CRS
Kennedy[391]	1998	3b	Prospective case control	CRS having ESS (n = 24); controls (n = 9) undergoing ethmoid surgery	Ethmoid tissue grouped according to histologic appearance of bone and mucosa	Bone remodeling activity was increased in the CRS group compared to controls

(*Continued*)

TABLE VII-3. Continued

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Snidvongs[404]	2013	4	Retrospective cohort	CRSwNP (53%) and CRSsNP (47%) patients receiving surgery	CT, histopathology, endoscopy, and QoL measures. KOS, GOSS	51% of patients had osteitis; higher prevalence with revision surgery. No correlation between QoL and osteitis
Snidvongs[407]	2012	4	Retrospective case study	88 patients with CRSwNP or CRSsNP undergoing ESS	LM scores histopathology, SNOT-22 scores, asthma, aspirin sensitivity	51% of patients had osteitis; tissue and serum eosinophilia correlated with osteitis
Bhandarkar[78]	2011	4	Prospective case series	190 patients with CRS undergoing ESS	LM CT scores, SIT, endoscopy, presence of osteitis on CT, RSDI, CSS	Osteitis correlated with increased age, revision surgery, NPs, asthma, and ASA intolerance, and less postoperative QoL improvement
Lee[392]	2006	4	Prospective case series	Patients undergoing ESS for CRS	Presence of concurrent osteitis based on imaging and histopathology	CT showed osteoneogenesis in 36%, with 53% showing signs of osteitis on pathology
Cho[389]	2006	4	Retrospective case series	Patients undergoing primary ESS for CRS	LM CT scores, HU of ethmoid region on CT, histopathologic analysis of ethmoid mucosa and bone	HUs increased with higher LM. Histopathologic bony grades increased with higher mucosal grades
Kim[387]	2006	4	Retrospective case series	Patients undergoing primary ESS for CRS	CT scans for evidence of hyperostosis, postoperative endoscopic outcomes	60% of patients showed hyperostosis, associated with poorer postoperative outcome

KOS = Kennedy Osteitis Score; NBF = new bone formation.

6 months of PPI treatment for reflux. Neither the Pincus et al.[412] nor the DiBaise et al.[413] study had a control group.

Ozmen et al.[414] showed a higher prevalence of pharyngeal reflux events (29/33) and positive nasal pepsin assay (26/33) in medically refractory CRS patients, as compared to controls (11/20 for each). Loehrl et al.[415] found positive pharyngeal pH probes in 19 of 20 surgically refractory CRS patients, and positive nasal pepsin assays were found in all 5 patients tested.

In a prospective case control study, DelGaudio[416] reported statistically significant higher incidences of reflux events in the distal esophagus ($p = 0.007$), hypopharynx ($p = 0.006$), and nasopharynx below pH 4 ($p = 0.004$) and pH 5 ($p = 0.00003$) in 38 surgically refractory CRS patients as compared to 10 successful ESS patients and 20 normal controls. Wong et al.[417] detected over 800 reflux events at a pH cutoff of <4 in 37 medically refractory CRS patients who were candidates for ESS: 596 at the distal esophagus, 187 at the proximal esophagus, 24 at the hypopharynx, and only 2 at the nasopharynx. Based on their results, Wong's group concluded that nasopharyngeal reflux is a rare event in CRS, and that the pathophysiology of reflux in CRS is likely an alternative mechanism than direct contact with nasal mucosa.[417] Comparing this study to the DelGaudio study,[416] the patients in the cohort in Wong et al.[417] were medically (and not surgically) refractory CRS patients, thereby resembling the successful ESS control group in the DelGaudio study, having significantly less nasopharyngeal reflux events than the patients with refractory CRS. Another significant difference is that the pH cutoff in the Wong et al.[417] article was <4, which may have missed reflux events that occurred between pH 4 and 5. The findings in these studies therefore suggest a larger role for reflux directly affecting the nasal mucosa in more severe cases of CRS that are refractory to surgical management, as compared to less severe CRS cases which can be controlled either medically or surgically.

Jecker et al.[418] reported that 20 surgically refractory CRS patients had significantly more reflux events in the esophagus than 20 healthy control patients. Interestingly, this was not observed in the hypopharynx, suggesting that refractory CRS is associated with gastroesophageal reflux disease (GERD) but not with extra-esophageal reflux (EER).[418] This may suggest a vagally-mediated response.

Včeva et al.[410] reported that *Helicobacter pylori* DNA was identified in the NP tissue of 10 of 35 study group patients, but it was not detected in the concha bullosa

with normal mucosa specimens of 30 control patients, even though *H. pylori* DNA was found in the gastric mucosa samples of all study and control subjects. Ozdek et al.[419] illustrated the presence of *H. pylori* RNA by PCR in 4 of 12 ethmoidal tissue samples in patients with CRS and in none of 13 concha bullosa specimens in patients without CRS. Although these studies suggest that *H. pylori* is associated with CRS, evidence of a causal relationship has not been demonstrated.

PND is a symptom frequently attributed to both reflux and RS. In a randomized-controlled double-blind crossover study of 75 patients with complaints of PND, Vaezi et al.[420] reported improvement of symptoms in 50% of patients treated with a PPI compared to 5% in the placebo arm. The authors concluded that these findings support a role for reflux in PND symptoms.

Data in the published literature are frequently conflicting. A recent evidence-based approach concluded weak support for causation between GERD and RS.[421] There is significant evidence demonstrating a coexistent relationship between reflux and CRS, although causation cannot be clearly demonstrated. It is not entirely clear with the evidence currently available whether extraesophageal reflux of gastric acid directly injures the sinonasal mucosa, whether reflux events cause vagally-mediated neuroinflammatory changes, or if it is a combination of both of these factors.

- Aggregate Grade of Evidence: B (Level 1b: 1 study; Level 2b: 6 studies; Level 4: 3 studies: Table VII-4).

VII.C.1.f. CRSsNP Pathophysiology Contributing Factors: Vitamin D Deficiency. Vitamin D (VD_3) circulates in its inactive form ($25VD_3$) and is converted to its active form ($1,25VD_3$) by 1α hydroxylase in peripheral tissues. This active form has anti-inflammatory and antibacterial actions,[422–424] thus prompting studies on its potential role in CRS, especially CRSwNP, the eosinophilic, Th2-skewed form of the disease. CRSsNP typically represents a different immunologic profile than CRSwNP, with less eosinophilia and less of a Th2 cytokine profile. The literature on the effects of VD_3 on CRS consists primarily of studies comparing CRSsNP to CRSwNP and is limited to case series, case-control, and in vitro studies.

Clinical studies show that VD_3 may not be low in CRSsNP in the absence of smoking exposure. A series of case-control studies have consistently found no significant difference in circulating or sinonasal tissue $25VD_3$ levels of CRSsNP patients vs controls in both adult and pediatric patients.[425–427] Pinto et al.[428] found that African Americans with severe CRS—diagnosed by consensus on symptoms, nasal endoscopy, and CT scan results—had significantly lower serum $25VD_3$ levels than both Caucasian patients and race/sex matched controls. However, the composition of CRS patients was not defined and may have included a heterogeneous group of CRSwNP and CRSsNP. While systemic $25VD_3$ levels are normal in CRSsNP patients, active or passive smoke exposure is associated with decreased systemic and local $25VD_3$ levels in these patients.[427] Consistent with the CRS studies, active smoking was previously shown to decrease serum $25VD_3$ and $1,25VD_3$ in perimenopausal women.[429]

In considering immunologic studies, both Sultan[430] and Mulligan[427] found that CRSsNP sinonasal epithelial cells have the ability to convert $25VD_3$ to $1,25VD_3$. Mulligan et al.[427] found that exogenous cigarette smoke exposure impairs this conversion step. In contrast to CRSwNP, there does not appear to be any relationship between systemic or local dendritic cells and VD_3 in adult or pediatric CRSsNP patients.[425,426]

Others have examined osteoblasts and VD_3 in CRS. Sugimoto et al.[431] showed that ethmoid bone osteoblasts in CRS produced greatest mineralization and secreted greatest osteocalcin (a marker of bone mineralization) when incubated in a VD_3/vitamin K culture solution. Additionally, VD_3/vitamin K–cultured cells produced significantly more transforming growth factor beta 2 (TGFβ2), a cytokine involved in osteoneogenesis. However, the specific form of VD_3 used was not stated and these effects were not apparent when using VD_3 alone. The authors proposed that VD_3 may have a role in modulating optimal sinus bone turnover and speculated whether it might reduce the sinus bone erosion observed in some CRS cases. This work may partly explain the inverse correlation between $25VD_3$ levels and bone erosion noted in some clinical studies.[426,432,433]

Two statements can be made about VD_3 in CRSsNP:

1. CRSsNP is not associated with systemic $25VD_3$ deficiencies
   - Aggregate Grade of Evidence: C (Level 3b: 4 studies; Table VII-5).
2. Smoke exposure in CRSsNP patients can lower systemic and local $25VD_3$ levels
   - Aggregate Grade of Evidence: C (Level 3b: 1 study; Table VII-5)

VII.C.1.g. CRSsNP Pathophysiology Contributing Factors: Superantigens. At this time, a single article reports an association between toxic shock syndrome toxin (TSST-1) superantigen and CRS patients.[434] In this article, CRS patients with and without polyps are noted to have significantly increased *S. aureus* nasal carriage rates and TSST-1 vs controls. Some questions have been raised by experts in the field regarding the reliability of TSST-1 detection in tissue by passive latex agglutination and PCR, as described.

In summary, unlike CRSwNP, there is little to no evidence supporting the role of superantigens in the etiology or pathogenesis of CRSsNP.

VII.C.1.h. CRS Pathophysiology Contributing Factors: Microbiome Disturbance. *Because of limited data, CRSwNP and CRSsNP are combined in this analysis.*

TABLE VII-4. Evidence for CRSsNP and reflux as a contributing pathogenic factor

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Vaezi[420]	2010	1b	RCT (n = 75)	Chronic PND patients randomized to lansoprazole 30 mg BID or to placebo	PND symptoms at 8 and 16 weeks	Therapy significantly improved PND symptoms, suggesting reflux as a causative factor in PND
Loehrl[415]	2012	2b	Case-control	1. Post-ESS with inflammation (n = 38); 2. Post-ESS with no inflammation (n = 10); 3. Controls (no CRS, no ESS; n = 20)	PARE with 24-hour triple-probe pH monitoring at the NPx (events of pH <4 and <5), UES, and the distal esophagus	Patients with persistent CRS after ESS have more reflux at the NPx, UES, and distal esophagus than controls; largest difference is NPx reflux
Ozmen[414]	2008	2b	Case-control	1. CRS (n = 33); 2. Controls (n = 20)	PARE with 24-hour dual-probe pH monitoring	Higher prevalence of PARE and nasal pepsin in CRS suggests an association between CRS and LPR
Jecker[418]	2006	2b	Case-control	1. Recurrent CRS (n = 20); 2. Healthy volunteers (n = 20)	24-hour pH probe monitoring: number of reflux events, fraction of time pH < 4	CRS patients had more esophageal but not hypopharyngeal reflux events
DelGaudio[416]	2005	2b	Case-control	1. Post-ESS with inflammation (n = 38) patients; 2. Post-ESS with no inflammation (n = 10); 3. Controls (no CRS, no ESS; n = 20)	PARE with 24-hour triple-probe pH monitoring at the NPx (events of pH <4 and <5), UES, and the distal esophagus	Patients with persistent CRS after ESS have more reflux at the NPx, UES, and distal esophagus than controls; largest difference is NPx reflux
Ozdek[419]	2003	2b	Case-control	1. Mucosa from 12 CRS patients; 2. Mucosa from 13 controls	*Helicobacter pylori* DNA/RNA	*H. pylori* found in 4/12 CRS patients and 0/13 patients without CRS
Ulualp[411]	1999	2b	Case-control	1. Refractory CRS (n = 11); 2. Healthy controls (n = 11)	PARE documented around UES and lower esophageal sphincter	Higher prevalence of PARE in CRS, suggests GERD contributes to pathogenesis of CRS
Pincus[412]	2006	4	Cohort	30 refractory CRS patients tested for reflux; 15 of 25 patients with reflux treated with PPI	Sinus and GERD symptoms	Improvement in sinus and GERD symptoms, suggests a role for reflux in the pathophysiology of CRS
Wong[417]	2004	4	Cohort	40 patients with CRS	Incidence of PARE with 24-hour 4-probe pH monitoring at the NPx, hypopharynx, proximal esophagus, and distal esophagus	NPx reflux events are rare in patients with CRS; pathogenesis of CRS and reflux likely not direct acid contact
DiBaise[413]	2002	4	Cohort	11 CRS patients tested for GERD and then treated with PPI	Individual sinus symptoms and global satisfaction measured at 12 weeks	High prevalence of GERD in CRS, with symptom improvement after GERD treatment

LPR = laryngopharyngeal reflux; PARE = pharyngeal acid reflux event; UES = upper esophageal sphincter.

Newer methods for bacterial detection have demonstrated that healthy sinuses are not sterile.[435] The Human Microbiome Project has revealed a broad spectrum of microbes associated with human function in health and disease,[436] and the microbiome is proposed to exist as a functional bacterial community[437] rather than a transient assemblage of organisms. The significance of these concepts with respect to CRS is not yet understood. Although the presence of bacteria in sinus cultures continues to be considered pathologic, it is possible that some microbes may serve beneficial roles at the epithelial surface, including pathogen exclusion, production of local antimicrobial

TABLE VII-5. Evidence for CRSsNP and vitamin D as a contributing pathogenic factor

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Mulligan[427]	2014	3b	Case-control	1. 21 control (CSF leak/pituitary tumor patients); 2. 40 CRSsNP; 3. 45 CRSwNP	1. $25VD_3$ level; 2. CYP27B1 gene expression; 3. $25VD_3$ to $1,25VD_3$ conversion	No difference in $25VD_3$ between CRSsNP and controls. Cigarette smoke associated with lower $25VD_3$ level
Wang[433]	2013	3b	Case-control	1. 25 CRSwNP; 2. 20 CRSsNP	1. $25VD_3$ level; 2. Polyp grade; 3. LM score; 4. Total IgE	No difference in $25VD_3$ level between CRSsNP and controls
Mulligan[425]	2012	3b	Retrospective case-control	1. 14 control patients; 2. 17 CRSsNP; 3. 5 CRSwNP; 4. 14 AFRS	1. $25VD_3$ level; 2. Number of CD209+ dendritic cells in nasal biopsy/high-powered field	No difference in $25VD_3$ between CRSsNP and controls
Mulligan[426]	2011	3b	Retrospective case-control	1. 14 control (CSF leak); 2. 20 CRSsNP; 3. 9 CRSwNP; 4. 14 AFRS	1. $25VD_3$ level; 2. Dendritic cells as percentage of total peripheral blood mononuclear cells	No difference in $25VD_3$ between CRSsNP and controls
Pinto[428]	2008	4	Case-control	1. 68 controls; 2. 86 CRS	1. $25VD_3$ level	$25VD_3$ levels are lower in urban African Americans with CRS than controls or whites with CRS
Sultan[430]	2013	5	In vitro	1. 8 patients including healthy, CRSwNP and CRSsNP subjects	1. 1α hydroxylase mRNA/protein staining; 2. $1,25VD_3$ level; 3. Cathelicidin mRNA expression	Human sinonasal epithelial cells express 1α hydroxylase, can generate the active $1,25VD_3$ and cathelicidin
Sugimoto[431]	2007	5	In vitro	1. 6 patients with CRS	1. Osteocalcin concentration; 2. TGFβ concentration; 3. Mineralization area	Vitamin D_3/vitamin K combination creates greatest osteoneogenesis by ethmoid bone osteoblasts

factors, barrier fortification, immune system development, and metabolic functions. To date, much research has focused on bacteria, but host and bacterial interactions with viruses and fungi also are likely at play in shaping the sinus microbiome.

Literature exploring the role of microbes in CRS has historically relied primarily on culture-based methods in both the clinical and research realm. Culture remains the clinical standard, but research into genetics-based techniques has shown that bacterial culture detects only a small percentage of resident bacteria.[438,439] Even dominant bacteria may be identified by culture in less than 50% of cases. [440] Previous culture-independent methods, such as organism-specific PCR assays and immunostaining, provide only limited ability to characterize the microbial community as a whole. This limitation has been recently overcome by 16S ribosomal DNA (rDNA) sequencing.

In health, the anterior nasal cavity, middle meatus, and sphenoethmoidal recess are populated by a temporally stable microbiome[441] that appears to be highly individualized.[442] Yan et al.[441] demonstrated differences between microbiota of the anterior nares vs the deeper anatomic subsites, but a thorough comparison within the sinuses has yet to be published. In contrast to the rich assemblages of bacteria that populate the sinuses in the healthy state, CRS patients are colonized by a similar quantity of bacteria overall, but display qualitatively different microbial communities than their healthy counterparts.[439,443–445] For instance in CRS, next-generation bacterial sequencing methods have noted a larger relative abundance of anaerobes than had previously been identified, perhaps because of the difficulty in growing these species in culture.[330,438,439] Particular species (namely *Lactobacillus* and *Corynebacterium spp*) may be more abundant in the healthy or diseased state, although these preliminary findings have yet to be replicated.[444,446] A preliminary bacterial metagenomics study showed that community-wide alterations in bacteria and their extracellular vesicles were associated with CRS. In this study, CRS patients exhibited more bacterial abundance but less diversity in nasal lavage specimens.[447] In a large cohort of patients, Ramakrishnan et al.[445] examined microbiome alterations by phenotype and noted that CRS patients with asthma or purulence had markedly different microbiota. In this study, the

authors did not find differences in overall diversity indices of CRS patients when compared to controls but demonstrated that bacterial diversity was a predictor of surgical outcome, suggesting that a diverse microbiome may be beneficial to restoration of sinus health.

Although CRS could be associated with shifts in microbiota and may be associated with decreased bacterial diversity, it is unclear whether there is a causal relationship between these alterations and disease progression or if they are a byproduct of either the pathogenic process or ensuing medical therapies.[448] For instance, antibiotic administration results in a dramatic decrease in richness and diversity of resident bacterial communities, as observed in the gut of healthy subjects and in a study of AECRS.[449,450] Observed alterations in local microbiota in CRS may result from repeated and prolonged medical therapies.[439,451] In the Feazel et al.[439] study, prior sinus surgery and the presence of *S. aureus* were also associated with less diversity, but this observation requires further exploration to determine if this is a disease-association or a result of the extensive medical and surgical therapies used in recalcitrant CRS.

In addition to the bacterial dysbiosis that may be present in CRS, the host reaction to microbiota may also be dysfunctional. For example, Aurora et al.[452] found minimal differences between the bacterial and fungal microbiomes of CRS vs healthy subjects, but when peripheral leukocytes were exposed to microbiota, CRS patients produced significantly more IL-5.

Although microbiome studies are in their infancy in CRS, overall composition and diversity disturbances have been observed. It is worth noting that some of these findings have not been replicated, because of small study cohorts and variable experimental methods. The results in the literature are varied and difficult to interpret in aggregate. Although there are common taxa present in both healthy and CRS patients, no consistent enrichment of a particular species has been uniformly identified, although the role of *Staphylococci* remains curious. There is considerable interest and functional relevance in the microbial community that may contribute to sinus health and disease. Further investigations of the sinonasal microbiome may promote better understanding of the disease, leading to novel therapeutic interventions with potential opportunity for personalized medicine.

VII.C.1.i. CRSsNP Pathophysiology Contributing Factors: Anatomic Variation. Anatomic variations that may contribute to the pathophysiology of CRSsNP (ostensibly by narrowing sinus ostia) are generally divided into those that affect the OMC or those that affect frontal sinus drainage, although both pathways may be affected.[16,99,101,102,108,453–459] Examples of OMC variations include concha bullosae, paradoxical curvature of the MT, infraorbital ethmoid (Haller) cells, and NSD. Frontal sinus drainage obstruction may be caused by Type 1–4 frontal sinus cells, supraorbital cells, suprabullar cells, frontal bullar cells, and intersinus septal cells. However, the presence of these anatomic variations in the general population suggests other or additional factors are required to develop CRSsNP and underscores the difficulty of defining anatomic contributions to pathophysiology. Studies reviewing paranasal sinus CTs of patients with and without sinus symptoms are contradictory about whether anatomical variants correlate to sinus disease (typically defined using LM scores). Much of the literature on anatomic variations is older and does not strictly differentiate CRSwNP, CRSsNP, and ARS, but uses CT evidence of RS rather than more accurate symptomatic definitions.

Caughey et al.[101] found patients with infraorbital ethmoid cells had overall increased LM 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 LM scores for maxillary sinuses only. The form of RS (CRS vs ARS) was not delineated.

Jain et al.[16] found a significantly higher average number of anatomical anomalies (accessory ostia, conchae bullosae, infraorbital ethmoid cells, lateralized uncinate processes, and paradoxical MTs) in patients with limited sinus involvement on CT compared to a cohort with pansinusitis or control group without disease. They proposed that these anatomical variants are only related to impairment of the OMC and primary mucosal abnormality is responsible for individuals with more global disease. Sedaghat et al.[458] found sinonasal anatomic variants predispose to progression to CRS in patients with underlying AR. In contrast, Nouraei et al.[457] and Bolger et al.[99] found no relationship between anatomical variations of the MT or other structures that could affect the OMC and impact on LM score. Similarly, Cho et al.[102] noted no correlation between MT variations or NSD and presence of sinus inflammation on CT scan.

Frontal cells are thought to contribute to the development of frontal sinus disease, but are noted to be prevalent in patients without symptoms of CRSsNP.[460–462] In 2 studies 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.[462,463] Additionally, no association was found by DelGaudio et al.[463] between frontal sinusitis and size of the frontal recess. When specifically studying frontal sinus anatomy, DeConde et al.[464] showed that the frontal sinus outflow dimensions, presence of an intersinus septal cell, and an anterior ethmoid artery on the mesentery did not impact QoL gains from endoscopic frontal sinus surgery. However, Lien et al.[461] demonstrated an increased incidence of frontal sinusitis in cells that affect the posterior or posterolateral aspect of the frontal recess (suprabullar, supraorbital, and frontal bullar cells) with no association found with type 1–4 frontal cells. Langille et al.[465] showed a significant relationship between the presence of frontal cells and mucosal thickening on CT imaging.

In conclusion, evidence indicates anatomic variations may contribute to CRSsNP, although some of the data are

conflicting and many studies do not differentiate between CRSsNP, CRSwNP, and ARS. Although there appears to be a causal association in some studies, sinus anatomical abnormalities do not likely play a large role in the pathogenesis of CRSsNP.

- Aggregate Grade of Evidence: C (Level 2b: 3 studies; Level 3b: 4 studies; Level 4: 7 studies). Results of studies are conflicting (Table VII-6).

VII.C.1.j. CRS Pathophysiology Contributing Factors: Septal Deviation. *Because of limited data, CRSwNP and CRSsNP are combined in this analysis.*

NSD is difficult to compare among patients and studies because it may change along the anterior-posterior axis and may be quantified by investigators in different ways.[103,466–469] Moreover, like many studies of anatomic sinus variants and RS, CRS and ARS are often not differentiated in studies on NSD.

Two large reviews have examined the role of NSD and RS. Collet et al.[109] performed a nonsystematic review of 25 papers and found methodologies and results were often contradictory. This review could not establish a definite role for the nasal septum as a pathogenic cause of, nor as a contributing factor, for CRS. More recently, Orlandi[108] systematically reviewed 13 papers and concluded that many of the previous studies were insufficiently powered to establish any association between RS and NSD. By systematically combining the studies, he concluded that NSD is associated with an increased prevalence of RS, although the impact of this anatomic anomaly is limited. Interestingly, the risk of RS increased on both the convex and concave sides, suggesting airflow alterations rather than simple "crowding" of the sinus anatomy may play a role.

Several studies have been published after these reviews. Kamani et al.[470] examined histopathological changes in septal and nasal mucosa of patients with NSD. This study determined significantly higher rates of squamous metaplasia and lymphocytic infiltration in septal mucosa opposite the deviation compared to the control group, implying NSD may render patients susceptible to CRS. Poorey and Gupta[471] found patients with increasing septal angles were associated with a higher incidence of maxillary sinus mucosal changes. The study reemphasized the concept that NSD may lead to obstruction at the OMC. Mundra et al.[472] also found a strong association of increasing angles of NSD with corresponding patterns of disease in the OMC. They concluded that obstruction at the OMC and anterior ethmoid secondary to NSD is a key factor causing CRS. Fadda et al.[473] also found that NSD—as well as other anatomic variants—correlates with the presence of sinus mucosal disease.

In 2008, Mladina et al.[474] classified NSDs into 7 different types and suggested that the degree and the type of septal deformity has importance in nasal and systemic diseases. Poje et al.[475] performed a multicenter comparative study to elucidate whether or not some of the Mladina types of septal deformities are more frequent in CRS patients. The incidence of 1 type of deviation (the "Passali" deformity[474]) was found to be significantly higher in the CRS patient group than in the control group. Similarly, Cingi et al.[476] demonstrated an increased prevalence of so-called vertical septal deformities (Mladina types 2 to 4) among those with CRS.

Contrastingly, Kaygusuz et al.[477] examined patients with CRS who had undergone ESS and found no statistically significant correlation between sinonasal anatomical variations and paranasal sinuses pathologies. They concluded that sinonasal anatomical variation did not increase the possibility of developing CRS and/or increase the severity of preexisting CRS. Prasad et al.[478] similarly found no significant relationship between NSD and CRS.

The aggregate LOE for publications evaluating the correlation of NSD with CRS is grade C, with most studies at level 3 or 4. It should be noted that the apparent limited effect, many studies with small sample sizes, the heterogeneity of the definition of NSD, and the limitations of the univariable analysis complicate drawing firm conclusions on the role of NSD in CRSsNP (Table VII-7).

- Aggregate Grade of Evidence: Grade C (Level 1b: 1 study; Level 3b: 3 studies; Level 4: 6 studies).

VII.C.1.k. CRSsNP Pathophysiology Contributing Factors: Innate immunity. Multiple innate immune mechanisms exist at the sinonasal mucosa 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 complement. One example of a pathogen-specific innate immune mechanism is pattern recognition receptors (PRRs). The 2 best-characterized classes of PRRs are the TLR family and the nucleotide-binding oligomerization domain-like receptors (NLR) family.[480] It has been hypothesized that dysregulation of PRR pathways and innate immune effectors likely contribute to the inflammatory state in CRS.

Studies that have examined the activity of innate immunity in CRSsNP are summarized in Table VII-8. The evidence is presented in 2 categories: (1) key antimicrobial proteins and peptides in innate immunity; and (2) PRRs in innate immunity.

(1) Key antimicrobial proteins and peptides

Five 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 antimicrobial protein was decreased in innate immunity of patients with CRSsNP.

Lee et al.[481] showed that surfactant protein A (SP-A) messenger RNA (mRNA) and protein levels were

TABLE VII-6. Evidence for CRSsNP and anatomic variants as a contributing pathogenic factor

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
DeConde[464]	2015	2b	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[458]	2013	2b	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 1 anatomic variant
Jain[16]	2013	3b	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
Cho[102]	2011	3b	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
Caughey[101]	2005	3b	Case-control series	250 consecutive sinus and orbital CT scans	Presence and size of concha bullosa, infraorbital ethmoid cells, NSDs, and severity of mucosal thickening	Concha bullosa, infraorbital ethmoid cells, narrow nasal cavities associated with sinus disease. No associations of frontal sinus disease and anatomic variants
Jones[466]	1997	3b	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
Eweiss[462]	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
Langille[465]	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
Lien[461]	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[457]	2009	4	Retrospective case series	300 CT scans from patients with symptoms of CRS	Anatomic variants and LM scores	No relationship was a found between anatomical variations and LM score
DelGaudio[463]	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[459]	2004	4	Case series	1450 paranasal sinus CTs examined over a 5-year period	Presence of 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[103]	2004	4	Retrospective case series	CT scans of 1095 consecutive patients with sinus complaints	Presence of concha bullosa, sinus mucosal thickening, and NSD	Concha bullosa significantly correlated to contralateral nasal NSD but not paranasal sinus disease

EMS = ethmomaxillary sinus.

TABLE VII-7. Evidence for CRSsNP and septal deviation as a contributing pathogenic factor

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Orlandi[108]	2010	1b	Systematic analysis	Review of 13 previously published studies	Presence and angle of NSD and presence of RS	NSD is associated with RS. The clinical effect was modest, with OR of 1.47
Kamani[470]	2014	3b	Case-control	20 CRS patients, 10 controls	Squamous metaplasia and lymphocytic infiltration in septal mucosa	NSD predisposes to chronic mucosal inflammation and squamous metaplasia
Poje[475]	2014	3b	Case-control	127 CRS patients, 64 controls	Mladina NSD classification; diagnosis of CRS	Mladina type 7 deformities were found to be significantly higher in the group of CRS patients
Kaygusuz[477]	2014	3b	Case-control	65 CRS patients, 34 controls	Mladina's NSD classification associated to CRS	There was no significant relationship between NSD and CRS
Cingi[476]	2014	4	Case series	505 patients	Mladina NSD classification, diagnosis of CRS	Patients with CRS have a high prevalence of vertical deformities (types 2, 3, and 4)
Mundra[472]	2014	4	Case series	61 CRS patients	OMC disease and anterior sinus mucosal disease in relation to direction of NSD	Strong association of increasing angles of NSD with disease in OMC; no side predilection
Poorey[471]	2014	4	Case series	67 CRS patients	Degree of septal angles, maxillary sinus mucosal changes	Higher degree of NSD associated with obstruction at OMC
Prasad[478]	2013	4	Case series	120 CRS patients	Mladina's NSD classification, diagnosis of CRS	There was no significant relationship between NSD and CRS
Fadda[473]	2012	4	Case series	200 CRS patients	Association between NSD and sinus mucosa disease assessed by CT imaging	Statistically significant association was found between NSD, and the presence of sinus mucosal disease
Li[479]	2012	4	Case series	56 CRS patients	Differences in aerodynamics in patients with mild, moderate, or severe NSD	No aerodynamic differences around the OMC could be detected with increasing severity of NSD

significantly increased in sinonasal tissue of CRSsNP compared to that of normal controls. This study indicated constitutive expression of the SP-A gene in the paranasal sinus mucosa; this expression was upregulated in patients with CRSsNP.

Woods et al.[482] found that immunostaining of lysozyme was significantly increased in mucosal biopsy specimens of CRSsNP compared to control, but not the mRNA level. Schlosser et al.[483] demonstrated that factor B and complement components C3 and C5 mRNA levels were significantly higher in sinus mucosa biopsy specimens of CRSsNP compared to that of control patients. Interestingly, Cui et al.[484] also showed that serum C3 level was significantly increased in CRSsNP compared to controls.

Trefoil factor family (TFF) proteins are involved in epithelial protection and repair. Li and Turner[485] showed that TFF1 and TFF3 mRNAs and protein levels were significant higher in ethmoid tissue of CRSsNP compared to control patients. They concluded that the putative role of TFF peptides may be important regulators of the sinonasal epithelial barrier in patients with CRSsNP.

Cumulatively, these studies suggest that enhanced innate responses may play important roles in the inflammatory response seen in CRSsNP.

On the contrary, another study shows decreased innate peptide activity in CRSsNP, although in a different family of proteins. Richer et al.[486] analyzed the expression of epithelial genes involved in epithelial barrier maintenance and repair in CRS. They collected epithelium from inferior turbinates and uncinate processes and examined mRNA levels of cell-surface proteins S100A7, S100A8, and S100A9. They found that mRNA levels were significantly decreased in CRSsNP when compared with controls. This study indicates that reduction of epithelial genes involved

TABLE VII-8. Summary of studies on altered 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[485]	2014	1. CRSsNP (12); 2. CRSwNP (12); 3. Control (7)	Sinonasal tissue (CRS); sinonasal tissue (control)	RT-PCR; IHC	TFF1, TFF3	TFF1 and TFF3 mRNAs and protein levels were significant higher in ethmoid tissue of CRSsNP vs control	Increased
Woods[482]	2012	1. CRSsNP (37); 2. CRSwNP (39); 3. Control (6)	Sinus mucosa (CRS); sinus mucosa (control)	RT-PCR; IHC	Lysozyme	Lysozyme protein, but not the mRNA, was increased in patients with CRSsNP vs control	Increased
Schlosser[483]	2010	1. CRSsNP (7); 2. AFRS (8); 3. Control (6)	Polypoid/inflamed mucosa (CRSsNP, AFRS); normal mucosa (control)	RT-PCR; IHC	Factor B, C3, C5, C7	Factor B, C3, and C5 mRNAs level were significantly higher in sinonasal tissue of CRSsNP vs control	Increased
Cui[484]	2009	1. CRSsNP (72); 2. CRSwNP (95); 3. Control (110)	Blood (CRS); Healthy blood (control)	ELISA	C3, C4	Serum C3 level was significantly increased in CRSsNP compared with control	Increased
Richer[486]	2008	1. CRSsNP (23); 2. CRSwNP (18); 3. Control (21)	Epithelial cells from the inferior turbinate; nasal polyps; uncinate tissue (CRSsNP, control)	qRT-PCR; IHC	S100A7, S100A8, S100A9	S100A7, S100A8, and S100A9 mRNAs levels in the nasal tissue were significantly decreased in CRSsNP	Decreased
Lee[481]	2006	1.CRSsNP (10); 2. Control (10)	Maxillary sinus mucosal tissues (CRSsNP, control)	RT-PCR; IHC	SP-A	SP-A was increased in CRSsNP vs control	Increased
Pattern recognition receptors							
Detwiller[489]	2014	1. CRSsNP (19); 2. CRSwNP (17); 3. 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[488]	2013	1. CRSsNP (40); 2. CRSwNP (38); 3. Control (23)	Nasal polyps (CRS); nasal tissue (control)	qRT-PCR; IHC	TLR2, TLR4, TLR7	TLR2, TLR4, and TLR7 mRNAs and protein levels were lower in CRSwNP compared to controls	Decreased
Van Crombruggen[487]	2012	1. CRSsNP (22); 2. CRSwNP (19); 3. 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

esRAGE = endogenous secretory RAGE; mRAGE = membrane-bound RAGE; SP-A = surfactant protein A; sRAGE = soluble RAGE.

in epithelial barrier maintenance and repair may contribute to the development of CRSsNP.

(2) PRRs

Although investigations have demonstrated altered regulation and downregulation of PRRs in CRSsNP, all studies to date have shown decreased PRR activity in this condition, with no study yet demonstrating an upregulation of PRRs. Van Crombruggen et al.[487] examined the receptor for advanced 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, whereas the membrane form was decreased. Zhang et al.[488] showed that TLR4 and TLR7 mRNAs and protein levels were significantly lower in sinonasal tissue of CRSsNP compared to that of CRSwNP and controls. Similarly, Detwiller et al.[489] revealed that patients with CRSsNP showed lower mean expression of TLR2 mRNA in mucosal biopsy specimens compared to controls. These studies suggest that altered PRR responses may play a role in CRSsNP.

Summary

In patients with CRSsNP, the data demonstrate that key innate immune mediators are differentially expressed. The current evidence is relatively sparse, with no cohesive picture yet forming. Additional work in this area will shed meaningful light on the pathophysiology of CRSsNP.

VII.C.1.l. CRS Pathophysiology Contributing Factors: Epithelial Barrier Disturbance. *Because of limited data, CRSwNP and CRSsNP are combined in this analysis.*

The sinonasal mucosa functions as an epithelial barrier to an array of exogenous agents, serving to limit and regulate secondary stimulation of the immune response. The basic components consist of a mechanical barrier and an innate immune barrier. When the barrier fails to exclude a pathogen, epithelial-derived cytokines and chemokines act to shape the subsequent immune response. Broadly speaking, CRS has been proposed to be a disease characterized by dysfunctional sinonasal mucosa in which defects at the epithelial surface may underlie the etiology and pathogenesis of the disorder.[490] It has been further suggested that the various phenotypes of CRS, including with or without NPs, may be associated with distinct upstream epithelial defect patterns.[486,491,492]

The mechanical component of the barrier consists of 2 parts, respiratory mucus and underlying epithelium. Respiratory mucus traps foreign material and it is moved toward the nasopharynx. The physical and chemical properties of the mucus likely play a significant role in the efficiency and selectivity of this process. Genetic and acquired defects in mucociliary flow are associated with a high incidence of CRS, and these entail variations in viscosity and ciliary activity.[493–496] Beneath the mucus reside the epithelial cells (ECs), which are linked by tight and adherens junctions. Tight and adherens junctions comprise the apical junctional complex (AJC), creating a relatively impermeable barrier. Exogenous agents often possess protease activity allowing them to degrade the junctional proteins, making the barrier more permeable.[497] The barrier is maintained via ongoing production of AJC proteins as well as protective antiprotease molecules. The polypoid form of CRS and a Th2 cytokine milieu have been associated with significantly decreased levels of AJC proteins[498–501] as well as diminished intrinsic protective antiprotease activity.[486,502] Functional studies have also documented increased barrier permeability in CRSwNP.[500,501,503] It has been further proposed that the protein oncostatin M may play a key role mediating a leaky barrier in polyps.[503] Furthermore, a global gene microarray meta-analysis indicated that polyp epithelia exhibited a less mature gene signature typically associated with an epithelial to mesenchymal transition, which would predict a loss of barrier integrity.[504] Taken together, these studies suggest that mucociliary dysfunction may play a role in the pathogenesis of CRS broadly, whereas a porous barrier is more closely linked to CRSwNP.

The mechanical barrier provides the first line of defense, limiting access of foreign material. A second line of defense is provided by multiple cells types that express PRRs capable of recognizing pathogen associated molecular patterns (PAMPs) present on microbes.[505,506] In order to incite a sustained immune response, cell damage is typically also necessary, and this is associated with the release of endogenous cell products collectively termed damage-associated molecular patterns (DAMPs).[507–509] Multiple classes of PRRs recognize PAMPs and DAMPs (eg, TLRs), and although abnormal receptor signaling has been proposed to contribute to the development of CRS, data are thus far inconclusive.[506,510–513] In addition to classical PRRs, recent evidence has indicated that bitter and sweet taste receptors are also present on ECs, functioning as PRRs by detecting microbial products and triggering enhanced MCC and release of host defense molecules.[354,514]

Nasal ECs, which are typically the first cells to encounter PAMPs, secrete host defense molecules into the nasal mucus at baseline, with levels augmented upon PRR stimulation.[515–517] The pattern of host defense molecule secretion exhibits regional specialization, with high levels of the antibiofilm protein palate, lung, and nasal epithelium clone protein (PLUNC) present at the uncinate process.[518] Presumably, this regional pattern of host defense molecules is mirrored by a complementary regional variation in the local nasal microbiome. Decreased expression of some host defense molecules has been associated with CRS.[334,519–521] A precise molecular pathway for this defect has not been proposed, but the cytokine IL-22 and its receptor IL-22R are key regulators of mucosal host defense,[522] acting in large part through the transcription factor STAT 3.[523,524] Diminished expression of IL-22R[525] and blunting of the STAT 3 pathway[526] have been reported; these defects

appear to be associated with CRS broadly, and are not specific for the presence or absence of NPs.[527] Taken together, these data provided support for the hypothesis that a primary sinonasal innate immune defect may predispose to the development of CRS.[528]

In addition to host defense molecules, ECs respond to PRR stimulation with the secretion of cytokines and chemokines that foster inflammation and attract and activate innate effector cells.[362,515,529–532] In addition, the EC cytokines play a key role in shaping any subsequent adaptive immune response. Cytokine crosstalk between ECs, innate lymphoid cells (ILCs), and dendritic cells matches the appropriate innate and adaptive response to particular foreign stimuli. In health, this maintains mucosal homeostasis with (1) tolerance of allergens and commensals and (2) defense against pathogens. In CRS, the mucosal inflammation remains chronic, with a persistent innate cellular and adaptive response. CRSwNP in whites is most commonly characterized by an excessive Th2 inflammation. In asthma, the specific epithelial cytokines IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) have been implicated in pathogenesis via effects on dendritic cells and type 2 ILCs.[533–535] In support of this hypothesis in CRSwNP, polyps exhibit large numbers of type 2 ILCs[536,537] and dendritic cells.[538,539] The critical upstream epithelial cytokine is not completely clear, but high levels of TSLP activity have been identified in polyp homogenates.[540,541] Some evidence suggests that IL-33 may play a role as well, but these studies have yet to demonstrate increased expression of this cytokine at the protein level in NP tissue.[374,542–544] In regard to IL-25, evidence in CRS is scant. As mentioned earlier in this section EC chemokines also play a major role in the attraction and activation of innate effector cells including eosinophils, mast cells, neutrophils, macrophages, and likely ILCs. Local release of factors from these effector cells is widely believed to be the proximate cause of the tissue damage and remodeling changes associated with both forms of CRS. In regard to pathogenesis, most interest has centered on eosinophils[545] and mast cells,[546,547] although elevated levels of neutrophils and macrophages are also present and phagocytic activity may be impaired in CRS.[548]

ECs express enzymes involved in the generation of reactive oxygen species and reactive nitrogen species that are important in multiple epithelial processes, including mucin production, epithelial repair, innate immunity, and response to environmental toxins.[549] Variations in activity of these enzyme systems have been proposed to impair barrier function and innate immunity in CRS.[550–554] EC enzyme systems also likely contribute to tissue levels of eicosanoids, which have been implicated in subtypes of CRSwNP.[321,555] The overall relevance of these enzymes to CRS remains unclear but at least theoretically, underactivation could predispose to microbial colonization and overactivation could trigger barrier damage and/or inflammation.

CRS has been most frequently characterized by the adaptive immune response present in the tissue, yet it is unclear that these downstream signatures are critical from the standpoint of etiology and pathogenesis. From this latter perspective, CRS has been proposed as a broad disorder characterized by an upstream dysfunctional host-environment interaction at the sinonasal interface.[490] Similar concepts have been proposed with regard to asthma pathogenesis[535] and although the association of asthma and CRS is well established, the prevalence of other chronic inflammatory disorders within the CRS population is close to background.[288,556] These observations suggest that host defects in CRS will be centered in the airway mucosa, giving rise to the "immune barrier hypothesis," which proposes that genetic and epigenetic variation in the coordinated mechanical barrier and/or the innate immune response of the sinonasal epithelium manifests as CRS.[530] Diminished innate host defense coupled with a porous barrier should theoretically lead to altered microbial colonization, accentuated barrier damage, and a compensatory adaptive immune response.[491,528] Although somewhat distinct, CRSsNP and CRSwNP both exhibit innate immune and mechanical barrier defects. The immune barrier hypothesis does not specifically address the Th1 or Th2 subset skewing observed in many CRS subtypes, including the Th2 pattern and B cell infiltrate observed in Western CRSwNP patients.[557,558] This implies additional, as yet undetermined, mechanisms that may be centered on TSLP and ILC signaling and which may foster an inappropriate local adaptive response. An excessive and/or inappropriate Th2 adaptive response in this setting may further compromise barrier function and diminish innate immunity, thereby creating a self-perpetuating cycle of disease.

VII.C.1.m. CRSsNP Pathophysiology Contributing Factors: 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.[559] 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.[560,561] During infection, CBF increases to stimulate mucus clearance[562] as well as to disseminate innate immune products.[563] Microbes directly impact ciliary function, and can often "hijack" normal ciliary regulation to prevent appropriate mucus movement.[560]

In CRS, patients may have dysfunctional ciliary beating from direct effects of the organisms or from an inappropriate inflammatory response. Mucociliary stasis is a common finding of CRS, which propagates the disease because the stagnant mucus can harbor infection and sustain inflammatory mediators.[494] Although 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.[564,565] This blunted response to ciliostimulatory substances may underlie the perpetuation of pathology in CRS. Pathogens such as *P. aeruginosa*, *H. influenzae*, *Streptococcus pneumoniae*, and *S. aureus* secrete toxins that directly suppress ciliary motion.[566–569] 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.[570] *H. influenzae* toxins destroy cilia entirely at high concentrations, resulting in mucus stasis from ciliary loss.[571] 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 causing some of the CRS ciliary pathology. TNF-α, IL-1β, IL-5, and IL-8 are consistently elevated in CRS cases, [572] and chronic elevation of these factors often blunts ciliary response. TNF-α has been shown to prevent CBF increases in response to mechanical stimulation,[573] whereas cycles of inflammation can cause ciliary loss or ciliary abnormalities in a chronic setting.[560] 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, because the cilia have to work harder to transport the same load.[574] Cigarette smokers have increased rates of CRS[575,576] in part because of the reduction in chloride transport caused by compounds in cigarette smoke precipitating a reduction in CBF.[577,578]

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 1 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.[495] Therefore, most effort clinically should be in treating the underlying CRS, as opposed to treating the dysfunctional cilia separately. Topical antimicrobial therapy results in not only symptomatic improvement, but in 1 study of 10 patients also showed an increase in CBF back to expected levels.[579] 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.[580] Other studies have hypothesized that the ciliogenesis process may be dysregulated.[304] 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.[581–584]

VII.C.1.n. CRSsNP Pathophysiology Contributing Factors: Immunodeficiencies. In the subset of adult patients who have CRS that is refractory to usual therapy, PID should be considered. The most common clinical manifestations of PID include chronic otitis media, RS, and chronic lung disease such as pneumonia and bronchiectasis.[585–589] 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.[15,155,590–596] The association is further strengthened by other studies that show an increased incidence of RS in patients with immune dysfunction.[586,587]

CVID, X-linked hypogammaglobulinemia, and several other disorders of humoral immunity are frequently referenced as contributing factors to chronic or recurrent recalcitrant RS.[15,588,589,596–599] A number of selective Ig deficiencies, specifically those involving IgG3 subclass, IgA, and IgM, have been consistently identified in this group of patients.[585,586,590,593,594,596–598,600–602] Preimmunization antipneumococcal titers have been shown to be decreased as well, particularly in patients with the more severe forms of immunodeficiency such as CVID.

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.[596] 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 and exactly which CRS patients benefit most from investigation and treatment of immunodeficiency. Additional research may also define optimal medical and immune supplementation therapy in those with PID and CRS (Table VII-9).

- Aggregate Grade of Evidence: C (Level 2b: 1 study; Level 3b: 8 studies; Level 4: 8 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.
- Benefits-Harm Assessment: The benefits of identifying patients with immune dysfunction outweigh any associated risks.
- Value Judgments: Otolaryngologists may be the first providers to see these patients given the frequent coexistence of immunodeficiency and RS. This provides for 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.

VII.C.1.o. CRSsNP Pathophysiology Contributing Factors: Genetic Factors. With a few notable exceptions, studies of the genetic basis of CRS have mainly

TABLE VII-9. Evidence for CRSsNP and immunodeficiency as a contributing pathogenic factor

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Quinti[597]	2007	2b	Prospective cohort	224 patients with CVID followed for a mean of 11 years	Prevalence of respiratory infections and other conditions at time of diagnosis and after IVIG	Intravenous Ig treatment was associated with reduction in acute infections. Progressive increase in the prevalence of patients with CRS was seen
Magen[601]	2014	3b	Retrospective case-control	Patients with selective IgE deficiency and randomly sampled control subjects	1. Serum total IgE levels; 2. Serum IgA, IgM, IgG levels	Patients with undetectable IgE levels had a higher prevalence of CRS
Cui[484]	2009	3b	Case-control	277 adult Chinese patients with CRS	1. Quantitative serum Ig; 2. Serum MDL levels	Ig and MDL deficiencies were not associated with CRS
Levin[595]	2006	3b	Case series; cross-sectional study	626 pregnant women	1. Serum IgE levels; 2. Diagnosis of RS	Low serum IgE levels were not associated with CRS
Seppanen[591]	2006	3b	Case-control	48 CRS or RARS patients; 50 ARS patients; healthy controls	1. Serum Ig levels; 2. Plasma C3, C4 levels	C4A nulls and low IgA, IgG, IgG1, IgG3, and IgG4 were more common in CRS and RARS. Low levels of IgG4 together with either IgG1 or IgG2 were more common in CRS/RARS patients than ARS patients
Yarmohammadi[587]	2006	3b	Retrospective case-control	113 patients with immune deficiency; 124 patients without immunodeficiency	Immune deficiency-related scores and specific medical conditions	CRS, otitis media, and bronchitis were more common in the immunodeficiency group
Tahkokallio[596]	2001	3b	Case-control	25 patients with severe RARS or CRS and matched controls	1. Serum Ig levels; 2. Pneumococcal antibody responses	Low serum IgA was associated with the presence of RS
Armenaka[594]	1994	3b	Case-control	30 CRS matched to 30 chronic rhinitis patients with normal CTs, and 30 healthy controls	1. Quantitative Ig levels; 2. IgG subclass levels	IgG3 levels are significantly decreased in adults with CRS
Karlsson[598]	1985	3b	Case-control	22 patients with CVID; 18 patients with selective IgA deficiency; 20 controls	Diagnosis of CRS	CRS was only found in patients with CVID, compared to selective IgA deficiency
Carr[277]	2011	4	Case series, retrospective review	129 CRS who had ESS and prior assessment for humoral immunodeficiency	1. Baseline antipneumococcal titers; 2. Functional antibody response	CRS patients had a high prevalence of low preimmunization antipneumococcal titers and specific antibody deficiency

(*Continued*)

TABLE VII-9. Continued

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Alqudah[603]	2010	4	Case series, retrospective review	67 refractory CRS patients who had prior ESS	1. Quantitative Ig levels; 2. IgG subclass levels; 3. Functional antibody response	High prevalence of humoral immune dysfunction in patients with refractory CRS
Bondioni[588]	2007	4	Case series	27 patients with CVID 18 patients with agammaglobulinemia	1. CT evidence of CRS; 2. CT evidence of bronchiectasis	Pulmonary CT findings do not correlate with severity of sinus involvement
Chee[275]	2001	4	Retrospective review	79 adult patients diagnosed with CRS	1. Quantitative serum Ig; 2. Pneumococcal vaccine response; 3. Allergy skin testing; 4. T-cell function	High incidence of immune dysfunction in patients with CRS
Sethi[592]	1995	4	Case series	20 patients with refractory recurrent RS and immunologic abnormalities	1. Serum Ig levels; 2. Functional antibody responses	8 were IgA-deficient, 5 had low Ig with poor vaccine response, and 4 had low Ig with normal vaccine response
Manning[585]	1994	4	Case series, retrospective review	23 adult patients with severe refractory RS and PID	1. IgG subclass levels; 2. Pneumococcal vaccine response; 3. IgA levels 4. Response to Ig therapy	8/23 had IgG3 deficiency with antibody hyporesponsiveness to pneumococcal vaccine; 5/23 had antibody hyporesponsiveness with normal Ig levels
Scadding[602]	1994	4	Case series	74 adult patients with CRS or RARS	Serum levels of total Ig and IgG subclasses	31% had one or more IgG subclass deficiencies, with the majority being IgG3
Snow[599]	1993	4	Case series	13 patients with PID receiving IVIG therapy	1. Past and current sinonasal symptoms; 2. Sinus CT scores	CT findings varied widely. No relationship between CT findings and the start of IVIG

MDL = mannose-binding lectin.

focused on CRS regardless of NP status, making it difficult to determine precisely whether similar genetic variations underlie the CRSwNP and CRSsNP phenotypes. A genetic basis to CRS has long been suspected from aggregation studies showing clustering of CRSwNP in families[604–606] and by monogenic disorders that include CRSwNP in their phenotype. The concept of a genetic basis to CRS is further supported by genetically modified (knockout) mouse studies where altered function of certain specific genes are associated with development of signs and nasal findings reminiscent of human CRS.[607]

In cystic fibrosis (CF), mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene are associated with development of CRS in a high proportion of affected individuals.[608] However, disease evolution cannot be predicted according to identified genotype.[609] Other monogenic diseases include CRS in their phenotype. Primary ciliary dyskinesia (PCD) is associated with RS as 1 of the elements of disease presentation.[610,611]

Although genetic syndromes with CRS implicate genes logically linked with disease such as epithelial function[612] and defects in innate and adaptive immunity,[7] this is not always the case. Numerous genetic associations have been suggested that are difficult to link mechanistically to CRS development.[613] This underlines both the potential power of these technologies to identify novel mechanisms and pathways implicated in CRS development and the need for more research in this promising area.

Screening for genetic associations has been dramatically simplified by the use of single-nucleotide polymorphisms (SNPs) as markers of gene variation and position.[614] Unfortunately, all published gene association studies in CRS lack the power to conclusively demonstrate association at a significance approaching that seen in other diseases. Investigators have nevertheless suggested a number of candidate genes associated with CRS, which has led to some interesting observations with intriguing implications. Reviews of genetics of CRS[615–617] have been presented elsewhere and identified genes are presented as a tabulated list (Table VII-10).

In the sole article assessing CRSsNP separately from CRSwNP, Zhang et al.,[618] in Han Chinese in China, compared genetic variations in the acetyl hydroxylase (AOAH) gene in 300 CRSwNP, 300 CRSsNP, and 300 control subjects. Differences in the p value and risk for both CRSwNP and CRSsNP populations, as well as genetic variations in the AOAH gene, were only seen in the CRSsNP group (CRSsNP: OR, 0.30, $p = 8.11 \times 10^{-11}$; CRSwNP: OR, 0.96, $p = 0.64$). This suggests that different mechanisms may underlie the development of CRSsNP and CRSwNP, again highlighting the need for more studies in other populations.

Three candidate SNPs have been replicated in separate publications: TNF,[619–623] IL1A,[619,624] and AOAH.[613,618] TNF and IL1A are important proinflammatory cytokines, and AAOH inactivates lipopolysaccharides.[625] This suggests that dysregulated inflammatory responses may play

TABLE VII-10. Genes implicated in the pathogenesis of CRS

Gene name	Reference	Year	Phenotype (if delineated)
Immune function			
ALOX5	Al-Shemari[628]	2008	
ALOX5AP	Al-Shemari[628]	2008	
AOAH	Bossé[613]	2009	
AOAH	Zhang[629]	2011	CRSsNP
BDKRB2	Cormier[630]	2014	
CD58	Pasaje[631]	2011	CRSwNP
CD8A	Alromaih[632]	2013	
CDH23	Cormier[630]	2014	
CNTN5	Cormier[630]	2014	
COX2	Sitarek[633]	2012	
CYSLTR1(X)*	Al-Shemari[628]	2008	
HLA-DQB1	Schubert[634]	2004	CRSwNP
IL10	Bernstein[635]	2009	
IL10	Zhang[618]	2012	
IL1A	Karjalainen[636]	2003	
IL1A	Mfuna Endam[624]	2010	
IL1A	Erbek[619]	2007	
IL1B	Bernstein[635]	2009	
IL1B	Erbek[619]	2007	
IL1RL1	Castano[637]	2009	
IL1RN	Cheng[638]	2006	
IL22RA1	Endam[639]	2009	
IL33	Buysschaert[640]	2010	
IL4	Zhang[641]	2012	
IRAK-4	Tewfik[626]	2009	
IRAK-4	Zhang[629]	2011	CRSwNP
K6IRS2	Cormier[630]	2014	
K6IRS4	Cormier[630]	2014	
K6IRS4	Cormier[630]	2014	
MET	Sitarek[633]	2012	
MET1	Castano[637]	2009	
MMP9	Wang[642]	2010	
NOS1	Castano[637]	2009	
NOS1	Zhang[629]	2011	
NOS1AP	Zhang[629]	2011	
PDGFD	Cormier[630]	2014	
PI3Kγ	Bojarski[621]	2013	

(*Continued*)

TABLE VII-10. Continued

Gene name	Reference	Year	Phenotype (if delineated)
PRKCH	Cormier[630]	2014	
RAC1	Cormier[630]	2014	
TGFß1	Kim[643]	2007	
TAS2R38	Adappa[353]	2014	
TAS2R38	Mfuna Endam[644]	2014	
TNFA	Batikhan[620]	2010	
TNFA	Bernstein[635]	2009	
TNFA	Erbek[619]	2007	
TNFAIP3	Cormier[645]	2009	
TP73	Tournas[646]	2010	
Epithelial/extracellular matrix function			
IGFBP7	Cormier[630]	2014	
LAMA2	Bossé[613]	2009	
LAMB1	Bossé[613]	2009	
LF	Zielinska-Blizniewska[647]	2012	
Solute carriage			
CACNA1I	Bossé[613]	2009	
CACNA2D1	Cormier[630]	2014	
CACNG6	Lee[648]	2010	
KCNAM1	Purkey[627]	2014	
KCNQ5	Purkey[627]	2014	
KIAA1456	Bossé[613]	2009	
SLC13A3	Cormier[630]	2014	
Other/unknown function			
C13orf7	Cormier[630]	2014	
CIITA	Bae[649]	2013	CRSwNP
DCBLD2	Pasaje[650]	2012	CRSwNP
DPP10	Kim[651]	2015	CRSwNP
FAM79B	Cormier[630]	2014	
GFRA1	Cormier[630]	2014	
MSRA	Bossé[613]	2009	
MUSK	Bossé[613]	2009	
NARF	Cormier[630]	2014	
NAV3	Bossé[613]	2009	
OSF-2	Zielinska-Blizniewska[647]	2012	
PARS2	Bossé[613]	2009	
PHF14	Cormier[630]	2014	
PIGT	Cormier[630]	2014	
RPGR	Bukowy-Bieryłło[652]	2013	
RYBP	Bossé[613]	2009	
RYBP	Cormier[630]	2014	
SERPINA1	Kilty[653]	2010	
TOMM34	Cormier[630]	2014	
TRHDE	Cormier[630]	2014	
TRIP12	Bossé[613]	2009	
UBE3A	Cormier[630]	2014	
UBE3A	Cormier[630]	2014	
UBE3C	Pasaje[654]	2011	CRSwNP

(*Continued*)

a role in genetically-determined CRS. It is unclear whether the gene variation(s) associated with CRS favors increased or reduced inflammation.

Relevance of other reported candidate genes may be supported by demonstration of a functional impact of the candidate genotype. Studies with functional impact include interleukin-1 receptor-associated kinase 4 (IRAK-4), where candidate SNPs identified in the CRS population are associated with genotype-specific variation in IgE level.[626] Gene variations in the TAS2R38 taste receptor[353,354] are associated with gram-negative bacterial carriage and poor response to surgery.

Certain SNPs not associated with immune function may also be implicated. Among possible candidates are epithelial and ECM dysfunction. Top candidate SNPs in a modified genomewide association study of refractory CRS identified SNPs in 2 genes coding for elements of ECM as top candidates.[613] This suggests that dysfunction in ECM composition or of ECM–integrin interactions may be implicated in CRS.

In the only study of pediatric CRS, Purkey et al.[627] demonstrated variations in the KCNAM1 and KCNQ5 genes, suggesting that potassium channel genes may play a role in early developing CRS. The role of potassium channel dysfunction in development of CRS remains to be described, but may involve altered solute balance and/or focal adhesion mechanisms important for epithelial cell regulation. This underlines the power of these evolving technologies for identifying new mechanisms.

Although clearly still in its infancy, identification of genetic components will continue to progress with discovery of novel genes and gene mechanisms through advances in technology and sequencing of the genome. Intriguing concepts continue to emerge that anticipate further exciting developments.

TABLE VII-11. The diagnostic criteria for CRSsNP

Greater than or equal to 12 weeks of:
2 or more of the following symptoms:
Mucopurulent discharge (rhinorrhea or PND)
Nasal obstruction and congestion
Decreased or absent sense of smell
Facial pressure or pain
AND
1 or more of the following findings:
Evidence of inflammation on paranasal sinus examination or CT
Evidence of purulence coming from paranasal sinuses or OMC
AND
Lack of polyps

VII.D. CRSsNP: Diagnosis

CRSsNP is defined in Section IV.B. The symptoms associated with CRS can be grouped into 4 categories[9]: nasal symptoms (obstruction, discharge, absence or impairment of sense of smell); facial symptoms (facial pressure, facial pain, headache); oropharyngeal symptoms (ear pain, halitosis, PND, dental pain, cough); and systemic symptoms (general malaise, fatigue). The most common symptom is nasal obstruction.[617] These symptoms are highly sensitive individually, but not specific.[655,656] Evidence has shown combining 2 or more symptoms together along with objective findings of disease (imaging, endoscopy) substantially increases diagnostic specificity and positive predictive value.[9,15,657] Although the original guidelines used major and minor criteria,[11] there has been no consensus or evidence whether this categorization is based on prevalence, sensitivity, or specificity of symptoms. As a result, the present definition includes the most sensitive symptoms as part of the diagnosis. Other symptoms such as halitosis, dental pain, and cough may be present and related to the patient's CRS, but are not included in the diagnosis definition. The evidenced-based definition of CRSsNP is shown in Table VII-11.

Dividing CRS into categories of polyposis and no polyposis is supported by histologic and inflammatory cytokine findings in CRS without polyposis.[9,658] Differences in treatment responses and recurrence rates of the disease also support separating the categories,[659] with CRSsNP showing improved outcomes to standard treatments and a decrease in recurrence rate. However more precise biomarker-based categorization may be possible in the near future.

VII.D.1. CRSsNP Diagnosis: Differential Diagnosis

Because of the broad differential for CRSsNP, it is frequently not easy to differentiate it from other diseases without diagnostic modalities including nasal endoscopy and radiologic examination.[660,661] AR is a hypersensitivity of the nasal mucosa to foreign substances mediated through IgE antibodies.[662] In most cases, sneezing and itching are clues to distinguish AR from CRS, though not in all cases.[663] 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.[271,664] Although only a small proportion of patients with purulent CRS without coexisting chest disease complains of cough, CRS should be differentiated from GERD 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.[665–667] 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 as well. 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.[668] History of trauma and surgery, and salty taste of discharge are important clues for diagnosis.[669] Detection of β2-transferrin in nasal secretions confirms CSF.[670]

VII.D.2. CRS Diagnosis: Cost Effective Work Up

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

Prior evidence-based reviews have generally lacked recommendations for the cost-effective diagnosis of adult CRS. Since 1997, expert groups on RS have proposed different diagnostic criteria for RS, with varying combinations of symptoms and symptom duration, but more recent iterations require confirmation with CT imaging or endoscopy to arrive at a CRS diagnosis.[7,15,21,155,202,671,672]

Despite the requirement to document objective findings of sinonasal inflammation, few studies have addressed the timing and sequence of testing used to validate a CRS diagnosis in an accurate and cost-efficient manner. Published algorithms recommend establishing a symptom-based definition of CRS through the patient history, followed by nasal endoscopy.[673–675] Diagnostic imaging, especially CT imaging, has been recommended for symptomatic patients with equivocal or normal findings on endoscopy.[676] A 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, and potential complications related to

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 United States, based on existing evidence (Table VII-12).

VII.D.2.a. CRS Diagnosis Using "Symptoms Alone"

The symptom-based component for CRS diagnosis currently emphasizes the 4 cardinal symptoms of nasal obstruction, nasal discharge, facial pain or pressure, and reduction or loss of smell and no longer utilizes minor symptoms (headache, fever, halitosis, fatigue, dental pain, cough, and ear symptoms) because of their frequent absence in CRS and overlap with other medical conditions.[11,655,656,661] Of the cardinal symptoms, prior studies consistently show that discolored nasal discharge and smell loss—individually and especially in combination—enhance the positive predictive value of symptom criteria for CRS diagnosis.[656,660,676,677] 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.[660,675,678,679] Other studies suggest that facial pain (but not pressure) is not universal and its presence may also decrease the likelihood of a CRS diagnosis.[676–678] Together, these studies suggest that refining symptom wording and increasing the emphasis of specific symptoms (eg, smell loss) can change the probability of CRS diagnosis. They also demonstrate that using symptoms alone to diagnose CRS is not a cost-efficient strategy for most patients given the expected pretest probability of CRS among an appropriately symptomatic population. Prior studies comparing symptoms against a CT gold standard have suggested the specificity of symptoms in the range of 2% to 12% and positive predictive values ranging between 35% and 54%.[7,655,657]

- Aggregate Grade of Evidence: B (Level 2b: 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 (eg, time lost from work and potential adverse effects from treatments).
- Cost: Low–performed at all specialist and nonspecialist visits.
- Benefits-Harm Assessment: Harm over benefit, if used as the sole clinical method for CRS diagnosis, because 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.

VII.D.2.b. CRS Diagnosis with Nasal Endoscopy

The diagnostic utility of nasal airway examination to evaluate for CRS is well established in the literature.[676,680–682] Although anterior rhinoscopy may reveal mucopurulent drainage or severe nasal polyposis, this examination technique may not consistently provide sufficient illumination and visualization of structures beyond the inferior turbinate. Nasal endoscopy provides a more thorough examination of sinus drainage pathways in the middle meatus, sphenoethmoidal recess, and nasopharynx. Applicable findings for CRSsNP include purulent mucus in the sinonasal cavities or less specifically, mucosal edema of the middle meatus or ethmoid regions. Additionally, nasal endoscopy can assist with obtaining cultures of targeted sinonasal locations and evaluating for alternative pathologies that may be symptomatically similar to CRS, such as intranasal tumors, adenoid hypertrophy, or posterior NSDs. 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[657] 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.

From a cost-efficiency standpoint, nasal endoscopy is an important diagnostic tool in individuals with a high pretest probability for CRS, as determined by their symptoms. When performed by experienced specialists, nasal endoscopy is regarded as a safe and effective method to evaluate patient symptoms that are concerning for CRS. If appropriate endoscopic findings are found for CRS diagnosis, additional imaging for diagnostic confirmation may not be unnecessary, although it may still be indicated for preoperative planning or evaluation of complications arising from RS. It is also cost-inefficient to obtain a CT to confirm the diagnosis if the nasal endoscopy is suggestive of CRS.[676] Alternatively, a negative endoscopy in a symptomatic patient also decreases the likelihood of CRS to about 20%.[657,676] Therefore, although nasal endoscopy entails significant upfront costs related to the purchase, maintenance, and processing of equipment along with the expertise of specialists, the evidence supports its use as a cost-effective strategy related to potentially avoiding the need to obtain a CT scan of the sinuses.

Despite the high specificity and positive predictive value of nasal endoscopy in confirming a CRS diagnosis,

TABLE VII-12. Evidence for cost-effective diagnosis of CRSsNP and CRSwNP

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Symptom-based criteria						
Amine[675]	2013	2b	Cohort study	1. Patients with 2 or more CRS-associated symptoms; 2. patients with 1 CRS-associated symptom	Diagnosis of CRS based on CT imaging or endoscopy	Patients with more CRS symptoms had a higher likelihood of CRS diagnoses confirmed by CT. Nasal obstruction was the most sensitive, while hyposmia was the least sensitive
Ferguson[677]	2012	2b	Cohort study	1. CRS-associated symptoms and radiographic evidence of CRS; 2. 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[678]	2011	2b	Cohort study	Patients with active CRS symptoms but negative endoscopy	LM grading of CT scans	Nasal obstruction was the only presenting symptom positively associated with positive scan results
Pynnonen[656]	2007	2b	Cohort study	Patient presenting for evaluation of CRS-associated symptoms		The prevalence of CRS was 60% in patients complaining of CRS-associated symptoms, with chronic purulent rhinorrhea and hyposmia individually and in combination as significant predictors of CRS diagnosis
Tahamiler[688]	2007	2b	Cohort study	1. CRS-associated symptoms and atopy; 2. 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[660]	2006	2b	Cohort study	1. CRS-associated symptoms and radiographic evidence of CRS; 2. 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[655]	2003	2b	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[661]	2002	2b	Cohort study	Patients meeting subjective criteria for definition of CRS	History, physical examination including anterior rhinoscopy and endoscopy, and upfront CT imaging	47% concordance between subjective symptomatology and CT imaging for a CRS diagnosis. There was no significant difference between symptom severity and CT positivity

(*Continued*)

TABLE VII-12. Continued

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Dietz de Loos[689]	2013	4	Case-control study	1. CRSwNP; 2. CRSsNP	Scoring of each patient-reported symptoms (RSOM-31)	Total symptomatology scores were similar, though specific symptom prevalences differed between groups
Tan[676]	2013	4	Case-control study	1. CT-confirmed CRS; 2. 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						
Wuister[681]	2014	2a	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[682]	2010	2b	Cohort study	Patients presenting for evaluation with facial pain	Diagnosis of CRS based on nasal endoscopy findings and CT imaging	Good correlation between nasal endoscopy findings and CT imaging results
Bhattacharyya[657]	2010	2b	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[680]	2002	2b	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, whereas negative endoscopy correlated to a lesser degree with CT imaging
Diagnostic imaging						
Tan[686]	2011	1b	Randomized control trial	1. Symptoms suggestive of CRS but negative nasal endoscopy who received point-of-care CT scan at the initial visit; 2. 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[684]	2014	2c	Economics-based decision analysis model	1. Patients with presumed CRS diagnosis based on symptomatology but negative endoscopy in the primary care setting; 2. Patients who received upfront CT scans in the primary care setting	Standardized costs incurred for diagnostic, treatment, and potential adverse event costs were calculated for each study group	Use of CT in the primary care setting can save US$297–US$321 in costs per patient when compared to diagnosing based on symptoms alone
Leung[685]	2011	2c	Economics-based decision analysis model	Two algorithms were evaluated: 1. Upfront CT for patients with CRS-associated symptoms but negative endoscopy; and 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

endoscopy is notably less sensitive and thus has a high false-negative rate compared to CT. Published estimates of sensitivity and false-negative rates are 30% to 46% and 35% to 70%, respectively, when compared to CT.[657,675,680–682] The lower sensitivity is related to the difficulty or inability of rigid and flexible endoscopy to assess the interior of all of the sinonasal cavities, especially in unoperated patients.

- Aggregate Grade of Evidence: B (Level 2a: 1 study; Level 2b: 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 endoscopy exam will still require a CT scan of the sinuses because of the potential for a false-negative endoscopy. Mild discomfort associated with the procedure.
- Cost: For 2014, the Centers for Medicare & Medicaid Services (CMS) in the United States set a national payment average for a diagnostic nasal endoscopy (Current Procedural Terminology code 31231) at US$212.07, which accounts for both service and facility reimbursements for the diagnostic intervention. 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.
- 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 instead of nasal endoscopy.

VII.D.2.c. CRS Workup with Diagnostic Imaging

Practice guidelines acknowledge that CT imaging, as opposed to the plain radiography or MRI, is the diagnostic modality of choice for confirming CRS[683] or as an alternative to nasal endoscopy.[4] Some guidelines, however, suggest that CT imaging as a diagnostic modality is not essential in all cases, but should only be considered in situations with disease that is refractory to maximal medical therapy, or for surgical planning.[7,202,671] Other studies examining costs and expected treatment outcomes for correct and incorrect CRS diagnosis suggest that upfront CT imaging for specialty care patients with a negative endoscopy or primary care patients is less costly than an extended course of symptom-based empiric antibiotic therapy.[675,684] Based on CMS costs and published drug cost information in the United States, an extended course of antibiotic therapy is similar to that of obtaining a CT, and adopting an upfront CT results in substantially reduced antibiotic utilization in symptomatic patients with alternate diagnoses such as rhinitis or atypical facial pain.[685,686] These benefits are traditionally weighed against additional imaging-related concerns such as radiation exposure and access. The availability of alternative CT imaging modalities such as 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.[687] Despite this, it is still important that practitioners obtain imaging when patients are not having an isolated acute URI, because radiologic changes in ARS and CRS are similar. 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 skull-base integrity, or tumor-associated sinonasal inflammation.

- Aggregate Grade of Evidence: B (Level 1b: 1 study; Level 2c: 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 2014, the CMS-based national average payment for CT imaging without contrast material of the maxillofacial area (Current Procedural Terminology code 70486) was US$208.85. 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.
- Benefits-Harm Assessment: Variable, dependent on the pretest 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 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 preoperative planning. It is an option for confirming CRS instead of nasal endoscopy.

VII.E. CRS: Management

This discussion focuses on CRSsNP management (Fig. VII-1). The management of AECRS is discussed in Section IX.C.

VII.E.1. CRS Management: Saline Irrigation

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

Nasal saline irrigation is a common treatment adjunct in the management of CRS. The favorable safety profile, lack of systemic pharmaceutical absorption risk, and patient acceptance make it an appealing long-term topical therapy strategy.[690] Although irrigation solutions often include either isotonic (ie, normal) or hypertonic saline, there is substantial variability in the volume (low or high), pressure (passive or active), and frequency of saline irrigation protocols. Adverse effects of saline irrigations are rare, but include local irritation, ear pain, nose bleeds, headache, nasal burning, nasal drainage, and bottle contamination.[690,691]

This review identified 12 studies evaluating saline irrigation for the management of CRS (10 RCTs, 1 systematic review, and 1 meta-analysis).[206,209,692–701] (Table VII-13). Five RCTs evaluated saline irrigation in patients who had not undergone surgery. All 5 demonstrated improved symptoms and QoL outcomes in patients with CRS. The randomized trials by Bachmann et al.[692] and Hauptman and Ryan[206] evaluated the effects of isotonic and hypertonic saline irrigations and demonstrated that both solutions improve sinonasal symptoms, although there were no significant differences between groups. The study by Rabago et al.[209] randomized patients into 2 groups (hypertonic saline irrigations and no treatment) and evaluated CRS-specific QoL, general QoL, symptom scores, and medication usage. The results demonstrated that daily hypertonic nasal saline irrigations significantly improved CRS-specific QoL, symptom scores, and decreased medication usage. However, there was no difference in the general QoL outcomes using the SF-12 questionnaire. The randomized trial by Heatley et al.[697] compared isotonic saline irrigations, using both bulb syringe and pot irrigations, to reflexology as a control. The results demonstrated that all groups received CRS-specific QoL improvements, and surprisingly there were no difference between the reflexology and saline irrigation groups. The highest quality randomized trial by Pynnonen et al.[700] compared high-volume (240 mL) low-pressure isotonic saline irrigation to low-volume saline spray and evaluated CRS-specific QoL (SNOT-20) and symptom scores at 2, 4, and 8 weeks posttreatment. The results demonstrated that both groups received improvement in QoL at 8 weeks; however, there was a significantly larger improvement in both outcome measures in patients using high-volume saline irrigations.[700]

Two randomized trials by Friedman et al. in evaluated the effectiveness of Dead Sea salt (DSS) irrigations on QoL.[694,695] The salt and mineral content of DSS has been reported to have beneficial anti-inflammatory effects. The 2006 study failed to report the CRS cohort surgical history and the 2012 study included CRS patients with and without prior ESS. The 2006 study evaluated DSS irrigations (did not state the volume or delivery device) compared to hypertonic saline irrigations and demonstrated that DSS irrigations were superior to hypertonic saline irrigations in symptom and QoL improvement. The 2012 study compared DSS irrigations (syringe 20 mL per naris BID) to hypertonic saline irrigations plus INCS. The outcomes demonstrated that the DSS irrigations alone were as effective as hypertonic irrigations plus once daily INCS.

The systematic review and meta-analysis by Harvey et al.[696] included 8 studies that evaluated the following designs: saline vs no treatment; saline vs placebo; saline as an adjunct to INCS therapy; saline vs INCS therapy; and isotonic vs hypertonic saline irrigations. A few studies included pediatric patients with CRS and AR. The results showed that saline irrigations improve symptom outcomes when used as the sole CRS treatment modality; however, saline was shown to be less effective compared to INCS therapy. There is evidence to support that saline can improve symptoms when used as an adjunct to INCS therapy. Isotonic and hypertonic saline solutions appear to have similar effects on patient symptoms and QoL; however, hypertonic solutions may improve objective outcomes, such as radiographic imaging. van den Berg et al.[701] reported in their systematic review that the 2007 RCT by Pynnonen et al.[700] was the only study of high enough quality to discuss, and therefore concluded that high-volume normal saline irrigations may provide better outcomes compared to low-volume saline sprays in the management of CRS.

There is substantial evidence to support the use of nasal saline irrigations in the management of CRS. Because of the excellent safety profile of saline irrigations and low cost (approximately US$0.24 per day),[702] there is a preponderance of benefit over harm. Isotonic saline irrigations may produce minor adverse events in 5% to 10% of cases, including nasal burning, ear plugging, and nausea. Evidence suggests that hypertonic saline irrigations may result in a higher rate of minor adverse events (10-25% of cases). No major adverse events were recorded from a meta-analysis of 22 trials.[696] However, in 2011, there were 2 deaths from amoebic meningoencephalitis suspected to be related to irrigating with *Naegleria fowleri*–contaminated water.[703] Until further research elucidates the safety of using tap water, it is recommended to use a clean water source (avoiding well water) for irrigation solution.

Bacterial contamination of saline irrigation bottles has been reported in up to 50% and 80% of bottles after 1 and 2 weeks, respectively.[691] Although there is no association between irrigation bottle contamination and clinical infection for patients with CRS, it has been suggested to regularly disinfect and replace bottles. A recent review suggests that postirrigation microwave decontamination is an effective disinfecting strategy.[704]

Given the preponderance of benefit in combination with an aggregate grade A of evidence, a "Strong

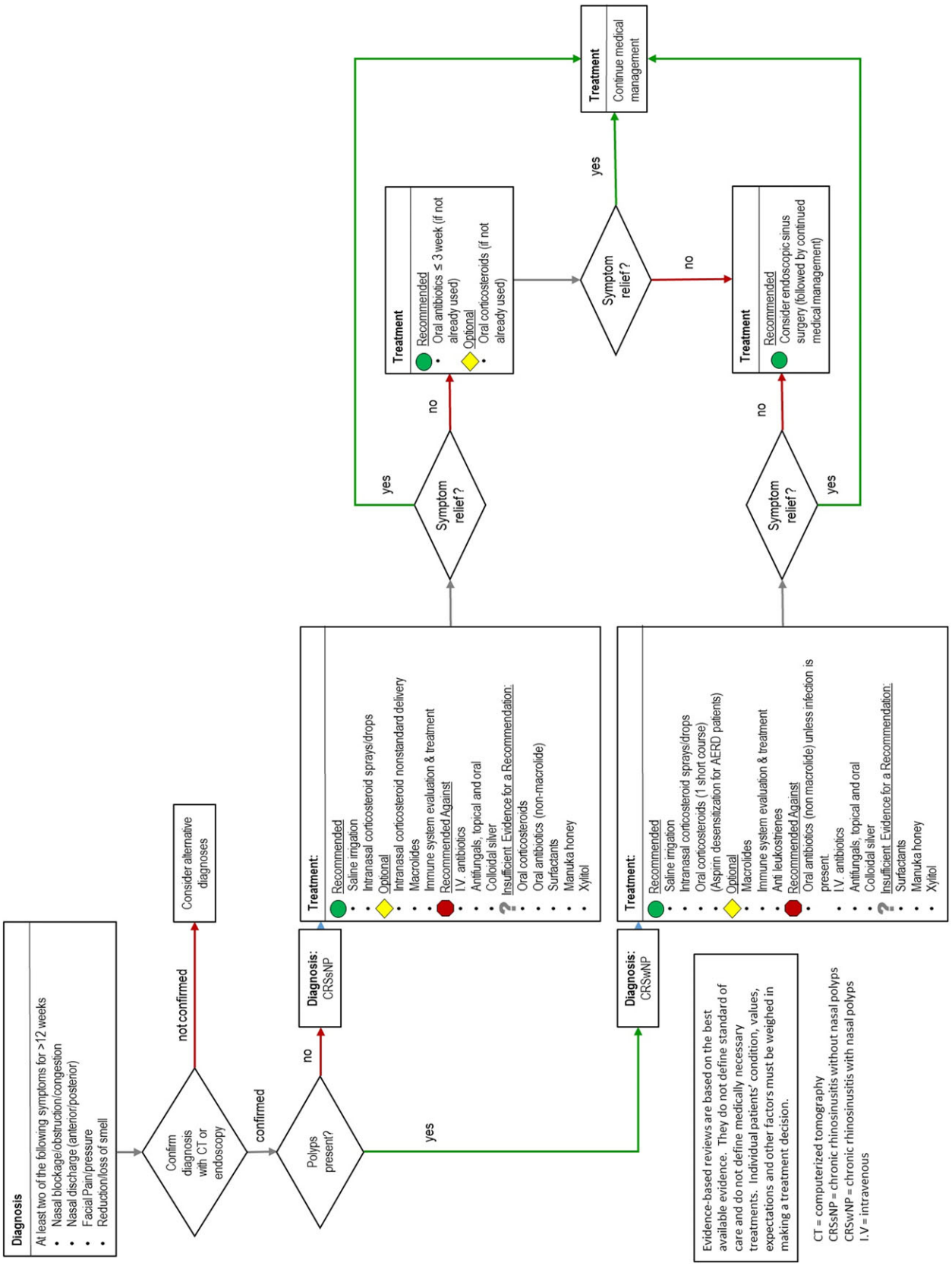

FIGURE VII-1. Evidence-based recommendations for diagnosis and treatment of chronic rhinosinusitis.

TABLE VII-13. Evidence for CRSsNP and CRSwNP management with saline irrigation

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Harvey[696]	2007	1a	Meta-analysis	CRS patients	1. QoL; 2. Symptom; 3. Radiologic	Saline irrigations improve CRS symptoms as a sole modality and as an adjunct to INCS. Not as effective as INCS
Friedman[694]	2012	1b	RCT, double-blind	1. Dead sea salt irrigation; 2. Hypertonic saline + INCS	1. QoL (SNOT-20); 2. Endoscopy	Dead sea salt irrigation alone was equally as effective as INCS + hypertonic saline
Liang[698]	2008	1b	RCT, no blinding	CRS patients after ESS treated with: 1. NS plus debridement; 2. Debridement alone	1. Symptoms; 2. Endoscopy	Mild CRS had better symptom and endoscopy scores with irrigations added. No difference in moderate-severe CRS
Hauptman[206]	2007	1b	RCT	1. NS; 2. Hypertonic saline	1. Symptoms; 2. Acoustic rhinometry; 3. Saccharine clearance	Both treatments improved nasal stuffiness and obstruction. NS improved nasal airway patency
Pynnonen[700]	2007	1b	RCT	1. High-volume, low-pressure NS irrigation; 2. NS low-volume spray	1. QoL (SNOT-20); 2. Symptom	SNOT-20 improvement in both groups. High-volume low-pressure irrigation group received more
Friedman[695]	2006	1b	DBRCT	1. Dead Sea salt irrigation; 2. Hypertonic saline irrigation	RQLQ	Dead Sea salt irrigations received better symptom relief compared to hypertonic saline irrigations
Pinto[699]	2006	1b	DBRCT	1. NS; 2. Hypertonic saline; 3. No irrigations	Symptoms	No difference in symptoms between NS and no irrigation. Worse pain and nasal drainage with hypertonic irrigation
van den Berg[701]	2014	2a	Systematic review	Saline therapy for CRS	Only included and discussed 1 study with high enough quality	High-volume NS irrigation provides better QoL improvement then low-volume NS spray
Freeman[693]	2008	2b	RCT, no blinding	1. NS (low volume atomized spray); 2. No irrigations	Endoscopy	NS provided early (3 weeks) endoscopic improvement. No difference in long-term (3 months) endoscopic findings
Rabago[209]	2002	2b	RCT, no blinding	1. Hypertonic saline; 2. No treatment	1. QoL (RSDI; SF-12); 3. Symptom score)	Hypertonic saline irrigation improved RSDI and symptom scores. No improvement in SF-12
Heatley[697]	2001	2b	RCT, no blinding	1. NS in bulb syringe; 2. NS in pot irrigation; 3. Reflexology as placebo	RSOM-31; SNOT-20; SF-36	All groups had improvement in RSOM-31 and SNOT-20 scores. No difference between NS irrigation groups and reflexology
Bachmann[692]	2000	2b	RCT, no blinding	1. NS; 2. Hypertonic saline	1. Symptoms; 2. Endoscopy; 3. Mucociliary clearance; 4. Rhinomanometry; 5. Olfactometry	No difference between NS and hypertonic irrigation

Recommendation" for its use in the management of CRS is provided. Although nasal saline irrigations can improve symptom and CRS-specific QoL outcomes, it is important to recognize that it is often implemented as an adjunct to other topical therapy strategies. Isotonic and hypertonic saline irrigations appear to provide similar subjective outcomes and high-volume saline irrigation appears to be superior to low-volume nasal saline spray techniques.

- Aggregate Grade of Evidence: A (Level 1a: 1 study; Level 1b: 6 studies; Level 2a: 1 study; Level 2b: 4 studies).
- Benefit: Improved QoL, symptoms, and endoscopic, and radiologic outcomes. Well tolerated. No risk of systemic adverse effects. Low cost.
- Harm: Local irritation, nasal burning, headaches, and ear pain/congestion. Low risk of infection from contamination.
- Cost: Minimal (US$0.24/day). Patient time for application.
- Benefits-Harm Assessment: Preponderance of benefit over harm.
- Value Judgments: Important to use nasal saline irrigation as an adjunct to other topical therapy strategies. Higher-volume (>200 mL) irrigations appear to be superior to low-volume nasal sprays, but further trials are required.
- Policy Level: Strong recommendation.
- Intervention: High-volume (>200 mL) nasal saline irrigations are strongly recommended as an adjunct to other medical therapies for CRS.

VII.E.2.a. CRSsNP Management: Topical Corticosteroids. Topical corticosteroids may be delivered using standard sprays or using irrigations and other nonstandard methods. These delivery methods will be discussed separately.

VII.E.2.a. CRSsNP Management with Topical Corticosteroids: Standard Delivery (Sprays). INCSs 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. A search strategy was performed based on that used in Snidvongs et al.'s[705] 2011 Cochrane Review on INCS use in CRSsNP (Table VII-14).

Two high-quality systematic reviews with meta-analyses were included. In 2009, Kalish et al.[706] combined 5 trials[281,707–710] reporting overall response to treatment. There was no significant benefit found, with significant variability between studies noted (relative risk [RR], 0.75; 95% CI, 0.50 to 1.10; $p = 0.14$). Three trials[708,710,711] reported change in symptom scores, and showed a standardized mean difference (SMD) favoring INCS (RR, 0.63; 95% CI, 0.16 to 1.09; $p = 0.009$). Snidvongs et al.[705] published a Cochrane Review in 2011 that combined 5 trials[708,710–713] reporting symptom scores. A significant improvement in SMD 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. Both meta-analyses included 1 article (Lavigne et al.[710]) using direct sinus corticosteroid delivery via maxillary antrostomy sinusotomy tubes (MASTs) This article favored corticosteroids, and thus may act as a confounder for a conclusion on spray delivery methods alone. This was accounted for by Snidvongs et al.,[705] where the significant improvement was preserved with subgroup analysis of nasal delivery methods alone.

Two further randomized control studies were identified in a systematic review published after the July 2010 cutoff date for the Snidvongs meta-analysis.[705] Mosges et al.[714] randomized 60 CRSsNP patients in a double-blinded study to receive either mometasone furoate spray 200 μg BID or placebo for 16 weeks. 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 throughout the treatment course ($p = 0.002$). 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.[715] randomized 43 patients 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.

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

- Aggregate Grade of Evidence: A (Level 1a: 2 studies, Level 1b: 2 studies).
- Benefit: Improved symptom scores, improved endoscopy scores.
- Harm: Epistaxis, headache.
- Cost: Low to moderate (US$0.61 to US$4.80 per day depending on medication).
- Benefits-Harm Assessment: Preponderance of 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: Recommendation.
- Intervention: Standard metered dose INCS should be used in treatment of CRSsNP.

VII.E.2.b. CRSsNP Management with Topical Corticosteroids: Nonstandard Delivery. As discussed in the previous section, the use of standard INCS is recommended for the treatment of CRSsNP. Penetration of sprays

TABLE VII-14. Evidence for CRSsNP management with topical nasal corticosteroids (standard delivery with sprays)

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Snidvongs[705]	2011	1a	Meta-analysis	INCS	1. Symptom scores; 2. QoL; 3. Adverse events	INCS improved symptom scores. No change in QoL. No adverse events
Kalish[706]	2009	1a	Meta-analysis	INCS	1. Overall response to treatment; 2. Symptoms	Insufficient evidence to demonstrate a clear benefit with INCS. Possible improvement in symptom scores
Mosges[714]	2011	1b	DBRCT	16-week course: 1. Mometasone furoate 200 μg BID; 2. Placebo	1. Total symptom score; 2. Patient evaluation treatment response; 3. Endoscopy score; 4. Adverse events	No difference in total symptom score between groups. Significant improvement in endoscopic score
Zeng[715]	2011	1b	RCT, single-blinded, treatment comparison study	12-week course: 1. Mometasone furoate 200 μg once daily; 2. Clarithromycin 250 mg once daily	1. Symptom score; 2. Endoscopy score; 3. Overall symptom burden score	Improvement in symptom scores and endoscopy scores in both groups
Jorissen[712]	2009	1b	DBRCT	6-month course, starting 2 weeks postsurgery: 1. Mometasone furoate 200 μg BID; 2. Placebo	1. Endoscopic score; 2. Symptom scores; 3. Adverse events	No significant difference in total endoscopic score or symptom scores between groups
Dijkstra[707]	2004	1b	DBRCT	After ESS: 1. Fluticasone propionate 400 μg BID; 2. Fluticasone propionate 800 μg BID; 3. Placebo	1. Symptom scores (VAS); 2. Endoscopy score; 3. CT score (LM)	No reduction in recurrence rate of CRS after ESS
Lund[708]	2004	1b	DBRCT	20-week course: 1. Budesonide 128 μg BID; 2. Placebo	1. Combined symptom scores; 2. Individual symptom score; 3. HR-QoL (SF-36); 4. Peak nasal flow	Budesonide improved combined symptom score, individual symptom scores and peak nasal flow. No change in HR-QoL
Giger[716]	2003	1b	DBRCT	1. Beclomethasone dipropionate 200 μg BID; 2. Beclomethasone 400 μg morning, saline placebo evening	1. Symptom score; 2. Active anterior rhinometry; 3. Acoustic rhinometry; 4. Morning serum; cortisol; 5. Adverse events	Significant reduction in symptom scores in both groups, along with other outcome measures
Parikh[711]	2001	1b	DBRCT	16-week course: 1. Fluticasone propionate 200 μg BID; 2. Placebo	1. Symptom score; 2. Acoustic rhinometry; 3. Endoscopy scores; 4. Middle meatal swabs; 5. Blood tests	No difference between groups in any outcome measures
Qvarnberg[281]	1992	1b	DBRCT	12-week course: 1. Budesonide 200 μg BID; 2. Placebo	1. Symptom scores; 2. X-ray changes; 3. Microbiology	No significant differences in treatment outcomes between groups
Sykes[709]	1986	1b	DBRCT	2-week course: 1. 20 μg dexamethasone + 120 μg tramazoline + 100 μg neomycin; 2. 20 μg dexamethasone, 120 μg tramazoline; 3. Placebo	1. Proportion of patients with improved symptoms; 2. Nasal airway resistance; 3. Mucociliary clearance; 4. Sinus X-ray; 5. Bacteriology	Significant increase in patients with improved symptoms in both treatment arms. No difference between active treatment groups

HR = health-related.

beyond the nasal cavities into the paranasal sinuses has been shown to be limited, however, particularly in preoperative patients.[717,718] This fact has led to an increased use of novel delivery devices to attempt to improve intrasinus corticosteroid deposition, and thus potentially clinical outcomes.

Thirty articles were reviewed that addressed nonstandard nasal corticosteroid delivery, with 9 articles included in the final analysis (Table VII-15). Three article addressing the use of corticosteroid/saline sinus irrigations met inclusion criteria, all prospective cohort studies. In the largest study to date, Snidvongs et al.[719] published a prospective cohort of 111 patients, 49 of whom had a diagnosis of CRSsNP (analyzed separately). Treatment was with once-daily nasal irrigations of 1 mg budesonide/betamethasone in 240 mL of normal saline in the immediate postoperative period. Significant improvements were seen in SNOT-20 scores (2.3 ± 1.1 vs 1.2 ± 0.9), symptom scores (2.5 ± 1.1 vs 1.4 ± 1.0), and Lund-Kennedy endoscopy scores (4.3 ± 2.0 vs 1.9 ± 1.6). No adverse outcome analysis was reported. Two smaller studies were published by Sachanandani et al.[720] and Steinke et al.,[721] of 9 and 5 patients, respectively. Improvements in disease-specific QoL (SNOT-20), symptom scores and endoscopy scores were shown, but the small patient numbers limit the significance of the conclusions. There have been concerns about the potential for increased systemic absorption with subsequent adrenal suppression with corticosteroid irrigation use, yet 2 studies published to date have shown no evidence of this problem. [722,723]

Two studies were identified investigating the use of MASTs for corticosteroid delivery. Lavigne et al.[710] randomized 20 patients to receive either 256 μg budesonide or placebo via a unilaterally placed MAST for 3 weeks. The budesonide treatment group had a significant improvement in clinical response scores, as well as significant reductions in tissue biopsy eosinophil counts and IL-4 and IL-5 levels compared with placebo. Reported complications were tube migration (3 patients), epistaxis (3 patients), and 1 case of tube infection. Moshaver et al.[724] reported a prospective pilot cohort study of 13 patients who had bilateral MAST tube placement and once 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, which were maintained until the final 16-week follow-up. No treatment complications were noted. A significant issue with this method of drug delivery is the invasive nature of the tube insertion via a surgical inferior antrostomy, and the increased treatment time and cost associated with tube placement.

Hansen et al.[725] published a DBRCT of 20 patients using a bidirectional 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 and peak nasal flow were seen in the corticosteroid group. Overall RSOM-31 and endoscopy scores showed no statistically significant changes, however. The main weakness of this study was the small sample size (only one-half of the subjects required by power calculation). Adverse effects were limited to mild epistaxis, cough, and rhinorrhea. No evidence of adrenal suppression was found.

One article was identified investigating the use of mucosal atomization devices (MADs). Thamboo et al.[726] randomized 20 patients in an unblinded treatment comparison study to a 12-week course of either 1 mg budesonide via MAD, or 1 mg of budesonide in 120 mL of saline 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 formal threshold for diagnosis of adrenal suppression.

Shikani et al.[727] randomized 17 patients in a small unblinded trial to a 6-week course of either a combination of nebulized mometasone and culture-directed antibiotics plus weekly endoscopic-guided placement of mometasone and antibiotic-impregnated hydroxyethylcellulose gel or "standard treatment" of oral culture-directed antibiotics and mometasone sprays. Both treatment groups showed equivalent effects, making it difficult to assess the relative impact of corticosteroids vs the antibiotics from this treatment regime, however.

Finally, Furukido et al.[713] reported a single-blinded RCT utilizing the YAMIK sinus catheter. Twenty-five patients were treated with a 1-month course of weekly irrigations of either betamethasone (0.4 mg/mL) or saline. No difference was seen between treatment groups in either symptom scores or sinus X-ray scores. Treatment-related epistaxis was reported in 4 patients.

- Aggregate Grade of Evidence: Irrigations – C (Level 4: 3 studies), MAD – N/A (Level 1b: 1 study), MAST tubes – B (Level 1b: 1 study, Level 4: 1 study), YAMIK – N/A (Level 1b: 1 study).
- Benefit: Irrigations – Improvement in health-related (HR)-QoL, subjective symptom scores and endoscopic appearance in postoperative patients. MAD – Improvement in HR-QoL. MAST – Improvement in HR-QoL, subjective symptom scores, and endoscopy scores. YAMIK – No benefit seen.
- Harm: Irrigations – minor (epistaxis, nasal irritation). No evidence of adrenal suppression at studied doses. MAD – Trend toward reduced stimulated cortisol levels. MAST – Invasive insertion, epistaxis. YAMIK – Patient discomfort, epistaxis.
- Cost: Moderate to high (from US$2.50 per day for budesonide respules, MAST US$100 for each tube + variable costs associated with insertion).
- Benefits-Harm Assessment: Irrigations – Preponderance of benefit over harm, with relatively high cost. MAD – Balance of benefit and harm. MAST – Balance of benefit

TABLE VII-15. Evidence for CRSsNP management with topical nasal corticosteroids (nonstandard delivery)

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Thamboo[726]	2014	1b	RCT, unblinded	Twice daily treatments: 1. 1 mg budesonide via mucosal atomization device; 2. 1 mg budesonide in 120 mL saline via large volume irrigation	1. SNOT-22; 2. ACTH stimulation test; 3. Plasma cortisol levels	MAD-delivered budesonide improved SNOT-22. A slight reduction in ACTH-stimulated cortisol levels was seen
Hansen[725]	2010	1b	DBRCT	Bidirectional spray 12-week course: 1. Fluticasone propionate 400 μg BID; 2. Placebo	1. RSOM-31; 2. Subjective symptoms; 3. Nasal endoscopy; 4. Peak nasal flow; 5. Acoustic rhinometry; 6. MRI sinuses	Fluticasone improved nasal symptom scores, endoscopic nasal edema, and peak nasal airflow
Furukido[713]	2005	1b	RCT, single-blinded	1-month course of once-weekly irrigations via YAMIK sinus catheter: 1. Saline solution; 2. Betamethasone (0.4 mg/mL) solution	1. Clinical symptom score; 2. Radiologic (sinus X-ray score); 3. Sinus effusion cytokine levels	No difference between clinical or radiological scores in study groups
Lavigne[710]	2004	1b	DBRCT	Unilateral MAST catheter with 3-week daily irrigation with either: 1. 256 μg budesonide; 2. Placebo control	1. Nonvalidated clinical response score; 2. Tissue eosinophil counts; 3. Tissue IL-4 and IL-5 levels	Treatment improved clinical response scores and reduced eosinophil counts and IL-4/IL-5 levels
Shikani[727]	2013	2b	RCT, unblinded	6-week course of oral culture directed antibiotics and mometasone spray and: 1. Weekly intrasinus administration of gel impregnated with mometasone and culture-directed antibiotics; 2. nothing	1. Symptom scores; 2. Endoscopy scores; 3. Mucosal biopsy inflammation scores	A combined antibiotic and corticosteroid topical administration protocol is equivalent to standard treatment. Topical treatment did not impact histological score
Snidvongs[719]	2012	4	Prospective case-series	Once-daily irrigations of 1 mg budesonide/betamethasone in 240 mL saline	1. Symptom score; 2. SNOT-22; 3. Lund-Kennedy endoscopy score; 4. Need for revision surgery; 5. Need for oral corticosteroids	Improvement in symptom score and SNOT-22 scores in CRSsNP. High tissue eosinophilia predicted better response
Moshaver[724]	2010	4	Prospective, cohort, pilot study	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)	1. HR-QoL (SNOT-16); 2. Endoscopy scores	Significant reduction in both SNOT-16 and endoscopy scores, continuing to 16-week follow-up
Sachanandani[720]	2009	4	Prospective case-series	30-day course of 250 μg budesonide diluted into 5 mL of isotonic saline each nostril QID	1. SNOT-20; 2. Adrenal function	Topical budesonide improved SNOT-20 scores, and did not affect adrenal function
Steinke[721]	2009	4	Prospective, pilot, cohort study	3-month course of twice-daily budesonide irrigations (500 μg into >100 mL saline)	1. Endoscopy score	Budesonide irrigations may improve endoscopy scores

ACTH = adrenocorticotropic hormone; HR = health-related.

and harm. YAMIK – Limited evidence shows preponderance of harm over benefit.

- Value Judgments: Early evidence for irrigations is low level and there is a higher cost compared to sprays. Strongest evidence of improvement is seen in postoperative patients.
- Policy Level: Irrigations – Option in postoperative patients. MAD – Option. MAST – Option. YAMIK – Recommendation against.
- Intervention: Corticosteroid nasal irrigations are an option in CRSsNP. They may be most beneficial in postoperative patients. The use of MAD or MAST is an option.

Use of the YAMIK device is not recommended based on current evidence.

VII.E.3. CRSsNP Management: Oral Corticosteroids

There are 4 level-4 studies that evaluate the benefit of oral corticosteroids in patients with CRSsNP. All 4 include oral corticosteroids in a treatment regimen with other interventions such as antibiotics, topical corticosteroids, and saline irrigations. Three of the 4 include CRSwNP patients.

Lal et al.[728] reported on 145 patients, 82 of which had CRSsNP. All patients received 4 weeks of antibiotics, a 12-day corticosteroid taper, INCS, topical decongestants, and saline irrigations. Posttreatment, 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 of oral corticosteroids, antibiotics, and INCS together did not allow assessment of benefit due to oral corticosteroids alone.

Subramanian et al.[729] reported on 40 patients (23 CRSsNP) treated with a 10-day prednisone taper, 4 to 8 weeks of antibiotics, saline irrigations, and INCS. They reported significant improvements in symptom scores and LM CT scores posttreatment ($p = 0.0005$); however, no specifics were provided as to the timing of the posttreatment CT or symptoms scoring in these patients. Additionally, there was no way to determine the benefit from each component of the therapy.

Hessler et al.[730] prospectively followed CRS patients using the SNOT-20+1 (SNOT-20 plus olfaction). Fifty of the patients who completed the study had CRSsNP. Patients were treated with a combination of medical therapy (antibiotics, oral corticosteroids, nasal corticosteroids, antihistamines, antileukotrienes, herbal medications, and saline) without a universal treatment algorithm. Improvement in the SNOT-20+1 scores in patients using prednisone for ≥11 days failed to reach statistical significance ($p = 0.29$).

Ikeda et al.[731] evaluated the effect of corticosteroids alone on CRS symptoms. Twelve patients with nonallergic CRSsNP based on nasal endoscopy and imaging who had failed INCS underwent olfactory testing before and after a 10-day to 14-day taper of prednisone. The authors found significant improvements in both detection and recognition thresholds following the prednisone course ($p < 0.05$, $p < 0.01$, respectively).

Despite the common use of oral corticosteroids for CRSsNP, there is a lack of evidence supporting their use. Their inclusion in a multidrug regimen in all 4 studies limits the ability to draw any conclusions. Dosage and duration of therapy need to be elucidated, especially because higher doses are associated with more side effects.[732] The cost of oral corticosteroids itself is low, but potential costs accrued due to adverse effects must also be kept in consideration. A recent economic analysis of oral corticosteroid use in CRSwNP patients that took the cost of adverse events into account found that the breakeven threshold, favoring surgery over medical therapy, occurred when more than 1 corticosteroid course was given every 2 years in CRSwNP patients. Of note, CRSsNP patients were not included in the analysis.[733]

Given the potential risks of systemic corticosteroids, clearer evidence addressing the use of corticosteroids in CRSsNP patients is crucial to balance these risks. No published studies exist to determine the benefit of oral corticosteroids alone in CRSsNP, other than 1 study addressing olfaction. There are no current studies evaluating the benefit of oral corticosteroids in the perioperative period, representing a large gap in evidence and a potential area for future study. Because of the lack of clear evidence on the benefits of oral corticosteroids in CRSsNP, no recommendation can be made.

- Aggregate Grade of Evidence: not applicable.

VII.E.4. CRSsNP Management: Antibiotics

VII.E.4.a. CRSsNP Management with Antibiotics: Oral Nonmacrolide Antibiotics for <3 Weeks. 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 evidence in the literature. Recent high-quality prospective studies are lacking, but a total of 6 studies were found addressing the short-term treatment with antibiotics of CRSsNP.

Two studies identified were observational cohort studies. Gehanno and Cohen[734] observed 198 patients treated with ofloxacin for 12 days, whereas Matthews et al.[735] observed 44 patients on a 10-day course of cefixime. Both studies had cohorts achieving a >90% "improvement rate," but unfortunately there was no measurable objective outcome.

There were a total of four[736–739] double-blind randomized trials comparing 2 individual antibiotic regimens head to head without the inclusion of a placebo arm. Clinical resolution of RS was the main endpoint in each study, and there was no identifiable difference between treatment arms. One study,[739] however, did note a significant increase in the rate of relapse in patients treated with cefuroxime vs amoxicillin.

Within the general literature and cited in the previous 6 trials, there are well known side effects with oral antibiotics, mandating caution when considering their use. Although the courses of treatment in each of these studies were short (ie, <3 weeks), side effects were nevertheless noted. The most common included gastrointestinal complaints, genitourinary infections, cutaneous rashes, and *Clostridium difficile* colitis.

In the age of cost containment and cost-effective medicine, attempts have been made to determine the appropriate number of courses of antibiotics before surgical intervention is warranted. Unfortunately, suitable

cost modeling is lacking because of the lack of appropriate prospective data available in the literature.

The lack of rigorous clinical studies and the combination of AECRS and CRS in most studies precludes the ability to make recommendations regarding the use of nonmacrolide antibiotic for less than 3 weeks in CRSsNP.

- Aggregate Grade of Evidence: not applicable.

VII.E.4.b. CRSsNP Management with Antibiotics: Oral Nonmacrolide Antibiotics for >3 Weeks. Although there is significant literature on the role of prolonged treatment with macrolide antibiotics for CRSsNP, there is a paucity of literature with respect to similar treatment with nonmacrolide therapies. Two early studies[729,740] were observational, utilizing "maximal medical treatments" including antibiotics for 4 weeks in a total of over 240 patients, but with no classification of outcomes between the polyp and nonpolyp patients.

One more recent observational study by Dubin et al.[741] examined the treatment duration of oral antibiotics in CRSsNP patients. A total of 35 patients with CT scan–confirmed CRSsNP were prescribed culture directed antibiotics for a total of 6 weeks. Sequential CT scans were obtained at weeks 3 and 6 and compared to the baseline for any improvement using the 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 score = 8.9) and the interval scan at week 3 (LM score = 4.38). Although there were no significant improvements between week 3 and week 6 (LM score = 4.125), the authors noted that 38% of patients did have an improvement in CT scan scores. The safety profile of longer treatment was good, with the only event noted being gastrointestinal upset in 8% of patients. There were no cases of allergic reactions or super infection with *Clostridium difficile*. Based on the solely objective CT data in the study, the authors concluded that a longer course of therapy is safe and may be indicated to help patients achieve radiographic improvement and disease resolution.

With only 1 study in the literature and only 38% of the patient population showing improvement in the extended treatment duration, recommendation of nonmacrolide oral antibiotics for longer than 3 weeks in treatment of CRSsNP is limited by lack of appropriate evidence. Although the risks of adverse events in extended antibiotic treatment were not seen in this small observational study, prescribers must keep in mind the possibility when larger cohorts are treated.

- Aggregate Grade of Evidence: not applicable.

VII.E.4.c. CRSsNP Management with Antibiotics: Macrolide Antibiotics. Macrolides are known to have anti-inflammatory as well as antimicrobial properties and may therefore have a role in the treatment of CRS. The treatment of CRS with macrolide antibiotics stems from early studies of lower airway disease, where erythromycin was used in panbronchiolitis to improve clinical symptoms and 5-year survival rates.[742] Current understanding of the macrolides' mechanism of action suggests both antibacterial and immunomodulatory roles and the proposed effects of macrolides are diverse.[743,744] They are known to decrease proinflammatory cytokine production while altering leukocyte reaction by decreasing IL-8 and also inhibit a key proinflammatory transcription factor, nuclear factor kB (NF-kB).[745–748] Significant literature also suggests a role for macrolide disruption of neutrophilic action, particularly in limiting migration, adhesion, and oxidative response.[749,750]

In 2004, Ragab et al.[751] published an RCT that compared CRS patients randomized to surgery or medical therapy. Both CRSwNP and CRSsNP were included and analyzed separately. The medical therapy arm for CRSsNP patients was comprised of INCS, alkaline nasal irrigations, and long-term low-dose oral macrolide therapy. Erythromycin 500 mg BID was administered for 2 weeks, followed by 250 mg BID for 10 weeks. At the conclusion of the 12-week trial, patients treated with medical therapy and those treated with surgery had similar subjective and objective outcomes.

In 2013, Soler et al.[752] published a review of macrolides in CRS as part of a larger work on antimicrobials in CRS. They identified 17 studies that evaluated the use of macrolide antibiotics in CRS for their anti-inflammatory properties. The aggregate quality of the evidence was found to be B, with 2 placebo-controlled RCTs, 1 retrospective case-control study, and 14 observational cohort studies with no controls. The 2 RCTs[753,754] used robust CRS definitions and the duration of therapy was 3 months in both studies. Wallwork et al.[754] treated CRSsNP patients with roxithromycin 150 mg daily and found improved SNOT-20 and endoscopy scores compared to placebo, but no difference in other metrics, including olfactory function, peak nasal inspiratory flow (PNIF), saccharine transit time, and nasal lavage markers. These results were not sustained after cessation of treatment. Interestingly, patients without elevated IgE appeared to have better results.

Videler et al.[753] examined CRSsNP patients and CRSwNP patients with low-grade polyps using a similar combination of patient-reported outcome and objective measures and found that azithromycin 500 mg/week after an initial loading dose showed no benefit over placebo. Notably, CRSwNP patients comprised 52% of the 60 subjects. Limitations of this study beyond the mixing of CRSwNP with CRSsNP is the possible higher severity of disease, inasmuch as all patients had failed prior antibiotic or INCS treatments, and patients with prior ESS were eligible, averaging 2.5 prior ESS procedures.

Of the remaining 15 studies examined by Soler et al.,[752] three specifically examined CRSwNP, 1 was a nonclinical study examining rheologic properties of mucus, and 10 did not delineate polyp status. Interestingly, 1 study combined

both CRSwNP and CRSsNP patients and found that those without NPs responded better to macrolides.[755]

Soler et al.[752] provided a summary of the evidence and recommendations for macrolide use in CRS, finding a balance between benefit and harm and considering macrolides an option in the treatment of CRS. Unfortunately, like much of the literature on which their review and recommendations were based, Soler et al.[752] did not differentiate CRSwNP from CRSsNP. Others have more recently examined this same published data and have similarly found a general lack of high-level evidence, a propensity to combine CRSwNP and CRSsNP, and significant harms to balance benefits.[756–758]

Since these systematic reviews and meta-analyses were published, 2 additional studies have been published examining macrolide treatment in CRSsNP and 1 in CRSsNP combined with low-grade CRSwNP. Zeng et al.[715] compared oral clarithromycin to mometasone topical nasal spray in 43 patients with CRSsNP. They found comparable improvement in total symptoms, nasal obstruction, headache, and rhinorrhea, as well as endoscopic findings of mucosal swelling and nasal discharge at 4 weeks of therapy. As has been seen previously,[754] patients with AR did not have as robust a response to macrolide therapy. Luo et al.[759] treated CRSsNP patients with clarithromycin and found improved nasal symptom scores, as well as reductions in IL-8 and myeloperoxidase in nasal secretions. Macrolide therapy was found to be more effective in patients with high IL-8 levels prior to treatment. Majima et al.[760] examined the effect of clarithromycin in CRSsNP patients and CRSwNP patients with limited polyps. Subjects were treated with clarithromycin or clarithromycin and carboxymethylcysteine. Clarithromycin-treated patients showed statistically significant improvement in SNOT-20 and CT after 12 weeks of treatment.

One additional study of CRSsNP and CRSwNP patients examined the use of erythromycin following ESS, with evaluation of patient-reported outcomes and physiologic measurements.[761] Both CRSsNP and CRSwNP patients treated with erythromycin had better endoscopy scores than control patients, but CRSsNP patients demonstrated a greater improvement with erythromycin compared to similarly treated CRSwNP patients. CRSsNP patients also showed trends toward greater improvement than CRSwNP patients in SNOT-20 scores, olfaction, and saccharin transit times.

Maniakis et al.[762] performed a retrospective audit on a cohort of 21 patients who did not respond to topical budesonide irrigations. Twelve of the 21 received azithromycin 250 mg three times weekly, with 8 of the 12 showing a favorable response. The authors postulated topical corticosteroid-unresponsive CRS patients may represent a distinct clinical entity that may respond to macrolide therapy. Polyp status was not reported for these 12 patients.

Although most macrolide studies have utilized treatment duration of approximately 12 weeks, no specifications exist for ideal treatment length. Nakamura et al.[763] evaluated treatment duration using daily clarithromycin for 12-week or 24-week treatment courses in post-ESS CRS patients. CRSwNP and CRSsNP patients were included. Although both 12-week and 24-week treatment groups showed reduction in symptoms at early time points, only the 24-week treatment group demonstrated durable suppression of rhinorrhea and PND 12 months after ESS.

Few adverse events were noted in any published trials. Gastrointestinal disorders including mild diarrhea, vague abdominal discomfort, or nausea and vomiting were most common, reported in less than 5% of all patients.[753,754,761] In non-sinus studies, macrolides have been implicated in causing ototoxicity[764] and liver dysfunction.[765] Concerns about overuse resulting in host antibiotic resistance have been raised.[766] Perhaps most importantly, a growing body of literature has associated macrolide antibiotic use with ventricular arrhythmias and cardiac arrest, including azithromycin, which has a perceived lower risk of cardiotoxicity.[767,768] These findings have resulted in an FDA advisory cautioning against the use of macrolides in patients with high baseline cardiovascular risk.[769] Finally, macrolides are metabolized by the liver and have known interactions with other medications, predominantly due to their inhibition of CYP 3A4–mediated activity of cytochrome P-450.[765] Warfarin, cisapride, benzodiazepines, cyclosporine, antihistamines, and statins all have previously reported minor interactions with macrolides.[757]

In summary, a few RCTs concerning macrolides in CRSsNP have been published and 2 have rather compelling findings about the short-term efficacy, whereas 1 shows no benefit. Careful review of the evidence demonstrates that most systematic reviews are based on these RCTs with conflicting results and a large number of noncontrolled cohort studies. The subgroup of CRSsNP patients that best benefit from macrolides is not currently known. Various drugs and dosages have been studied so that the optimal drug and dosages are also not currently known. Macrolides have significant side effects and contraindications. Moreover, the long-term outcomes of macrolide-treated patients are not entirely known, with some evidence showing a lack of permanent effect. The efficacy of macrolides appear to differ by CRS phenotype, so that additional work will need to be performed in order to better clarify the balance between benefit and harm of macrolide therapy in CRSsNP (Table VII-16).

- Aggregate Grade of Evidence: B (Level 1a: 2 studies; Level 1b: 2 studies; Level 1a-2a: 2 studies; Level 2b: 3 studies).
- Benefit: Reduction in endoscopy scores and some symptoms in patients with CRSsNP, particularly in patients without elevated IgE. Effects appear to be comparable to INCS. Benefit may not last long following cessation of therapy.
- Harm: Significant potential for medication interactions. Rare mild adverse events. Potential for severe cardiovascular complications.

TABLE VII-16. Evidence for CRSsNP management with macrolide antibiotics

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Cervin[757]	2014	1a	Systematic review	CRSsNP and CRSwNP: 2 RCTs; 22 open/cohort studies		Support for macrolide use in refractory CRS in absence of high IgE levels
Pynnonen[756]	2013	1a	Meta-analysis of 3 RCTs	CRSsNP and CRSwNP: 183 (3 studies)		Insufficient evidence demonstrating a clinically significant impact of long-term macrolide therapy
Soler[752]	2013	1a	Systematic review of RCTs and cohort studies	CRSsNP and CRSwNP: 2 RCTs; 15 open/cohort studies		Recommendation level: option (especially patients with low IgE)
Piromchai[758]	2011	1a	Meta-analysis of 1 study, involving macrolides	CRSsNP: 64 (1 study)	1. Clinical cure rate; 2. Improvement scale; 3. Bacteriological cure rate; 4. Radiographic response rate; 5. Relapse rate; 6. Adverse effects	Insufficient response to recommend the use of any kind of antibiotic in CRS
Haxel[761]	2015	1b	RCT	1. Erythromycin 250 mg daily (n = 29); 2. Placebo (n = 29)	1. ECP and MPO in nasal secretions; 2. Multiple other patient reported and clinical measures	Improved nasal endoscopy score. Duration or low-dose of this trial not efficacious. High chance of Type II error
Ragab[751]	2004	1b	RCT	1. Surgical treatment (n = 45); 2. Erythromycin 500 mg BID, fluticasone 400 μg BID (n = 45)	1. SNOT-20; 2. VAS for symptoms; 3. Multiple other patient-reported and clinical measures	No difference in VAS or SNOT-20 between groups. CRSwNP better at 12 months in medical therapy group
Majima[760]	2012	2b	Cohort study	1. Clarithromycin 200 mg daily (n = 158); 2. Clarithromycin 200 mg daily + S-carboxymethylcysteine daily (n = 159)	1. SNOT-20; 2. CT score; 3. Subjective symptom score; 4. Nasal endoscopy findings	Combination group was more improved at 12 weeks. Improvement grew in both groups with longer treatment
Luo[759]	2011	2b	Cohort study	1. Clarithromycin 250 mg daily (n = 33)	1. Symptoms scores (VAS); 1. Nasal resistance; 2. IL-8, MPO levels; 3. SNOT-20; 4. SF-36	Improved symptoms and QoL CRSsNP patients. Reduction in IL-8 and MPO
Zeng[715]	2011	2b	Cohort study	1. Mometasone furoate 200 μg daily (n = 21); 2. Clarithromycin 250 mg daily (n = 22)	1. VAS; 2. Endoscopic score	INCS and clarithromycin had comparable effect for CRSsNP

MPO = myeloperoxidase.

- Cost: Low.
- Benefits-Harm Assessment: Benefits appear to outweigh harms. Benefit of treatment over placebo is seen in most but not all studies. Harm, though rare is significant.
- Value Judgments: Macrolides appear to confer a benefit in the short term. The benefit may not last following cessation of therapy. Optimal drug, dosage, and length of therapy are not known.
- Policy Level: Option.
- Intervention: Macrolides are an option for patients with CRSsNP.

VII.E.4.d. CRS Management with Antibiotics: Intravenous Antibiotics. *Because of limited data, CRSwNP and CRSsNP are combined in this analysis and recommendation.*

The evidence for IV antibiotics in the treatment of CRS is sparse, with no differentiation of CRSsNP vs CRSwNP in the literature. Three available studies were identified, primarily retrospective and observational cohorts (Table VII-17). Gross et al.[770] reported outcomes of 14 patients receiving culture-directed IV antibiotics in conjunction with ESS. The indications to pursue IV

TABLE VII-17. Evidence for CRSsNP and CRSwNP management with intravenous antibiotics

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Anand[771]	2003	4	Observational cohort	1. IV antibiotics	1. Symptom scores; 2. RSDI	No significant improvement in symptom scores
Fowler[772]	2003	4	Case series	1. IV antibiotics (culture-directed)	1. Resolution (defined by CT or endoscopy); 2. Relapse rate	29% with resolution; 89% with relapse at average of 11.5 weeks
Gross[770]	2002	4	Case series	1. IV antibiotics plus surgery	1. Short-term response	50% showed complete resolution

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. The duration of outpatient therapy was 4 weeks delivered via peripherally inserted central catheter. Clinical endpoints examined response to the treatments. Of the 14 patients treated, 79% were noted to show a partial or complete response. Adverse events were reported in 5 patients (35%), including 3 catheter-related events (2 patients with thrombophlebitis and 1 patient with deep vein thrombosis) and 2 allergic drug reactions.

Anand et al.[771] reported an observational cohort of 45 nonsurgical patients, diagnosed with osteitis of the paranasal sinuses on CT scans. All patients were treated with culture-directed antibiotics for a period of 6 weeks. Clinical endpoints included patient-reported symptom scores and RSDI scores. A variety of antibiotics were utilized during the study period, with significant improvement in patient reported symptom scores examined at 3 weeks after cessation of therapy. RSDI was also noted to improve but given the low number of available patients ($n = 7$) to compare, a p value was not available for calculation. Minor complications were reported in 16% of patients, which included elevations in liver enzymes, neutropenia, septicemia, bleeding, and rash. The authors conclude that given the response noted, IV antibiotics would be a viable option.

Fowler et al.[772] performed a retrospective case series of 31 patients with CRS failing 3 courses of oral antibiotics and subsequently treated with an average of 4.8 weeks of culture-directed IV antibiotics. CRS was defined by continuous symptoms and positive findings on sinus CT scan and/or sinus endoscopy lasting for greater than 3 months. Only 29% of patients were noted to have resolution of disease on CT scan or nasal endoscopy following treatment. Of these, 89% relapsed at an average of 11.5 weeks after cessation of therapy. Complications occurred in 26% including thrombophlebitis, peripheral venous thrombosis, catheter infection, diarrhea, and neutropenia.

Indeed, high complication rates have since been substantiated in a subsequent larger patient series. Lin et al.[773] examined 177 patients who underwent IV antibiotic therapy for CRS, with the majority receiving a combination of ceftriaxone and clindamycin. The overall complication rate was reported at 18%, with 16% antibiotic-related adverse events (ie, neutropenia, elevated liver function tests [LFTs], and rash) and 2% catheter-related adverse events (ie, thrombosis).

The high preponderance of adverse events noted in the literature in the treatment of CRS with IV antibiotics makes it difficult to recommend. Associated costs of line placement and the treatment of the potential adverse events preclude it from being a cost-effective option in the uncomplicated CRS patient. However, for the subset of patients with CRS complications or extrasinus manifestations of CRS, the benefits of treatment outweigh the cost and risk of possible adverse events.

- Aggregate Grade of Evidence: C (Level 4: 3 studies).
- Benefit: Possible improvement in patient-reported symptoms in cohort and case-controlled studies.
- Harm: Thrombophlebitis, neutropenia, sepsis, deep vein thrombosis, elevated liver enzymes, drug adverse events, rash, bleeding.
- Cost: High.
- Benefits-Harm Assessment: Risk of harm over the possible benefits noted.
- Value Judgments: Risk of adverse events and cost of treatment greatly outweighs possible benefit for routine use in CRSsNP.
- Policy Level: Recommendation against.
- Intervention: Intravenous antibiotics should not be used for routine cases of CRS. For patients with complications or extrasinus manifestations of CRS, the benefits of treatment may outweigh the cost and risk of possible adverse events.

VII.E.4.e. CRS Management with Antibiotics: Topical Antibiotics. *Because of limited data, CRSwNP and CRSsNP are combined in this analysis and recommendation.*

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. Disadvantages to topical antibiotic therapy include user-dependent variations in delivery technique, topical absorption, local adverse effects, and limited long-term data. Studies on topical antibiotic delivery do not distinguish between those with CRSwNP and CRSsNP.

TABLE VII-18. Evidence for CRSsNP and CRSwNP management with topical antibiotics

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Jervis-Bardy[341]	2012	1b	DBRCT	1. Mupirocin rinses (n = 9); 2. Saline rinses (n = 13)	1. Bacterial culture; 2. Symptoms; 3. QoL; 4. Endoscopy	Short-term effect on *S. aureus* clearance with mupirocin, but no effect on long-term outcomes
Wei[787]	2011	1b	DBRCT	1. Saline plus gentamicin; 2. Saline alone	1. LM scoring of CT; 2. QoL	No benefit seen with topical antibiotic
Videler[776]	2008	1b	DBRCT crossover pilot study	Total (n = 14): 1. Bacitracin-Colimycin with oral antibiotics; 2. Saline (placebo) with oral antibiotics	1. Symptoms (VAS); 2. QoL questionnaire; 3. Nasal endoscopy	No benefit seen with topical antibiotic
Desrosiers[777]	2001	1b	DBRCT	1. Tobramycin-saline nebulization; 2. Saline nebulization	1. Symptoms; 2. QoL; 3. Histology	No benefit seen with topical antibiotic
Sykes[709]	1986	1b	DBRCT	1. Neomycin, tramazoline, dexamethasone (n = 20); 2. Tramazoline, dexamethasone (n = 20); 3. Placebo (n = 10)	1. Nasal MCC; 2. Sinus X-ray; 3. Nasal rhinomanometry; 4. Bacterial culture; 5. Nasal endoscopy	No benefit seen with topical antibiotic
Lee[781]	2014	2a	Systematic review with heterogeneity			Topical antibiotic therapy not recommended as first-line therapy, but may be considered for recalcitrant CRS
Huang[780]	2013	2a	Systematic review with heterogeneity			Additional studies required to evaluate efficacy of topical antibiotics
Rudmik[702]	2013	2a	Systematic review with heterogeneity			Recommend against topical antibiotic due to insufficient clinical research
Soler[752]	2013	2a	Systematic review with heterogeneity			Use of topical antibiotics recommended against due to lack of evidence
Woodhouse[779]	2011	2a	Systematic review of RCT, with heterogeneity			Nebulized antibiotics cannot be recommended due to lack of evidence
Lim[782]	2008	2a	Systematic review with heterogeneity			Topical antibiotics may be effective, but further high level studies are required

Additionally the majority of studies focus on the postsurgical recalcitrant CRS patient. Studies have shown that ESS increases the penetration of topical irrigation therapy from minimal absorption (<2%) to greater than 95% absorption.[717,774,775] Four RCTs and 6 systematic reviews have examined topical antibiotics in CRS (Table VII-18).

Videler et al.[776] conducted a randomized, placebo-controlled, double-blind, cross-over pilot study in 14 people with refractory CRS post-ESS. Recalcitrant disease was defined by positive nasal cultures for *Staphylococcus aureus* after 2 treatments of oral antibiotics (>2 weeks duration) and nasal saline irrigations. The patients were initially randomized into 1 of 2 groups, either high-dose nebulized bacitracin-colimycin (8 weeks) and oral levofloxacin (2 weeks) or nebulized saline (control) and oral levofloxacin (2 weeks). Although the authors found that nebulization improved CRS symptoms, they did not find any added benefit of bacitracin/colimycin to the nebulized solution. The authors acknowledged the inadequate number of patients enrolled and calculated a minimum of

126 patients to achieve statistical significance. Moreover the use of oral levofloxacin may have confounded the results, although patients had failed prior oral antibiotics.

Sykes et al.[709] investigated the additive effective of neomycin in conjunction with a nasal spray of trazoline and dexamethasone compared to saline placebo. They studied 50 patients with symptoms of chronic purulent nasal drainage although there was no mention of prior surgical therapy. Their study utilized comprehensive outcome measures, which included 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 and Salas-Prato[777] looked at 20 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. After a 4-week washout period, they found that both groups improved in symptoms, QoL, and histologic changes in sinonasal mucosa and were unable to detect a significant difference with the addition of tobramycin. Tobramycin was found to improve pain more quickly than saline, but also led to the side effect of nasal congestion.

One RCT investigated the use of mupirocin irrigations in post-ESS patients to treat recalcitrant *S. aureus*. Jervis-Bardy et al.[341] performed a DBRCT study of 25 patients with either 1 month of mupirocin-saline irrigations or saline control irrigations. They found a short-term improvement in negative *S. aureus* cultures in those with mupirocin, but no improvement in long-term outcomes in regard to objective or subjective measures of CRS improvement. Interestingly, a subsequent study by the same group found a high failure rate of mupirocin in eradicating S. *aureus* and documented a case of mupirocin-resistanct *S. aureus* in 1 of their patients following treatment.[778]

Six systematic reviews have summarized the evidence on topical antibiotics in CRS. Woodhouse and Cleveland[779] confined their review to the 4 published RCTs; however, the RCTs were heterogeneous and therefore topical antibiotic use could not be recommended. The 5 remaining systematic reviews included lower-level studies, and all consistently recommended against the use of topical antibiotics because of the lack of evidence.[702,752,780–782]

Existing high-level evidence of topical antibiotics in CRS fails to consistently demonstrate benefits. Their routine use cannot be recommended. Some case series have reported effectiveness, particularly in recalcitrant cases of CRS,[783–786] suggesting there may be a role in unusual cases.

- Aggregate Grade of Evidence: B (Level 1b: 4 studies; Level 2a: 6 studies; Level 4: 4 studies).
- Benefit: RCTs failed to show any benefit from the use of topical antibiotics.
- Harm: Nasal congestion, irritation, epistaxis. Theoretical possibility of systemic absorption with topical aminoglycosides. Possibility of developing bacterial resistance.
- Cost: Moderate to high (US$2.64 to US$7.64) per dose, 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 CRS.

VII.E.5. CRSsNP Management: Antifungals

VII.E.5.a. CRSsNP Management: Oral Antifungals. Antifungal agents can be used as topical or systemic treatment and systemic antifungals are given orally or intravenously. It has been suggested by some that fungi are a cause/contributing factor of CRS in a large subgroup of patients, especially in those with eosinophilic inflammation. Antifungals have therefore been suggested as a potential treatment in this subgroup of CRS patients.

Only 1 study has examined the use of oral antifungals in CRS.[379] Kennedy et al.[379] recruited 53 adult CRS patients and randomized them into 2 groups in a DBRCT. Patients who had sinus surgery within the 3 months prior to screening were not considered for this study. There was no indication in the study as to whether or not the included patients had CRSwNP or CRSsNP. One group of patients received 625 mg of terbinafine orally (n = 25) while the other group received placebo tablets (n = 28) once daily for 6 weeks. At study initiation, all patients were required to have a positive fungal culture. This entry criterion was later relaxed so that any patient meeting the criteria for CRS was enrolled. The primary outcome was the percentage change from baseline in CT score using the LM scoring system. Secondary outcomes included changes from baseline in patient's and physician's evaluation of RS, patient's and physician's evaluation of therapeutic response, as well as RSDI scores. Four (16%) terbinafine patients and 5 (17%) placebo patients did not complete the study. In this trial, for both symptom and radiographic scores, there was no significant benefit of terbinafine over placebo.

On the basis of the 1 available study there is no evidence to support the use of systemic antifungal treatment in the routine management of CRSsNP.

- Aggregate Grade of Evidence: not applicable.

VII.E.5.b. CRSsNP Management: Topical Antifungals. The Cochrane review conducted by Sacks et al.[788] synthesized all RCTs investigating the use of topical antifungals in the management of CRS. They found 2 RCTs that address this topic. Liang et al.[380] studied 70 CRSsNP patients with no history of previous ESS. The patients were randomized into 2 groups that used nasal irrigation (60 mL) with either amphotericin B solution (5 mg/mL, daily amount of amphotericin B = 20 mg) or placebo for 4 weeks. The primary outcome was the

Chinese version of the RSOM-31 (CRSOM-31) and nasal endoscopy scores using the Lund-Kennedy system. Six (8.6%) patients did not complete the study: 4 (11.4%) in the amphotericin B group and 2 (5.7%) in the placebo group. The amphotericin B group showed no significant improvement in CRSOM-31 scores when compared to placebo. The amphotericin B group also showed no significant improvement in nasal endoscopy scores.

Ponikau et al.[378] studied 30 adult CRS patients, although it was unclear whether these were CRSsNP, CRSwNP, or both. Patients were randomized into 2 equal groups. Twenty-five patients had prior ESS, 13 (86.7%) in the intervention arm and 12 (80%) in the control arm. Both groups received 20 mL amphotericin B solution (250 μg/mL) or placebo in each nostril twice daily through a bulb syringe for 24 weeks (daily amount of amphotericin B = 20 mg). The primary outcome measure was to be the change from baseline in the percentage of inflammatory mucosal thickening measured by CT scan (proprietary scale). Secondary outcomes included change from baseline of mucosal thickening measured by endoscopic staging and the change from baseline in patient symptoms using the SNOT-20. Inflammatory mediators, intranasal *Alternaria* protein and blood eosinophilia were also measured. Five (33.3%) patients in the intervention group and 1 (6.7%) control patient did not complete the study. The amphotericin B group showed no significant improvement in SNOT-20 scores when compared to placebo. The amphotericin B group showed a statistical improvement in radiographic scores, though the clinical relevance was dubious.

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 (Table VII-19).

- Aggregate Grade of Evidence: A (Level 1a: 1 study, Level 1b: 2 studies).
- Benefit: RCTs failed to show any symptomatic benefit from the use of topical antifungal irrigations.
- Harm: The irrigations are generally well tolerated.
- Cost: Moderate.
- Benefits-Harm Assessment: No benefit with rare harm and moderate cost.
- Value Judgments: None.
- Policy Level: Recommendation against.
- Intervention: Topical antifungal agents are not recommended for CRSsNP.

VII.E.6.a. CRS Management with Topical Alternative Therapies: Surfactants. *Because of limited data, CRSwNP and CRSsNP are combined in this analysis and recommendation.*

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 mucous. 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.[789] 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.

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. 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.[790] An RCT of 1% baby shampoo vs hypertonic saline showed no significant differences in posttreatment symptom scores; however, 20% of patients receiving the surfactant irrigation solution discontinued use because of side effects.[791] The Sinusurf® surfactant solution was withdrawn from the market in 2011 because of adverse effects, including olfactory disturbance.[702]

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.[789,792]

In summary, 1 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, CBF, and MCC time. Cost of surfactant therapy is low. Although 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.

- Aggregate Grade of Evidence: not applicable.

VII.E.6.b. CRS Management with Topical Alternative Therapies: Manuka Honey. *Because of limited data, CRSwNP and CRSsNP are combined in this analysis and recommendation.*

Manuka honey and its active component methylglyoxal (MGO) have demonstrated in vitro effectiveness against both the planktonic forms and biofilms of *Staphylococcus aureus* and *Pseudomonas aeruginosa*.[793–795] Kilty et al.[793] demonstrated that higher effective concentrations of MGO are needed for biofilms of *S. aureus* and *P. aeruginosa*

TABLE VII-19. Evidence for CRSsNP management with topical antifungals

Study	Year	Study design	LOE	Study groups	Clinical endpoint	Conclusions
Sacks[788]	2011	1a	Systematic review with meta-analysis	1. Topical antifungal therapy; 2. Placebo	1. Collated symptom scores; 2. QoL; 3. Adverse events	No benefit of topical antifungal over placebo
Liang[380]	2008	1b	RCT	1. 20 mg amphotericin B daily (n = 51); 2. Placebo (n = 46)	1. Chinese RSOM; 2. Endoscopic scores	No benefit of topical antifungal over placebo
Ponikau[378]	2005	1b	RCT	1. 20 mg amphotericin B daily (n = 15); 2. Placebo (n = 15)	1. CT score; 2. SNOT-22	Improvement in CT over placebo. No improvement in symptom score

than for the planktonic forms. Jervis-Bardy et al.[794] 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.

In vivo animal studies have demonstrated the safety and potential efficacy of Manuka honey in the sinonasal cavity. To evaluate the effect on nasal respiratory epithelium, Kilty et al.[796] treated New Zealand rabbits with up to 14 days of daily irrigations of 1.5 mL of 33% mixture of Manuka honey with saline. The amount of MGO in the Manuka honey was not stated in the study. No epithelial damage of the nasal respiratory mucosa was seen on light microscopy or transmission electron microscopy. Paramasivan et al.[797] performed both a safety and efficacy study in an in vivo sheep model by performing frontal trephinations and irrigating the frontal sinuses with Manuka honey. In the safety arm, they found that a concentration of MGO up to 1.8 mg/mL did not cause any epithelial injury on standard microscopy and scanning electron microscopy; however, at an MGO concentration of 3.6 mg/mL, patchy ciliary denudation of the epithelium was demonstrated. In the efficacy arm, the frontal sinuses were infected with a biofilm-forming strain of S. aureus. Twice daily irrigations through 1 of the frontal sinus trephination were used for 5 days with the other sinus acting as the control. Biofilm mass was found to be equally decreased at an MGO concentration of 3.6 and 1.8 mg/mL. At a concentration of 0.9 mg/mL, the biofilm mass was reduced less, and at an MGO concentration of 0.5 mg/mL, there was no reduction in biofilm mass. The authors conclude that Manuka honey/MGO with MGO concentrations between 0.9 and 1.8 mg/mL is probably optimal.[793]

Only 2 clinical studies were found in the literature pertaining to the use of topical Manuka honey in patients with AFRS. Thamboo et al.[798] performed a single-blind study including 34 patients who met Bent and Kuhn criteria for AFRS who had failed standard medical treatments for 12 weeks post-ESS. Manuka honey–saline solution was applied via an atomization device into 1 sinonasal cavity, with the other cavity serving as the control. The authors found no significant difference in endoscopic mucosal scores after 30 days of treatments. Of note, 4 patients complained of nasal burning and 1 complained of nausea.[798] Wong et al.[799] reported a case series of 2 patients with AFRS who failed standard medical management post-ESS, at which point Manuka honey irrigations were added to their treatment regimen for 12 weeks. The authors report a decrease in SNOT-22 score and improvement endoscopically in both patients after addition of Manuka honey irrigations. They do note that the Manuka honey did increase the SNOT-22 score for 1 of the patients in the categories of need to blow nose, runny nose, and sneezing.[799] Both studies used commercially available Manuka honey but did not report the concentration of MGO.

In summary, there are no clinical studies on Manuka honey use in routine CRSwNP or CRSsNP. The only 2 clinical studies thus far on Manuka honey are small case series in AFRS. Extrapolating from in vitro and animal studies, potential benefits include improvement in endoscopic score, improvement in some domains of SNOT-22, and bactericidal and biocidal properties against *S. aureus* and *P. aeruginosa*. Nasal burning, irritation, and potential respiratory epithelial injury are potential harms. The cost is low (about US$10 for 250 g of Manuka honey). The concentration of MGO in Manuka honey is variable so that caution should be used in its use. Because of the paucity of evidence, no recommendation for the use of Manuka honey in CRSsNP and CRSwNP is possible.

- Aggregate Grade of Evidence: not applicable.

VII.E.6.c. CRS Management with Topical Alternative Therapies: Xylitol. *Because of limited data, CRSwNP and CRSsNP are combined in this analysis and recommendation.*

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 the respiratory secretions. Brown et al.[800] demonstrated that simultaneous administration of xylitol with *Pseudomonas aeruginosa* into the maxillary sinus of a rabbit produced an increase in bacterial killing after 20 minutes. However, they found that preadministration of xylitol into the sinus or administration of xylitol in an infected sinus did not decrease bacterial counts when compared with

saline. In a human study, Zabner et al.[801] 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.

Weissman et al.[802] performed the only human study evaluating the effect of xylitol in patients with CRS. This study was 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. There were 10 subjects in each group, and only 15 (75%) completed the study. The xylitol group showed a greater improvement in the SNOT-20 score than the saline group. There was no difference in the VAS score between the groups. There were no adverse events with only 1 patient reporting minor stinging.[802]

In summary, 1 small RCT with 25% dropout has shown limited symptom benefit with xylitol. In vitro studies have shown enhancement of innate immunity. Potential harm is limited to minor irritation and cost of therapy is low. Due to the limited amount of evidence, no recommendation regarding xylitol therapy in CRSsNP and CRSwNP is possible.

- Aggregate Grade of Evidence: not applicable.

VII.E.6. CRSwNP Management: Topical Alternative Therapies

VII.E.6.d. CRS Management with Topical Alternative Therapies: Colloidal Silver. *Because of limited data, CRSwNP and CRSsNP are combined in this analysis and recommendation.*

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 nonmedical 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% to 18% and seems to be distributed to all organ systems, with the highest levels being observed in the intestine and stomach.[803] Argyria involves the deposition of silver granules in the skin, mucous membranes, and internal organs, including the central nervous system, resulting in the hallmark blue-gray discoloration of the skin generally associated with chronic low-dose exposure to silver-containing products. Consumption of large doses of colloidal silver can result in significant morbidity including gastrointestinal ulceration, hemolysis, agranulocytosis, and neural toxicity.

Although 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 control in an in vitro study,[804] it remains an unregulated alternative medicine. Colloidal silver products of unknown formulation were tested and found to vary from ineffective to dangerous to possibly life threatening. These findings led the FDA in 1999 to rule that all over-the-counter drug products containing colloidal silver ingredients or silver salts for internal or external use were not generally recognized as safe and effective and were misbranded.[805]

In addition to these safety concerns, no evidence exists regarding the efficacy of topical silver treatment in CRSsNP or CRSwNP. Topical silver is not recommended in CRSsNP and CRSwNP.

- Aggregate Grade of Evidence: not applicable.

VII.E.7 CRS Management: Distribution of Topical Medications and the Influence of Head Position, Device, Surgery, and Nasal Anatomy

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

The evidence based review by Thomas et al.[806] examined how the distribution of topical therapies is affected by surgery, delivery device, head position, and nasal anatomy. Thirty-two studies published between 1987 and 2011 examining topical medication distribution in the nose and sinuses were included. Only 1 further study[807] has been published since that time (Table VII-20).

The Influence of Sinus Surgery. Eight studies have examined the effect of sinus surgery on the distribution of topical medications in the nose and sinuses in both CRSwNP and CRSsNP.[806] Surgical interventions ranged from sinus ostium dilation to modified Lothrop frontal sinus surgery and medial maxillectomy. Unoperated sinuses appeared to receive little topical therapy, with more extensive procedures resulting in increasing distribution in general.[774,808–810] Specifically, a 4-mm to 5-mm ostial size has been shown to predict sinus penetration with high volume irrigators.[774] Standard sinus surgery increases distribution of topical therapies to all sinuses, but has no impact upon nasal cavity delivery.[809,810] Although 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.[806]

The Influence of Delivery Device. Delivery is best achieved with large-volume devices.[774] 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 (>60 mL, but generally >100 mL) or heavy irrigators have been found to

TABLE VII-20. Evidence for influence of head position, device, surgery, and nasal anatomy on topical delivery

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Thomas[806]	2013	3a	Systematic review	Surgery; Device; Head position; Nasal anatomy	Sinus distribution of topical fluid from intranasal deliveries	Surgery and high-volume delivery devices are the critical factors in sinus delivery
Habib[807]	2013	5	Cadaver, experimental	MAD delivery of saline in the: 1. Head-Down and Forward position; 2. Lying-Head-Back position	Endoscopic evaluation of captured images	The Lying-Head-Back position was superior

improve delivery into the sinuses.[811,812] This definition of "high-volume" is rather arbitrary, but clinical evidence suggests it may play an important role for mechanical cleaning or lavage and drug delivery.[700] High-volume devices can unfortunately carry unwanted side effects, with Eustachian tube dysfunction and local irritation reported in up to one-fourth of patients. However, these are often mild and compliance is high.[706] Low-volume devices such as drops, sprays, and nebulizers are successful alternatives if nasal cavity delivery is needed, but they do not reliably reach within the sinuses and provide no mechanism for lavage. The shear force achieved by high-volume irrigations, and their ability to clear thick mucus, is poorly defined in many studies. There is clinical evidence such a difference exits between low-volume and high-volume devices.[700]

The Influence of Head Position. Head position impacts delivery in the previously operated patient, especially for low-volume devices. 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.[811,812] The head down and forward position appears to be optimal for topical delivery into the sinuses 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 postoperative state.

The Influence of Nasal Anatomy. Although it may seem axiomatic that correcting local septal and turbinate deformities would enhance local drug delivery, there is little evidence to support this assumption. In evaluation of the potential benefits and harms of altering nasal anatomy and/or using longstanding decongestants to improve topical medication delivery, Thomas et al.'s[806] evidence-based review did not find significant data supporting this practice. 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 positioning. Nasal surgery or a chronic topical vasoconstrictor use, without documented airflow obstruction, is unproven and increases the risk for harm and cost.

Summary. The goal of topical therapy in CRS is to facilitate clearance of mucus and address the mucostasis that characterizes this condition. Enabling effective local pharmacologic management is also important as "sinus" distribution of topical therapies, primarily corticosteroids, antibiotics, and mucolytics. The mechanical shear force that is provided by high-volume irrigations in the postoperative state is underevaluated and 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 devices.

- Aggregate Grade of Evidence: C (Level 3b: 5 studies, Level 4: 39 studies).
- Benefit: Sinus surgery increases distribution of topical therapies to all sinuses. High-volume (>100 mL) irrigation or heavy irrigators improve both sinus and nasal cavity distribution of topical treatments. Head position has the greatest impact when using low-volume devices but does not affect high-volume device delivery. No benefit in altering nasal anatomy with surgery or decongestants for high-volume delivery. Impact on low-volume delivery is unknown.
- Harm: Surgery is associated with potential complications and recovery. High-volume irrigation may be associated with nasal irritation and Eustachian tube dysfunction.
- Cost: Costs for high-volume delivery devices are generally low. With regard to the impact of surgery on topical therapy delivery: (1) Direct costs: High cost associated with ESS. Topical delivery caries moderate costs depending on choice of device, (range, US$9.97 to US$149.00) and preparation. (2) Indirect costs: Indirect costs may occur from surgery due to missed work and decreased productivity in the perioperative period.

- Benefits-Harm Assessment: Benefit exceeds harm when local therapies avoid systemic therapy risks.
- Value Judgments: The decision for topical therapies must evaluate the risks and costs of surgery with ongoing systemic medications. The ability to deliver topical medications and remove mucus may impact decision-making when considering sinus surgery.
- Policy Level: Recommendation for large-volume irrigation to deliver topical medication following sinus surgery. Recommendation to address head position if using low-volume topical medication delivery following sinus surgery. Recommendation against the alteration of nasal anatomy with surgery or decongestants in order to facilitate high-volume delivery into the sinuses in the absence of nasal airway obstruction.
- Intervention: When topical medication delivery or mucus evacuation is indicated, high-volume delivery following sinus surgery is recommended. When using low-volume delivery following sinus surgery, use the head down and forward position. Alteration of nasal anatomy through surgery or decongestants is not recommended for topical medication delivery in the absence of nasal airway obstruction.

VII.E.8 CRS Management: Immune Workup and Treatment

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

In patients with CRSsNP refractory to standard treatment, immunodeficiency should be considered. Testing for PID may include quantitative serum immunoglobulins, and specific antibody responses.[155,277,585,590–592,813] Certain selective Ig deficiencies may be associated with other diagnoses, such as the linkage between IgG3 deficiency and atopy, stressing the importance of an adequate assessment and treatment for allergies in these patients.[595]

A systematic review of the literature for immunodeficiency treatment in CRS identified 1 randomized, double-blind cross-over trial, 2 level 2b and 3b studies each, 1 level 4 study and 6 level 5 studies as follows:

- Prophylactic antibiotics
  - Level 4: 1 study; Level 5: 4 studies
- Early culture-directed antibiotics
  - Level 5: 4 studies
- Immunoglobulin replacement
  - Level 2b: 2 studies; Level 3b: 1 study, Level 5: 4 studies
- Other immune therapy: thymic hormone preparation thymostimulin
  - Level 1b: 1 study; Level 5: 1 study
- ESS
  - Level 3b: 1 study; Level 5: 1 study

Tas et al.[814] performed a randomized control study using thymic hormone preparation thymostimulin (TP-1) and placebo in a crossover trial. TP-1 was proven to be effective in patients with recurrent CRS who were immunologically deficient in cell-mediated immunity.[814] 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.[815] There is debate on the role of Ig replacement. Roifman and Gelfand[816] evaluated sinopulmonary disease frequency after high-dose and low-dose therapy with intravenous Ig (IVIG). High-dose Ig achieved minimal trough serum IgG levels and decreased symptoms and frequency of major and minor infections.[816] However, after a long-term follow-up of a large cohort of patients with common variable immunodeficiency, Quinti et al.[597] found Ig administration was associated with increased prevalence of CRS and bronchiectasis. This was supported by a study from Rose et al.[817] in which the inflammatory cytokines were markedly elevated in nasal lavage, which had a discrepancy with serum IgG level. 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.[818]

Prophylactic antibiotics and early culture-directed antibiotics were recommended by expert groups.[815,819–823] Yet there are no consensus guidelines on the use of antibiotics in refractory CRS with immunodeficiency.

Overall, because the current studies were small in scale and not based on controlled trials, the balance of risk to benefit is unclear. 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. 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.

The effect of Ig replacement is controversial; 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 RS is less encouraging. Still, Ig replacement is an approved treatment for CVID because 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 specific antibody deficiency or IgG subclass deficiencies remains controversial. Thymic hormone

preparation thymostimulin was shown to be effective and safe in 1 study but it is now not available in the market. Thus, thymostimulin cannot be recommended (Table VII-21).

- Aggregate Grade of Evidence: C (Level 1b: 1 study; Level 2b: 2 studies; Level 3b: 2 studies; Level 4: 1 study; Level 5: 6 studies).
- Benefit: Unclear benefit from prophylactic antibiotics and Ig replacement in immunodeficient patients.
- Harm: Potential for bacterial resistance with the use of prophylactic antibiotics. Potential for side effects with IVIG.
- Cost: Moderate to high, depending on regimen.
- Benefits-Harm Assessment: Balance of benefit and harm.
- Value Judgments: Most studies involving immune function testing are performed in "recalcitrant" patients who have not responded to typical medical and surgical therapy. This group is poorly defined. Moreover, the LOE is low.
- Policy Level: Option.
- Intervention: Treatment of immunodeficiency is an option for "recalcitrant" CRS patients (Table VII-22).

VII.F. CRSsNP: Complications

Complications secondary to CRSsNP may be classified into those which are major and often associated with infection and those that are minor and typically associated with localized tissue changes. Although complications of CRSsNP can be indolent, acute exacerbations can be life-threatening, particularly in immunocompromised patients or those with altered sinus anatomy. It is difficult to determine the true incidence of these complications because most of the data stem from case reports.

Major complications of CRSsNP typically occur as a result of worsening infection that involves the eye, brain, and/or lungs. The microbiology of these complications differs from that of ARS.[825] Direct involvement or chronic inflammatory changes near the orbit can lead to enophthalmos,[826] epiphora,[827] diplopia,[828] proptosis,[829] optic neuropathy,[830,831] and vision loss.[832–834] Fungal or bacterial invasion along the skull base can lead to an epidural abscess or cavernous sinus thrombosis. The chronic inflammatory response observed in CRS can worsen existing airway hyperreactivity, but it can also lead to adult-onset asthma.[293] Although the paranasal sinuses appear to 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,[835,836] and intrinsic narrowing and tortuosity of the frontal recess appears to be a predisposing factor for mucocele formation.[836] Tissue remodeling can also lead to osteitis,[390,394,395] bone erosion and expansion,[837,838] as well as osseous metaplasia.[839,840] Sinonasal mucosal remodeling, at times irreversible, can occur.[841,842] The varied medical therapies aimed at treatment of CRSsNP, including antibiotics and systemic corticosteroids, can also cause serious complications and add morbidity to the disease.[843–847]

VIII. Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

This discussion of CRSwNP pertains to adults with this condition only. Pediatric RS is discussed in Section XI.

VIII.A. CRSwNP: Incidence/Prevalence

Larsen and Tos[848] estimated the prevalence of NP to be 6.3 per 10,000 in Denmark. Interestingly, between 26% and 42% (2600 to 4200 per 10,000) of autopsy specimens contain NP.[849,850] Tan et al.[288] reviewed the electronic health records from 307,381 adults who received care at the Geisinger Clinic from 2007 through 2009 and determined the average incidence rate of CRSwNP was 8.3 ($\pm$1.3) cases per 10,000 person-years.

VIII.B. CRSwNP: Comorbid Asthma

Since the introduction of the united airway concept,[851] a large body of evidence from clinical epidemiology, pathophysiology, histology, and treatment outcomes has correlated asthma and nasal polyposis. CRSwNP and asthma coexist frequently and share similar features of inflammation and remodeling. This association has been supported by numerous observations of similar histopathological changes,[852] the same primary effector cell (eosinophil), and common inflammatory mediators.[853]

Moreover, there is evidence that markers such as interleukin (IL)-5 and staphylococcal enterotoxin (SE) IgE within the NP tissue are associated with comorbid asthma, supporting the idea of systemic immunologic crosstalk.[300] Kato,[854] in a recent review, described evidence suggesting that newly identified epithelial-derived cytokines (IL-25, IL-33, and TSLP) help shape the local activation of Th2 immunity, and the exaggerated expression of these cytokines induces Th2 inflammation, which is associated with bronchial asthma and CRSwNP. There is evidence that, apart from a similar immunologic environment, defects in airway epithelial barrier function are associated with asthma and CRSwNP. These defects in barrier function could play a critical role in the pathogenesis of CRSwNP by allowing an influx of foreign antigens into the submucosa where they may trigger or exacerbate an inflammatory response. In an attempt to phenotype patients with asthma, Moore et al.[855] performed a cluster analysis of asthmatic patients. They found the subjects with concurrent asthma and sinus disease had less atopy but a higher prevalence of severe asthma, worse QoL, and later-onset disease.

Bronchial asthma is more prevalent in patients who suffer from CRS than in patients without.[7,293,856] Similarly, patients with asthma have a greater prevalence of CRS.[857] Three large epidemiological studies have demonstrated

TABLE VII-21. Evidence for immunodeficiency treatment in CRSsNP management

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Tas[814]	1990	1b	Randomized control trial; double-blind crossover trial (n = 20)	1. TP-1 then placebo; 2. placebo then TP-1	Endoscopy, DTH skin test, lymphocyte subsets, MIF assay, and other laboratory tests	R-CRS patients were successfully treated with TP-1, restoring some laboratory parameters
Quinti[597]	2007	2b	Multicenter prospective study	CVID patients on IVIG for a mean of 11.5 years (n = 224)	Ig level, lymphocyte subsets, culture test, CT	IVIG is more effective in reducing lower respiratory infections than reducing RS
Roifman[816]	1988	2b	Prospective crossover 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[818]	2010	3b	Case-control study	1. CRS with immune dysfunction or autoimmune disease (n = 22); 2. CRS control (n = 22)	QoL measurement, nasal endoscopy, sinus CT	Immune dysfunction CRS patients had similar outcomes as control CRS patients
Rose[817]	2006	3b	Case-control study	1. CVID (n = 13); 2. Selective IgA deficiency (n = 10); 3. Control (n = 14)	1. MRI; 2. 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
Buehring[824]	1997	4	Prospective case series (open trial)	16 R-CRS treated with azithromycin, N-acetylcysteine, and topical intranasal beclomethasone	1. MRI; 2. Nasal lavage for ECP, IL-8, TNF-α; 3. Nasal culture	Treatment was of little benefit in patients with R-CRS with an underlying immunodeficiency
Ocampo[819]	2013	5	Expert opinion			Recommended prophylactic antibiotics, Ig replacement if indicated, and early ESS
Kuruvilla[823]	2013	5	Commentary/review			Approximately one-half of the therapeutic dose is proposed for prophylactic antibiotics, with rotation to avoid drug resistance
Dalm[815]	2012	5	Expert opinion			Thymosin 1α may have an effect on monocyte function, a possible new target for therapy in R-CRS
Ryan[820]	2010	5	Expert opinion			Recommended prophylactic antibiotics; early, aggressive, culture-directed antibiotic treatment; and possible use IVIG
Ferguson[821]	2009	5	Expert opinion			Culture-directed antibiotics should be administered more promptly than in patients with normal immunity
Ryan[822]	2008	5	Expert opinion			Advocated prompt treatment with culture-directed antibiotics and the use of IVIG

TABLE VII-22. Recommendations for treatment of immune deficiency in "recalcitrant" CRS patients

Treatment	Grade of evidence	Balance of benefit to harm	Recommendation	Protocol
Other immune therapy	A	Equal	Recommendation *against*	Thymic hormone preparation thymostimulin
Immunoglobulin replacement	B	Equal	Optional	Common variable immunodeficiency
Prophylactic antibiotics	C	Equal	Optional	
ESS	C	Equal	Optional	
Early culture-directed antibiotics	D	Equal	Optional	

the association between these 2 diseases. The first study involved 52,000 subjects,[857] the second 6037 asthmatic patients,[858] and the third 488 asthmatic patients.[859] Regarding asthma severity in relation to CRSwNP, asthmatic patients have more concomitant CRSwNP (7%) than the general population (4%).[858] In nonatopic asthma and late-onset asthma, CRSwNP was found even more frequently, reaching 53% to 63%.[855] More than 60% of CRSwNP patients have lower airway involvement.[860] Often, CRSwNP and asthma patients show higher LM scores[70] as well as more severe nasal obstruction and hyposmia.[856]

Treatment of CRS decreases the severity of asthma (Table VIII-1).[319,861,862] Using objective and subjective sinonasal and asthma outcome measures, studies have demonstrated significant clinical improvement following ESS.[320,861,863–866] In patients with asthma and NPs, ESS was shown to improve asthma severity scores, reduce the need of inhaled corticosteroids and reduce the frequency of asthma-related emergency room visits.[863] Ehnhage et al.[864] showed in a prospective randomized trial that patients with CRSwNP had a significant improvement in nasal and lower airway symptoms after ESS. But they failed to show a benefit of postoperative INCS use. The same authors recently followed a cohort of CRSwNP patients after ESS and found an improvement in asthma symptoms score, daily peak expiratory flow, and nasal inspiratory flow.[867] Zhang et al.[868] observed in their retrospective analysis that patients with both NP and asthma experience a larger QoL improvement measured by SNOT-22 at 1 and 3 months, when compared to patients without asthma or NPs. In a smaller series of patients with NP, ESS did not affect the asthma state.[866] Alobid et al.[869] evaluated different outcomes of patients with CRSwNP and found that asthma, and especially persistent asthma, have an accumulative impact on the loss of smell. These authors suggested that CRSwNP could be used as a benchmark tool to identify asthma severity. Other authors have also found lower olfactory outcomes in patients who have associated CRSwNP and asthma compared to controls.[864]

Despite the number of publications suggesting that nasal conditions may trigger lower airway pathology in susceptible individuals and vice versa, these views are not universal.[7] Asthma and CRSwNP are not always clinically present together and Williamson et al.[870] found no correlation between nasal condition and spirometry results.

In conclusion, the preponderance of published evidence demonstrates an association between CRSwNP and asthma. Asthma as a comorbidity should be considered during the evaluation of a patient with CRSwNP.

- Aggregate Grade of Evidence: B (Level 1b: 3 studies; Level 2a: 3 studies; Level 2b: 5 studies).
- Benefit: Early diagnosis of asthma in patients with CRSwNP.
- Harm: Inconvenience of office visit and diagnostic testing.
- Cost: Moderate for associated diagnostic testing and possible consultation.
- Benefits-Harm Assessment: Balance of benefits over harm.
- Value Judgments: Asthma is highly prevalent in patients with CRSwNP.
- Policy Level: Recommend.
- Intervention: Asthma screening should be considered in all patients with CRSwNP.

VIII.C.1. CRSwNP: Pathophysiology

VIII.C.1.a. CRSwNP Pathophysiology Contributing Factors: Allergy. IgE-mediated allergy has been among the multiple etiologies suggested to cause CRSwNP. Allergy is strongly associated with a Th2-mediated response. Multiple studies suggest a prominent role for Th2-mediated inflammation in the pathogenesis of CRSwNP.[875–880] Elevated levels of Th2 cytokines IL-5 and IL-13 have been isolated in NP tissue and eosinophilic inflammation is commonly identified in both atopy and CRSwNP. In addition, mast cells and basophils are also significantly increased in NPs and their counts correlate with the increased eosinophils in polyp tissue. Inasmuch as mast cells and basophils are the cells involved in IgE-mediated allergic inflammation, their presence suggests that eosinophils, mast cells, and basophils are associated in the ongoing Th2 inflammatory response observed in CRSwNP. This indirect evidence of an association between

TABLE VIII-1. Evidence for CRSwNP and asthma as a comorbidity

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Swierczyńska-Krępa[871]	2014	1b	Prospective randomized trial	1. AERD patients with NPs; 2. Non-AERD patients with NPs	1. Nasal clinical and biochemical parameters; 2. Lung clinical and biochemical parameters	Only patients with AERD had clinically beneficial effects of ASA desensitization on nasal and bronchial symptoms
Ehnhage[864]	2009	1b	Prospective randomized trial	CRSwNP and asthma, after ESS: 1, INCS; 2, placebo	1. Nasal symptoms; 2. Polyp score; 3. Lower airway symptoms	ESS improved nasal and lower airway symptoms. No significant differences between INCS group and placebo
Ragab[319]	2006	1b	Prospective randomized trial	1. Surgical group (CRSsNP and CRSwNP); 2. Medical group (CRSsNP and CRSwNP)	1. Asthma symptoms and control; 2. FEV1 and peak flow; 3. Medication use; 4. Hospitalization	Improved symptoms in medical group. Improved FEV1. Lower medication needs. Lower hospitalization rate
Vashishta[872]	2013	2a	Systematic review	CRS patients with at least one asthma outcome reported	1. Overall asthma control; 2. Asthma attacks; 3. Number of hospitalizations; 4. Use of oral corticosteroids	ESS in patients with concomitant bronchial asthma improves clinical asthma outcome measures, but not lung function testing
Dejima[574]	2006	2b	Prospective controlled trial	1. CRS with asthma undergoing ESS; 2. CRS without asthma undergoing ESS	1. Lower airway symptoms; 2. Sinonasal symptoms	Improved symptoms. Reduced medication needs. Improved FEV1
Ikeda[862]	1999	2b	Prospective controlled trial	1. CRSwNP undergoing ESS; 2. CRSsNP undergoing ESS	1. Sinonasal and pulmonary symptoms; 2. Medication use	Improved FEV1 and reduced medication needs
Ehnhage[867]	2012	2b	Cohort study	CRSwNP patients with asthma, after ESS	1. Dyspnea/cough scores; 2. Mean daily peak expiratory flow rate; 3. Spirometry; 4. Butanol test; 5. Olfaction score; 6. PNIF; 7. polyps score	Improvement in asthma symptoms score. Improvement in daily peak expiratory flow. Improvement in all nasal parameters
Uri[866]	2002	2b	Prospective cohort	CRSwNP and asthma patients undergoing ESS	1. Asthma and nasal symptoms; 2. Spirometry; 3. Medication use	Improved symptoms. Lower medication needs. No changes in FEV1
Lamblin[873]	2000	2b	Prospective cohort	CRSwNP and asthma patients followed for 4 years	1. Nasal symptoms; 2. Lower airway clinical and biochemical parameters	CRSwNP patients requiring surgery developed nonreversible airflow obstruction during the observation period
Senior[874]	1999	2b	Prospective cohort	CRS with asthma undergoing ESS	1. Symptoms score; 2. Asthma exacerbations; 3. Medication use	Improved symptoms. Fewer asthma relapses. Lower medication needs
Nishioka[865]	1994	2b	Prospective cohort	CRSwNP and asthma patients undergoing ESS	1. Symptoms score; 2. Medication use; 3. Number of emergency visits	Improved symptoms
Zhang[868]	2014	4	Retrospective case series	Adults with CRS after ESS	SNOT-22	CRS patients with both asthma and NP have a larger QoL benefit after ESS than CRS patients without asthma or polyps

(*Continued*)

TABLE VIII-1. Continued

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Batra[861]	2003	4	Retrospective case series	CRSwNP and asthma patients after ESS	1. Symptoms score; 2. Medication use; 3. Number of emergency visits; 4. FEV1 change	Improved symptoms. Lower medication needs. Lower number of emergency visits. Improved FEV1
Dunlop[320]	1999	4	Retrospective case series	1. CRSwNP and asthma patients after ESS; 2. CRSsNP and asthma patients after ESS	1. Symptoms score; 2. Medication use; 3. Number of emergency visits; 4. FEV1 change	Improved symptoms. Lower medication needs. Lower hospitalization rates. Improved FEV1

allergy and CRSwNP is not, however, confirmed with direct clinical evidence, where the data are often unclear or contradictory.

In 2014, Wilson et al.[322] reviewed the role of allergy in CRSwNP and CRSsNP. They considered only studies that delineated the presence of polyps or not, so that studies examining "CRS" alone were excluded. 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 CRSwNP specifically, they found 18 epidemiologic studies that addressed the role of allergy in CRSwNP. Ten of these studies (1 level 2b, 9 level 3b) supported an association, 7 (3 level 3b, 4 level 4) did not, and 1 (level 3b) was equivocal.

Tan et al.[881] found a higher number of inhalant sensitivities in CRSwNP patients compared to CRSsNP and rhinitis patients, although the overall sensitivity rates were similar. Houser and Keen[882] evaluated for allergy using intradermal testing or radioallergosorbent testing in surgical CRSwNP and CRSsNP patients. In CRSwNP patients, a statistically significant association was identified only for perennial allergens, most notably dust mites. Similarly, Asero and Bottazzi[883] identified higher prevalence of dust mite sensitivity in polyp patients when compared with non-polyp counterparts. Munoz del Castillo et al.[884] further implicated dust mite allergy in CRSwNP patients. Using skin-prick testing, they found 63.2% had at least 1 positive result, most frequently to dust and *Olea europaea*. Pumhirun et al.[885] found elevated dust and cockroach in CRSwNP. Asero and Bottazzi[886] found positive skin testing to at least 1 fungal species at higher rates in CRSwNP patients when compared to both allergic controls and CRSsNP patients. Among these patients, the only genus to reach statistical significance was *Candida*.

Other studies have not found a significant association between CRSwNP and allergy based on either rates of sensitivity or disease outcomes. Pearlman et al.[887] found no significant difference in atopic rates between CRSwNP and CRSsNP groups. Keith et al.[888] found that ragweed-allergic CRSwNP patients did not have worse symptoms during the ragweed season. Erbek et al.[889] divided patients with CRSwNP by atopic status. No difference was identified in NP size, CT scores, symptoms, or recurrence of disease based on atopic status.[889] Similarly, Bonfils' group[890,891] did not identify any difference in the presenting symptoms or postoperative course of CRSwNP patients regardless of their allergic status.

Contradictory results in these studies likely reflect differences in study design, inclusion criteria, and populations studied. Taken together, these data suggest that inhalant allergy may be a disease-modifying factor in CRSwNP, but a direct link to causation is lacking.

Taking the totality of these studies into account, Wilson et al.[322] concluded that allergy testing should be considered an option in CRSwNP patients, inasmuch as there was a theoretical benefit of finding inflammatory triggers, there is little harm, and the low aggregate LOE did not support a strong recommendation either for or against this practice.

Although food allergies have been postulated to play a role in CRSwNP, there is no evidence that substantiates this view. A few studies show higher sensitization rates to foods in patients with CRSwNP compared to controls, but the clinical implications are not known.[892,893]

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. Well-designed, prospective studies with defined inclusion and exclusion criteria among defined populations should shed additional light on this relationship.

- Aggregate Grade of Evidence: D (Conflicting observational studies—case control and cohort design).
- Benefit: Management of allergy symptoms is low risk and may reduce 1 potential source of inflammation contributing to CRSwNP.
- Harm: Discomfort from allergy testing, sedation from oral antihistamine, epistaxis from INCS.
- Cost: Direct costs: diagnostic testing and treatment. Indirect costs: time off work for immunotherapy, decreased productivity during peak allergy seasons.
- Benefits-Harm Assessment: Low-risk treatment to achieve improvements in allergic symptoms and QoL.
- Policy Level: Option.
- Value Judgments: Allergy testing and treatment (avoidance, medication, immunotherapy) are an option for patients with CRSwNP.

VIII.C.1.b. CRSwNP Pathophysiology Contributing Factors: Biofilms. Biofilms in general are addressed in Section VII.C.1.b. With regard to CRSwNP, biofilm presence and polyp status in CRS seem to have a relatively insignificant relationship. One study showed no association,[323] whereas another study showed a trend toward an increased number of bacterial species in CRSwNP; this result did not reach significance. Interestingly, fungi were only detected in the presence of NPs, although this was a rare finding.[330] In CRSwNP, there was no qualitative difference in inflammatory cells between patients with or without biofilms.[894] Quantitatively, there is an association between biofilms and increased eosinophilic content, in accordance with other evidence that biofilms encourage a more potent Th2 response of the immune system.[895,896]

VIII.C.1.c. CRSwNP Pathophysiology Contributing Factors: Fungus. *Because of limited data, CRSwNP and CRSsNP are combined in Section VII.C.1.c.*

VIII.C.1.d. CRSwNP Pathophysiology Contributing Factors: Osteitis. *Because of limited data, CRSwNP and CRSsNP are combined in Section VII.C.1.d.*

VIII.C.1.e. CRSwNP Pathophysiology Contributing Factors: Reflux. *Because of limited data, CRSwNP and CRSsNP are combined in Section VII.C.1.e.*

VIII.C.1.f. CRSwNP Pathophysiology Contributing Factors: Vitamin D Deficiency. VD_3 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.[422,423] The literature on VD_3 in CRSwNP largely consists of case series, case-control, and in vitro studies.

In the United States, several reports have linked CRSwNP and low $25VD_3$. Adult CRSwNP and AFRS patients had significantly lower $25VD_3$ than controls and low $25VD_3$ correlated with greater sinus bone erosion as measured on CT scan.[426] Likewise, in a pediatric population CRSwNP and AFRS patients had significantly lower $25VD_3$ levels than controls.[425] CT findings were not reported in these patients.

Recently, in a retrospective analysis of 70 CRSwNP patients Schlosser et al.[432] found 55% were $25VD_3$ insufficient (<30 ng/mL) and an additional 30% were $25VD_3$ deficient (<20 ng/mL). The lowest levels were found in African American patients with nearly 80% insufficient. Severity of mucosal disease (defined by LM score on CT) also correlated with low $25VD_3$ level. Wang et al.[433] found significantly lower $25VD_3$ in Taiwanese CRSwNP patients compared to CRSsNP patients. Low $25VD_3$ also correlated with more severe polyp grade. Although the proportion with $25VD_3$ deficiency (<20 ng/mL) was higher in CRSwNP (45.5%) than CRSsNP (6.3%), this was not reported as statistically significant. $25VD_3$ was inversely related to LM score, consistent with U.S. patients.[432]

With regard to allergic status, Ozkara et al.[897] found Turkish patients with concurrent CRSwNP and AR had significantly lower $1,25VD_3$ than healthy controls. This effect was not seen in CRSwNP without AR, implying that allergy is a necessary condition. This contrasts with U.S. reports where CRSwNP alone was associated with low $25VD_3$. The 2 groups, however, measured different molecules, with the Turkish work measuring the active $1,25VD_3$ and the U.S. studies measuring $25VD_3$, conventionally considered the more accurate marker of VD_3 status due to its longer half-life. The Taiwanese study examining interplay of allergic factors in CRSwNP reported an inverse correlation between $25VD_3$ and total IgE, though this was not statistically significant.[433]

Passive or active cigarette smoke exposure appears to decrease both systemic and local sinus tissue levels of $25VD_3$. This finding was consistent across CRSwNP and control patients.[427]

In vitro studies also support the role of VD_3 in CRSwNP pathogenesis. Sultan et al.[430] found in a heterogeneous group (healthy, CRSwNP and CRSsNP) that human sinonasal epithelial cells constitutively express 1α hydroxylase, the enzyme responsible for converting $25VD_3$ to the active $1,25VD_3$. Mulligan et al.[427] confirmed that epithelial cells convert $25VD_3$ to $1,25VD_3$ in a dose-dependent manner, but that CRSwNP epithelial cells appear to have lower levels of 1α hydroxylase and are less efficient at $25VD_3$ activation. Exogenous insults with smoke extract further impaired epithelial cell conversion of $25VD_3$ into the biologically active $1,25VD_3$. Finally, addition of $1,25VD_3$ to smoke exposed cells inhibited their secretion of proinflammatory cytokines (IL-6, IL-8, CCL20), alluding to its potential to influence immune tolerance.

CRSwNP patients have $25VD_3$ deficiencies that correlate with increased numbers of systemic and local dendritic cells. This finding is consistent in both adults and children with CRSwNP, independent of atopic status[425,426] and may explain the Th2 skewing noted in these patients.

Active $1,25VD_3$ and its analogue tacalcitol significantly inhibit activated NP fibroblast proliferation.[898] Furthermore, combined tacalcitol/budesonide was better at suppressing fibroblast proliferation than tacalcitol alone, raising the possibility of an additive or synergistic action between tacalcitol and corticosteroid.[899] In addition to suppressing fibroblast proliferation, $1,25VD_3$ and tacalcitol inhibited production of the proinflammatory cytokines IL-6, IL-8, and RANTES (an eosinophil/lymphocyte chemoattractant) by activated human NP fibroblasts.[900,901] With regard to suppressing RANTES production, a synergistic effect was observed when budesonide was added to $1,25VD_3$ or tacalcitol as compared to monotherapy. Finally, studies

on 1,25VD_3 or tacalcitol-exposed fibroblasts did not show a shift in BCL-2/BAX gene expression in a proapoptotic direction.[902]

In summary, available evidence indicates that 25VD_3 deficiency is common in CRSwNP and correlates with severity of mucosal and bone disease in CRSwNP.

- Aggregate Grade of Evidence: C (Level 3b: 5 studies, Level 4: 1 study; Table VIII-2)

VIII.C.1.g. CRSwNP Pathophysiology Contributing Factors: Superantigens. Superantigens are a class of antigens that stimulate T cells less specifically than normal antigens, causing nonspecific and polyclonal activation of T cells with massive cytokine release. The first description of a possible role of superantigens and IgE-antibodies to superantigen in CRSwNP dates from 2001.[875] The presence of IgE specific to staphylococcal enterotoxins A and B (SEA and SEB) pointed to the possible role of bacterial superantigens in the development of inflammation, as it was associated with increased levels of total IgE and eosinophilic inflammation in CRSwNP. It was later demonstrated that at least 1 toxin was detected in 14 of 29 patients with bilateral CRSwNP, but in none of 11 healthy controls and in only 1 of 13 CRSsNP samples.[903] Serum SEA-specific, SEB-specific, and toxic shock syndrome toxin 1 (TSST-1)-specific IgE antibodies were detected in 0% vs 75% of healthy controls vs CRSwNP, respectively, and 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.[904] The expansion of lymphocytes expressing T cell receptors with specific V beta-domains was limited to the polyp tissue, whereas much less bias was found in the blood.[905] The findings of superantigens in CRSwNP were independently confirmed by others,[906,907] and the association of those findings with an eosinophilic inflammation was also reported by multiple groups.[908,909] Interestingly, there were no differences in superantigen genes between *S. aureus* strains isolated from controls compared with those from NP patients.[910] To impact the disease, *S. aureus* may have to pass the epithelial barrier and release superantigens intramucosally.

Stimulation of mucosal tissue with SEB, the best studied superantigen, over 24 hours induced a significant increase of IL-1β, 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.[911] SEB also downregulates the anti-inflammatory prostaglandin PGE4[912] in CRSwNP fibroblasts, and induces growth factors and chemokines in nasal epithelial cells.[913] Most importantly, IgE antibodies to enterotoxins (SE-IgE) were associated with significantly higher concentrations of IgG, specifically of the IgG4 subclass, and IgE in NPs.[914] In CRSwNP, evidence for local IgE synthesis and class switch recombination was also provided[915]; 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. 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.[916,917] Among those IgE specificities, only staphylococcal enterotoxins have superantigenic activity. CRSwNP showed a significantly higher *S. aureus* culture-positivity and a higher detection rate of *S. aureus* superantigens and of specific SE-IgE in a recent meta-analysis.[918] This meta-analysis confirmed that superantigens may be a risk factor for CRSwNP, and the presence of superantigen also was related to disease severity.

In a cluster analysis, SE-IgE in the NP tissue was the best categorical value to predict comorbid asthma in CRSwNP patients[300]; 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,[919] it was associated with asthma in a Europe-wide epidemiological study[920] and associated with severe, often nonatopic late-onset asthma.[921,922] 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.[922]

In a study investigating the immune profiles of recurrent vs nonrecurrent 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 nonrecurrent CRSwNPs.[923]

S. aureus also is frequently found in patients with AFRS[924,925] and could be demonstrated to coexist with *Aspergillus sp*. in the sinuses, and to modulate the typical IgE immune response in those patients.[924]

In summary, based on a wealth of in vitro and some clinical data, superantigens appear to have a significant role in the pathogenesis of CRSwNP.

VIII.C.1.h. CRSwNP Pathophysiology Contributing Factors: Microbiome Disturbance. *Because of limited data, CRSwNP and CRSsNP are combined in Section VII.C.1.h.*

VIII.C.1.i. CRSwNP Pathophysiology Contributing Factors: Anatomic Variation. Anatomical remodeling occurs with increasing severity of CRSwNP as judged by CT scan imaging.[926] However, the degree to which anatomic variation in the paranasal sinuses might contribute to disease pathophysiology (ie, concha bullosae, paradoxical positioning of the MT, infraorbital ethmoid [Haller] cells, and NSD, among others) is less

TABLE VIII-2. Evidence for CRSwNP and vitamin D_3 deficiency as a contributing pathogenic factor

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Mulligan[427]	2014	3b	Case-control	1. Control (CSF leak/pituitary tumor patients) (n = 21); 2. CRSsNP (n = 40); 3. CRSwNP (n = 45)	1. $25VD_3$ level; 2. CYP27B1 gene expression; 3. $25VD_3$ to $1,25VD_3$ conversion	Lower $25VD_3$ in CRSwNP than controls. Cigarette smoke associated with lower $25VD_3$ level, impairs conversion to $1,25VD_3$
Wang[433]	2013	3b	Case-control	1. CRSwNP (n = 25); 2. CRSsNP (n = 20)	1. $25VD_3$ level; 2. Polyp grade; 3. LM score; 4. Total IgE	CRSwNP have lower $25VD_3$ than CRSsNP. $25VD_3$ is inversely correlated with polyp grade severity
Ozkara[897]	2012	3b	Case-control	1. Control (healthy volunteers) (n = 40); 2. CRSwNP and AR (n = 30); 3. CRSwNP (n = 30)	1. $1,25VD_3$; 2. IL-4, IL-10, IFNγ level	CRSwNP with AR have lower $1,25VD_3$ than control. CRSwNP with AR have TH2 cytokine profile
Mulligan[425]	2012	3b	Retrospective case-control	1. Control patients (n = 14); 2. CRSsNP (n = 17); 3. CRSwNP (n = 5); 4. AFRS (n = 14)	1. $25VD_3$ level; 2. Number of CD209+ dendritic cells in nasal tissue	$25VD_3$ is lower in pediatric CRSwNP and AFRS. Low $25VD_3$ correlates with increased dendritic cells
Mulligan[426]	2011	3b	Retrospective case-control	1. Control (CSF leak) (n = 14); 2. CRSsNP (n = 20); 3. CRSwNP (n = 9); 4. AFRS (n = 14)	1. $25VD_3$ level; 2. Dendritic cells as percentage of total peripheral blood mononuclear cells	$25VD_3$ is lower in CRSwNP and AFRS. Low $25VD_3$ correlates with increased circulating dendritic cells
Schlosser[432]	2014	4	Retrospective case-series	1. CRSwNP (n = 70)	1. $25VD_3$ level	$25VD_3$ insufficiency/deficiency is common in CRSwNP, especially in African Americans

IFN = interferon.

clear.[16,456,457,927] CRSwNP patient populations have rarely been independently studied to determine the influence of anatomic variation on disease. Any causality/relationship of anatomic variation and disease burden is therefore not well-understood in CRSwNP.

One study specifically examined CRSwNP patients. Leung et al.[928] investigated obstruction at the OMC in CRSwNP and CRSsNP and noted that OMC obstruction was associated with increasing LM scores in both forms of CRS. In CRSsNP, OMC obstruction was associated with adjacent sinus inflammation, whereas in CRSwNP, this correlation was absent. The authors concluded that paranasal sinus inflammation was not likely to be a postobstructive phenomenon in the setting of CRSwNP. Jain et al.[16] found a significantly higher average number of anatomical anomalies (accessory ostia, conchae bullosae, infraorbital ethmoid cells, lateralized uncinated processes, and paradoxical MTs) in patients with limited disease compared to a cohort with pansinusitis or control group without disease. These data again suggest that anatomical variants may be related to impairment of the OMC, whereas a primary mucosal abnormality contributes to more diffuse CRS disease.[16]

In conclusion, the relationship between anatomical variants and development of disease in patients with CRSwNP is impossible to ascertain given our current literature and understanding of this inflammatory disease. Studies that independently evaluate this group of patients suggest minimal influence on pathophysiology and instead favor a systemic inflammatory process leading to sinonasal disease.

Aggregate Grade of Evidence: not applicable

VIII.C.1.j. CRSwNP Pathophysiology Contributing Factors: Septal Deviation. *Because of limited data, CRSwNP and CRSsNP are combined in Section VII.C.1.i.*

VIII.C.1.k. CRSwNP Pathophysiology Contributing Factors: Innate Immunity. The topic of innate immunity of the sinonasal cavity was introduced in Section VII.C.1.k with regard to CRSsNP. Innate immunity's role in CRSwNP has been studied as well (Table VIII-3). The evidence examining innate immunity in CRSwNP can be divided into 2 categories: (1) key antimicrobial proteins and peptides, and (2) pattern recognition receptors.

(1) Key Antimicrobial Proteins and Peptides

Seven studies provide evidence of increased activity of antimicrobial proteins and peptides in innate immunity in patients with CRSwNP whereas 4 studies provide evidence

TABLE VIII-3. 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							
Li[485]	2014	1. CRSsNP (12); 2. CRSwNP (12); 3. Control (7)	Sinonasal tissue (CRS); sinonasal tissue (control)	RT-PCR; IHC	TFF1, TFF3	Similar TFF1 and TFF3 mRNA and protein levels in ethmoid tissue of CRSwNP and control	Normal
Salman[936]	2012	1. CRSwNP (21); 2. Control (15)	Nasal polyps; nasal tissue (control)	ELISA	SP-A, SP-D	No difference in SP-A and SP-D between 2 groups	Normal
Seshadri[521]	2012	1. CRSsNP (59); 2. CRSwNP (81); 3. 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[482]	2012	1. CRSsNP (37); 2. CRSwNP (39); 3. Control (6)	Sinus mucosa (CRS, control)	RT-PCR; IHC	Lysozyme	Lysozyme protein, but not the mRNA, was increased in patients with CRSwNP	Increased
Park[933]	2011	1. CRSwNP (202); 2. Control (11)	Nasal polyps IT tissue (control)	Immunofluorescence staining	AMCase, ChT	AMCase was increased in nasal tissue of CRSwNP	Increased
Wang[929]	2010	1. CRSwNP; 2. Control	Nasal polyps; nasal tissue (control)	RT-PCR; IHC	SP-A	SP-A was increased in sinonasal tissue of CRSwNP	Increased
Cui[484]	2009	1. CRSsNP (72); 2. CRSwNP (95); 3. Control (110)	Blood (CRS); healthy blood	ELISA	C3, C4	Serum C3 level was increased in CRSwNP	Increased
Ramanathan[935]	2008	1. CRSwNP (32); 2. 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[513]	2007	1. CRSwNP (22); 2. Control (11)	Ethmoid mucosa (CRSwNP, control)	RT-PCR	AMCase	AMCase mRNA level was increased in nasal tissue of CRSwNP	Increased
Claeys[512]	2005	1. CF-CRSsNP (14); 2. Non-CF-CRSwNP (15); 3. Control (10)	Sinonasal sample (CRS); IT tissue (control)	RT-PCR; ELISA	HBD-2, HBD-3, TLR2, TLR4	HBD-2 was increased in CF-CRSwNP vs Non-CF-CRSsNP and control. No difference in TLR2 and TLR2 was detected between non-CF-CRSwNP and control	Increased or normal
Chen[931]	2004	1. CRSwNP (12); 2. Control (7)	Nasal polyps; IT mucosa (control)	RT-PCR; IHC	LL-37	LL37 was significantly increased in CRSwNP	Increased

(*Continued*)

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TABLE VIII-3. Continued

Study	Year	Study groups (n =)	Tissue	Technique	Type of innate immunity	Findings	Innate immunity activity
Schicht[930]	2013	1. CRSwNP; 2. AR; 3. 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[934]	2003	1.Tonsillar disease; 2. Hypertrophic adenoids; 3.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							
Zhang[488]	2013	1. CRSsNP (40); 2. CRSwNP (38); 3. 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[487]	2012	1. CRSsNP (22); 2. CRSwNP (19); 3. Control (17)	Inflamed sinonasal tissue	qRT-PCR; IHC	sRAGE, mRAGE, esRAGE	sRAGE and mRAGE levels were decreased in CRSwNP compared to controls	Decreased
Lane[510]	2006	1. CRSwNP (30); 2. Control (10)	Nasal polyps; IT 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
Månsson[938]	2011	1. CRSwNP (24); 2. 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[937]	2011	1. CRSwNP (20); 2. Control (15)	Nasal polyps (CRS); turbinate tissue (control)	DNA microarray; RT-PCR; Western blot; IHC	125 genes for TLRs signaling pathways	TLR9 mRNA and protein level were increased in NPs of CRSwNP	Increased
Xia[939]	2008	1. CRSwNP (10); 2. Control (10)	Epithelial cell isolated from nasal tissue	Flow cytometry	TLR9	TLR9 epithelial cell isolated from nasal tissue was remarkably decreased in CRSwNP	Decreased
Ramanathan[932]	2006	1. CRSwNP (10); 2. 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

AMCase = acidic mammalian chitinase; ChT = chitotriosidase; esRAGE = endogenous secretory RAGE; IT = inferior turbinate; mRAGE = membrane-bound RAGE; sRAGE = soluble RAGE; SP = surfactant protein.

of decreased activity. In patients with CRSwNP only 2 studies report that antimicrobial proteins and peptides levels were normal.

Woods et al.[482] found that immunoreactivity of lysozyme was significantly increased in mucosal biopsy specimens of CRSwNP compared to control, but not the mRNA level. Wang et al.[929] found that SP-A mRNA and protein were significantly increased in sinonasal tissue of CRSwNP compared to controls. Conversely, another study did not detect any difference in SP-A between CRSwNP and controls nor did it find a difference in levels of SP-C or SP-D. However, it did demonstrate that SP-B protein levels were significantly increased in patients with CRSwNP.[930]

Cathelicidin (LL-37) is a peptide that regulates the innate immune response at the mucosal surface as an antimicrobial and as a proinflammatory peptide. LL-37 can be directly cytotoxic to epithelial cells and is thought to regulate the inflammatory response through effector cells such as mast cells, macrophages, and neutrophils. Chen and Fang[931] found that LL-37 is constitutively expressed on the surface of sinonasal epithelial cells and is significantly increased in patients with CRSwNP compared to controls. The study suggests that upregulation of LL-37 plays an important role in the heightened inflammatory response seen in patients with CRSwNP.

Cui et al.[484] showed that serum C3 level was significantly increased in CRSwNP compared to that of control. Ramanathan et al.[932] and Park et al.[933] both reported that acidic mammalian chitinase (AMCase) mRNA or protein level was significantly increased in nasal tissue of patients with CRSwNP compared to that of controls. The latter study also found that chitotriosidase (ChT) was significantly increased in NP tissue of CRSwNP. Last, Claeys et al.[512] found that human beta defensin (HBD)-2 expression is significantly higher in sinonasal tissue of CRSwNP without CF than that of CRSwNP with CF and control.

Two studies by Claeys et al.[512,934] showed that there were no significant differences in HBD2 and HBD3 mRNAs level between CRSwNP and control. In contrast, Ramanathan and Lee[935] found that HBD-2 protein level was significantly decreased in the sinonasal epithelial cells isolated from nasal tissue compared to that of control.

Seshadri et al.[521] found that expression of antimicrobial PLUNC family members PLUNC 1, PLUNC 2, and lactoferrin proteins was significantly decreased in NP tissues of CRSwNP compared to that of CRSsNP and control. Two recent studies reported that patients with CRSwNP have normal level of antimicrobial proteins TFF1, TFF3, SP-A, and SP-D when compared to that of healthy controls.[485,936]

Taken together, these studies provide significant evidence of altered antimicrobial protein and peptide activity in CRSwNP. Some protein families are increased whereas others are decreased and some studies show contradictory results.

(2) PRRs in Innate Immunity

Like studies in antimicrobial proteins and peptides, several studies of PRRs provide evidence of downregulated PRRs in CRSwNP whereas others show increased activity.

Zhang et al.[488] showed that TLR2, TLR4, and TLR7 mRNAs and protein levels were remarkably higher in sinonasal tissue of CRSwNP compared to that of CRSsNP and controls. Zhao et al.[937] found that both TLR-9 mRNA and protein level were increased in NPs of CRSwNP compared to nasal tissue of controls. Last, Månsson et al.[938] found that the NLR mRNA level was higher in NPs than in normal nasal mucosa.

Four studies revealed that mRNA or protein level of TLR9 and or TLR2 in epithelial cells isolated from nasal tissue or sinonasal tissue was markedly decreased in CRSwNP compared with controls.[510,513,935,939] These studies suggest that impaired innate immune responses via TLR-9 on sinonasal epithelial cells may represent a critical mechanism in chronic inflammatory process of CRSwNP. One study showed that there is no significant difference in TLR2 and TLR4 in sinonasal tissue between CRSwNP and controls.[512] Examination of soluble and membrane-bound RAGE in CRSwNP patients demonstrated that tissue protein levels of both forms were reduced.[487]

Summary. In summary, there is conflicting data suggesting either an upregulation or downregulation of expression of antimicrobial proteins, antimicrobial peptides, and PRRs in CRSwNP.

VIII.C.1.l. CRSwNP Pathophysiology Contributing Factors: Epithelial Barrier Disturbance. *Because of limited data, CRSwNP and CRSsNP are combined in Section VII.C.1.j.*

VIII.C.1.m. CRSwNP Pathophysiology Contributing Factors: Ciliary Derangements. Ciliary derangements in general are reviewed in Section VII.C.1.m in the context of CRSsNP. CRSwNP has more pronounced ciliary dysfunction in some cases, and there are several reasons that it manifests differently than CRSsNP. 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.[940] 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.[564] Chronically increased CBF has a potential consequence of downregulating endogenous stimulatory pathways, and the cell loses responsiveness to natural CBF stimulants and cannot be modulated normally.[495] Epithelial damage

in CRSwNP has also been associated with squamous metaplasia, and abnormal or absent cilia are often associated with this metaplastic change.[302,303,581–583] Scanning electron microscopy confirms the abnormal architecture, with cilia in CRSwNP presenting as overly dense, lengthened, and untidy. Ciliogenesis factors are correspondingly upregulated.[304]

VIII.C.1.n. CRSwNP Pathophysiology Contributing Factors: Immunodeficiency. Little evidence exists examining the role of immunodeficiency in CRSwNP. Tran Khai Hoan et al.[941] examined a prospective case series and concluded that a link between IgG subclass deficiency and CRSwNP seemed unlikely. Two case-control studies have also examined this subject. Seppanen et al.[591] 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.[591] Cui et al.[484] performed a case-control study in Chinese adult patients. They found that increased levels of C3 and mannose-binding lectin (MBL, a pattern-recognition molecule that can activate the lectin pathway of 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.,[277] in which 42% of CRS subjects were CRSwNP, demonstrated that patients with medically refractory CRS may have a high prevalence of low preimmunization antipneumococcal titer and specific antibody deficiency. However, no correlation was identified specifically in CRSwNP.[277] Baraniuk and Maibach[942] 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.

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 (Table VIII-4).

- Aggregate Grade of Evidence: C (Level 2: 1 study; Level 3b: 2 studies; Level 4: 3 studies).
- 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 and 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.

VIII.C.1.o. CRSwNP Pathophysiology Contributing Factors: Genetic Factors. A lack of direct comparison of genetic variation between CRSwNP and CRSsNP makes it difficult to determine precisely whether similar genetic variations underlie CRSwNP and CRSsNP phenotypes. Early work on genetics of CRSwNP performed on a Japanese CRSwNP population suggested a link with human leukocyte antigen (HLA) types.[943] This work was extended upon by assessing a white CRSwNP population affected with AFRS.[634] This study described a clustering of the HLA-DQB1*03 allele, implicating adaptive immune responses in the development of CRSwNP. In this study, no comparison with CRSsNP was performed so it is difficult to state whether this is specific to CRSwNP or a feature of CRS overall.

Differences between CRSwNP and CRSsNP have nevertheless been suggested in at least 1 other study. In a replication article, Zhang et al.[618] compared populations of Han Chinese in China with CRSwNP, CRSsNP, and control subjects. They replicated previously published associations in the RYBP, AOAH, IRAK-4, and IL1RL1 genes.[613,626,637] When assessed according to subgroup, and even with the loss of power afforded by the smaller subgroup analyses, certain differences were apparent between the 2 CRS populations. Although candidate SNPs in the RYBP gene were similar in allelic frequencies as well as p value and risk for both CRSwNP and CRSsNP populations, genetic variations in the AOAH gene were only seen in the CRSsNP group (CRSsNP: OR = 0.30, $p = 8.11 \times 10^{-11}$; CRSwNP: OR = 0.96, $p = 0.64$). Conversely, weaker associations seen for SNPs in the IRAK-4 gene were mainly limited to the CRSwNP population. This suggests that different mechanisms may underlie the development of CRSwNP compared to CRSsNP.

Certain asthmatic populations have been assessed as to presence or absence of CRSwNP. A large South Korean asthmatic population has been characterized as to presence or absence of nasal polyposis. The Park et al. group have identified CRSwNP candidate SNPs in genes coding for elements of the HLA system,[944] in UBE3C,[654] in DCBLD2,[650] and in CIITA.[649] These 4 genes are implicated in regulation of immune responses, suggesting a role in the development of CRSwNP. Again, given the nature of the population sampled, it is impossible to determine whether these are specific to CRSwNP.

The CRSwNP population has been further subdivided according to acetylsalicylic acid (ASA) intolerant and ASA-tolerant CRSwNP phenotypes. The candidate genes implicated (CD58, DPP10)[651] are quite novel and may lend

TABLE VIII-4. Evidence for CRSwNP and immunodeficiency as a contributing pathogenic factor

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Tran Khai Hoan[941]	2014	2b	Prospective case series	1. Operated (n = 118); 2. Not operated (n = 43)	Ig and IgG subclass levels, symptom scale, endoscopy	A link between IgG subclass deficiency and CRSwNP seems unlikely
Cui[484]	2009	3b	Case-control study	1. CRSwNP (n = 95); 2. CRSsNP (n = 72); 3. 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[591]	2006	3b	Case-control study	1. R-CRS (n = 48); 2. ARS (n = 50); 3. Unselected control (n = 150); 4. 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
Carr[277]	2011	4	Retrospective case series	129 CRS (42% with CRSwNP)	Incidence	R-CRS associated with low preimmunization antipneumococcal titer and specific antibody deficiency. No difference with CRSwNP
Baraniuk[942]	2005	4	Retrospective case series	99 CRS (50% with CRSwNP)	Incidence	Ig subclass deficiencies were more prevalent in CRSsNP than CRSwNP

themselves to new leads in investigation of pathophysiology of ASA intolerance.

An intriguing recent variation has been to assess genetics of CRSwNP based on type of bacteria colonizing the sinus surface. A pooling-based genomewide association study by Cormier et al.[630] compared CRSwNP patients according to *S aureus* carriage. Even though limited to 39 candidate SNPs, they identified several candidate genes, notably in the area of pathogen engulfment and destruction. Their data suggest alterations in immunity might predispose to colonization with secondary environmental modulators that influence subsequent development and persistence of disease.

An example and final caveat is that gene function may be altered in a transmissible fashion by means other than genetic variation. Epigenetic modification of the genome, which alters gene function in response to external environment, may occur and may be transmitted to replicating cells and progeny. Evidence of differences in gene methylation between ASA-intolerant and ASA-tolerant populations supports this concept.[945,946]

Taken together, these findings suggest that the genetic underpinnings of CRSwNP may differ somewhat from those of CRSsNP. Numerous genes have been implicated in the pathophysiology of both CRSwNP as well as CRSsNP. These genes, with their differential impact on phenotype (where known), are listed in Table VII-10.

VIII.C.1.p. CRSwNP Pathophysiology Contributing Factors: Aspirin Exacerbated Respiratory Disease. More often than previously thought, recurrent nasal polyposis is discovered to be associated with aspirin sensitivity and asthma. This clinical scenario, often referred to as Samter's triad, includes the presence of bronchial asthma, nasal polyposis, and respiratory reaction to aspirin and most nonsteroidal anti-inflammatory drugs (NSAIDs). Eosinophilic airway inflammation is also now accepted as part of the clinical presentation and defining diagnostic factors. The NSAID sensitivity often manifests as ASA intolerance, and the disorder is now generally referred to as aspirin (or NSAID)-exacerbated respiratory disease (AERD).[947–949] Prevalence rates of AERD in the general population have been estimated at 0.6% to 2.5% and in CRSwNP patients at 9.7%.[950,951] An incomplete triad might be observed in patients with recurrent nasal polyposis and asthma who do not yet report adverse reactions to NSAIDs.

The first symptoms usually occur within the fourth decade of life with rhinitis/RS followed by NPs. Asthma often develops several years later but may take longer to present, and then the clinical sensitivity to NSAIDs may also be delayed by years. The exact pathophysiological mechanism of AERD remains uncertain but previous data suggest dysfunction in the arachidonic acid metabolism pathway to be fundamental to disease development. NSAIDs such as aspirin affect the arachidonic acid pathway and cause inhibition of the cyclooxygenases (COX), which are necessary for metabolizing arachidonic acid into prostaglandins.[952] Due to this inhibition, the lipoxygenase pathway is further activated, which leads to

an imbalance of anti-inflammatory prostaglandins (PGs) and proinflammatory leukotrienes (LTs). On top of this physiological inhibitory effect, individuals with AERD are thought to be characterized by genetic polymorphisms that lead to a reduced activity of the constitutively expressed COX 1 isoenzyme as well as increased LT receptor affinity. Due to these changes in arachidonic acid metabolism, the PG/LT imbalance in these patients is altered favoring a proinflammatory state, which fuels the eosinophilic inflammatory changes characteristically seen in CRSwNP and asthma. Key cytokines and chemokines such as IL-5 and eotaxin are also elevated, leading to intense airway mucosal eosinophilic infiltration and activation.[953] Comparative histopathological analysis reveals the strongest tissue eosinophilia in patients with AERD, when comparing different clinical subgroups in a patient population with CRSsNP, inhalant allergies, and/or CRSwNP.[954]

However, much of the described pathophysiology of AERD is likely explained by genetic variations, of which a number of polymorphisms have been identified that potentially play a causative role.[955–957] 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 cysteinyl LTs (cysLTs). Sensitivity of LT receptors is upregulated and so is the expression of cysLT receptor 1. Also, the production of PGE2 is reduced and COX-2 as well as E-prostanoid receptor subtype-2 are downregulated.[953] All of these effects add to an aggravation of the eicosanoid imbalance. Recently, gene profiling studies have suggested that periostin is the most upregulated gene in NP tissue of AERD patients.[953,957]

The complexity in the interaction of inflammatory mediators in AERD is underlined by the dysregulation of the PG2-dependent control of LT production in peripheral granulocytes. When compared to those of patients with ASA-tolerant asthma or those of controls, granulocytes of patients with AERD generate more LTB4 and cysLTs, and are resistant to the PGE2-mediated suppression of LT generation.[958] This can be explained by an impaired protein kinase A function in AERD, which can lead to the deregulated control of 5-lipoxygenase activity by PGE2.

These pathophysiological and immunological considerations have become a key factor in understanding the nature of AERD and have led to development of in vitro tests. These tests may potentially evolve to be an alternative to classic provocation testing in identifying this important subgroup of CRSwNP patients.[959] Several such tests have been used in clinical trials, investigating their sensitivity and specificity. These observations have revealed comparable validity to provocation testing when mixed leukocyte cultures are used to evaluate the eicosanoid and neuropeptide release patterns.[959] Further work is necessary to validate in vitro testing as a reasonable alternative to current practice.

- Aggregate Grade of Evidence: C (Level 2a: 1 study; Level 2b: 3 studies; level 5: 10 studies; Table VIII-5).

VIII.D.1. CRSwNP: Diagnosis

CRSwNP is defined in Section IV.B. Diagnosis of CRSwNP is discussed in Section VI.D in general and the evidence-based definition of CRSwNP is shown in Table VIII-6.

VIII.D.2. CRSwNP Diagnosis: Differential Diagnosis

In addition to the differential diagnosis for CRSsNP (see Section VII.D.2), several space-occupying lesions in the nasal cavity appear like NPs and must be considered. Sometimes normal structural variants, such as concha bullosa and medialized uncinated 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.[963] Juvenile angiofibroma should be suspected in adolescent males. Malignant tumors simulating polyps include squamous cell carcinoma, salivary gland–type carcinoma, olfactory neuroblastoma, and lymphoma. Key features distinguishing sinonasal tumors from NPs are unilateral disease,[964] lack of sinus inflammation in some cases, and surface features, such as easy bleeding and ulceration.

Encephaloceles can masquerade as NPs.[965] This lesion typically arises in the midline nasal and anterior skull base and causes 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.[271]

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 wall of the maxillary sinus and extends into the choana through an accessory maxillary sinus ostium.[966]

NPs can be associated with comorbid diseases including ASA intolerance, asthma, AR, CF, and PCD.[967–971] Because NPs are usually secondary to continued inflammation caused by these comorbid diseases, the clinician should evaluate underlying conditions in order to more effectively treat NPs.

TABLE VIII-5. Evidence for CRSwNP and aspirin intolerance as a contributing pathogenic factor

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Baker[950]	2011	2a	Systematic review	Patients with AERD undergoing high-dose desensitization	GI side effects	GI symptoms are the primary risk in high dose desensitization
Mendelsohn[960]	2011	2b	Large retrospective cohort study	Patients undergoing ESS for NP (n = 549)	Recurrence (measured by Kaplan-Meier curves)	Revision rates are significantly higher in AERD
Gosepath[947]	2002	2b	Long-term cohort study	Patients with AERD undergoing long-term low-dose desensitization	Recurrence of NPs and need for surgical revisions	Long-term low-dose desensitization is clinically effective and can be monitored in vitro
Amar[961]	2000	2b	Case-control study	1.AERD; 2.CRS with and without asthma	1. Clinical effect of ESS; 2. Recurrent CRS; 3. Number of surgical interventions	Surgery is less effective long-term in patients with AERD
Chang[962]	2014	5	Bench research			No significant association between the FABP1 polymorphisms and AERD
Choi[953]	2014	5	Nonsystematic review/expert opinion			Update on pathophysiology in AERD
Kim[957]	2014	5	Bench research			Serum periostin levels are significantly elevated in AERD patients and are associated with disease severity
Laidlaw[958]	2014	5	Bench research			Impaired granulocyte PKA function in AERD may lead to dysregulated control of 5-lipoxygenase activity by PGE(2)
Losol[956]	2013	5	Bench research			A functional polymorphism in IL5RA may contribute to eosinophil and mast cell activation in AERD patients
Park[955]	2013	5	Nonsystematic review			Review on genetic variants responsible for risk of AERD after a genomewide association study
Stevenson[948]	2009	5	Nonsystematic review/expert opinion			Update on pathophysiology in AERD
Baenkler[959]	2008	5	Nonsystematic review/expert opinion			Update on pathophysiology in AERD
Szczeklik[952]	2003	5	Nonsystematic review/expert opinion			Update on pathophysiology in AERD
Kaldenbach[954]	1999	5	Bench research	CRSwNP; inhalant allergies; AERD	Role of eosinophilic granulocytes	Strongest eosinophilia seen in the group of patients with AERD

PGE(2) = prostaglandin E(2); PKA = protein kinase A.

TABLE VIII-6. The diagnostic criteria for CRSwNP

Greater than or equal to 12 weeks of:
2 or more of the following symptoms:
Mucopurulent discharge (rhinorrhea or PND)
Nasal obstruction and congestion
Decreased or absent sense of smell
Facial pressure or pain
AND
1 or more of the following findings:
Evidence of inflammation on paranasal sinus examination or CT
Evidence of purulence coming from paranasal sinuses or ostiomeatal complex
AND
Presence of polyps

VIII.D.3. CRSwNP Diagnosis: Cost Effective Work-Up

Because of limited data, CRSwNP and CRSsNP are combined in Section VII.D.3.

VIII.E. CRSwNP: Management

This discussion will focus on CRSwNP management (Fig. VII-1). The management of AECRS is discussed in Section IX.C.

VIII.E.1. CRSwNP Management:-Saline (Spray and Irrigation)

Because of limited data, CRSwNP and CRSsNP are combined in Section VII.E.1.

VIII.E.2.a. CRSwNP Management with Topical Corticosteroids: Standard Delivery (Drops and Sprays). The use of INCS for CRSwNP has been well studied. A systematic review of the literature was performed in which in general only RCTs were considered, which compared topical corticosteroid against placebo (35 studies).[707,712,864,972–1004] Among these, 8 trials also compared low-dose to high-dose topical corticosteroid[707,981,984,987,989,990,994,997] and 3 trials also compared 2 corticosteroid agents, fluticasone propionate and beclomethasone dipropionate.[983,985,993] In addition, 4 level 2b studies were included, 3 comparing active with no intervention[973,1005,1006]and 1 comparing active treatment with and without surgery.[1007] For 28 trials all or most of the patients had undergone sinus surgery immediately prior to the administration of the corticosteroid or had undergone surgery in the past. In 12 studies there was no preceding operation or the population was mixed.

A wide range of corticosteroid preparations were utilized, including: sprays, aerosols, or drops, in varying doses and for periods ranging from 4 to 260 weeks:

- Fluticasone propionate was studied in 16 trials.[707,864,982,983,985–988,993,995,996,999,1001,1002,1006,1007]
- Beclomethasone dipropionate was studied in 5 trials.[973,983,985,993,1005]
- Betamethasone sodium phosphate was studied in 1 trial.[977]
- Mometasone furoate was studied in 6 trials.[712,992,994,997,998,1000]
- Flunisolide was studied in 2 trials.[975,976]
- Budesonide was studied in 9 trials.[974,978–981,984,989–991]
- Triamcinolone was studied in 1 trial.[1003]

Outcomes included individual and overall symptoms scores, endoscopic/polyp scores, QoL questionnaires, objective assessments of olfaction and airway and occasionally asthma score, number and time to relapse, or prevention of reoperation. A summary of outcomes is provided in Table VIII-7, with the majority demonstrating a significant benefit from the use of INCS as sprays or drops.

A number of critical reviews and meta-analyses have been published.[7,702,1008–1012] When compared to placebo, pooled data analyses of symptoms, polyp size, polyp recurrence, and nasal airflow have demonstrated significant benefit in favor of the topical corticosteroid irrespective of the variations in which these outcomes have been reported. It has also been possible to do subgroup analysis[7] on:

1. Surgical status comparing those patients with prior sinus surgery vs those without sinus surgery. This showed benefit from having had prior surgery.
2. Topical delivery method showed nasal aerosols and dry powder inhaler were more effective than nasal spray in controlling symptoms but did not improve on reduction of polyp size or nasal airway. Both sprays and drops were statistically effective.
3. Corticosteroid type. Modern corticosteroids (mometasone, fluticasone, and ciclesonide) are not shown to be more effective than earlier versions (budesonide, beclomethasone, betamethasone, triamcinolone, and dexamethasone) for final symptom score or polyp size reduction.

No serious side effects are reported in any of the studies. Epistaxis is the most common event together with nasal irritation producing itching, sneezing, dryness, and rhinitis. Headache is also frequently reported and usually the side effects are found equally in the placebo arms suggesting that local trauma due to poor technique with the device is more relevant than the content. No increase in infection or specifically candidiasis has been detected. These minor or moderate adverse events are generally tolerated by patients. No difference in intraocular pressure or serum/urinary cortisol levels have been demonstrated in those few studies considering these issues.

TABLE VIII-7. 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
Vento[1003]	2012	1b	RCT	CRSwNP (by endoscopy); n = 60 (with ESS)	Triamcinolone; 220 μg daily; 36 weeks; aerosol	1. Polyp size; 2. Olfactory threshold; 3. Airway studies	Favor corticosteroid for polyp size in non-AERD patients. No difference in olfaction or airway measures
Olsson[1002]	2010	1b	RCT	CRSwNP (by endoscopy); n = 68 (with ESS)	Fluticasone propionate; 400 μg BID; 10 weeks; nasal drop	General health QoL (SF-36; 1-5)	Favor corticosteroid for mental component but not physical component
Ehnhage[864]	2009	1b	RCT	CRSwNP (by endoscopy); n = 68 (with ESS)	Fluticasone propionate; 400 μg BID; 10 weeks; nasal drop	1. Nasal and asthma symptom scores; 2. Polyp score	No difference for both measures
Jankowski[1001]	2009	1b	RCT	CRSwNP (by endoscopy); n = 242 (without ESS)	Fluticasone propionate; 200 μg BID; 4 weeks; spray	1. Symptom score; 2. Polyp score	Favor corticosteroid for both measures
Jorissen[712]	2009	1b	RCT	Mixed CRS (by endoscopy); n = 99 (with ESS)	Mometasone furoate; 200 μg BID; 24 weeks; spray	1. Symptom VAS; 2. Endoscopy; 3. Composite endoscopy score	No difference for both measures. Composite endoscopy score favored INCS
Stjarne[1000]	2009	1b	RCT	CRSwNP (by endoscopy); n = 159 (with ESS)	Mometasone furoate; 200 μg daily; 24 weeks; spray	1. Symptom scores; 2. Polyp relapse	INCS improved rhinorrhea but not congestion and sense of smell. Less polyps with corticosteroid
Vlckova[999]	2009	1b	RCT	CRSwNP, small to medium size NP (by endoscopy); n = 109 (with and without ESS)	Fluticasone propionate; 400 μg BID; 12 weeks; spray	1. Symptom scores; 2. Polyp score	Favor corticosteroid over placebo for both outcomes
Stjarne[998]	2006	1b	RCT	CRSwNP (by endoscopy); n = 310 (without ESS)	Mometasone furoate: Arm 1. 200 μg daily; Arm 2. 200 μg BID; 16 weeks; spray	1. Symptom scores; 2. Polyp score	INCS improved many symptoms, with BID treatment showing more effect than once-daily treatment
Stjarne[997]	2006	1b	RCT	CRSwNP (by endoscopy); n = 298 (with and without ESS)	Mometasone furoate; 200 μg daily; 16 weeks; spray	1. Symptom scores; 2. Polyp score	Favor corticosteroid over placebo for both outcomes
Aukema[996]	2005	1b	RCT	CRSwNP (by endoscopy and CT); n = 54 (with and without ESS)	Fluticasone propionate; 400 μg daily; 12 weeks; nasal drop	1. Symptom VAS; 2. Polyp volume	Treatment improved obstruction, rhinorrhea, PND, and loss of smell; also reduced polyp volume

(*Continued*)

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TABLE VIII-7. Continued

Study	Year	LOE	Study design	Study groups	Type of corticosteroid, dose, duration, delivery method	Clinical endpoint	Conclusions
Rowe-Jones[995]	2005	1b	RCT	CRSwNP (by endoscopy); n = 109 (with ESS)	Fluticasone propionate; 200 μg BID; 260 weeks; spray	1. Symptom VAS; 2. Endoscopic score (Lund-Kennedy)	No difference for total symptoms. INCS improved polyp score but not edema or discharge scores
Small[994]	2005	1b	RCT	CRSwNP (by endoscopy); n = 354 (without ESS)	Mometasone furoate: Arm 1. 200 μg daily; Arm 2. 200 μg BID; 16 weeks; spray	1. Symptom scores; 2. Polyp score	Both daily and BID regimens improved symptoms and polyps scores
Bross-Soriano[993]	2004	1b	RCT	CRSwNP (not stated); n = 142 (with ESS)	Arm 1. Fluticasone propionate; 400 μg daily; Arm 2. Beclomethasone dipropionate; 600 μg daily; 72 weeks; spray (after saline lavage)	Polyp recurrence	Favor corticosteroid over placebo
Dijkstra[707]	2004	1b	RCT	Mixed CRS (by endoscopy and CT); n = 162 (with ESS)	Fluticasone propionate: Arm 1. 400 μg BID; Arm 2. 800 μg BID; 52 weeks; spray	Polyp recurrence	No difference
Passali[992]	2003	1b	RCT	CRSwNP, medium to large size (by endoscopy); n = 73 (with ESS)	Mometasone furoate; 400 μg daily; at least 52 weeks; spray	Polyp recurrence	Favor corticosteroid over placebo
Johansson[991]	2002	1b	RCT	CRSwNP (by endoscopy); n = 98 (without ESS)	Budesonide; 128 μg BID; 2 weeks; spray	1. Symptom VAS; 2. Polyp score	Favor corticosteroid over placebo for both measures
Jankowski[990]	2001	1b	RCT	CRSwNP (by endoscopy); n = 183 (without ESS)	Budesonide: Arm 1. 128 μg daily; Arm 2. 128 μg BID; Arm 3. 256 μg daily; 8 weeks; spray	1. Symptom scores; 2. Overall efficacy; 3. Polyp score	Favor corticosteroid for all outcomes. Higher dose was no better
Filiaci[989]	2000	1b	RCT	CRSwNP (by endoscopy and MRI); n = 157 (without ESS)	Budesonide: Arm 1. 140 μg BID; Arm 2. 280 μg daily; Arm 3. 140 μg daily; 8 weeks; dry powder inhaler	1. Symptom scores; 2. Overall efficacy; 3. Polyp score	Favor corticosteroid over placebo. Higher dose more effective for some outcomes
Keith[988]	2000	1b	RCT	CRSwNP, small to medium size (by endoscopy); n = 104 (with and without ESS)	Fluticasone propionate; 400 μg daily; 12 weeks; nasal drop	1. Symptom scores; 2. Polyp score; 3. PNIF	Treatment improved symptoms. No effect on polyps score. Treatment improved PNIF
Penttila[987]	2000	1b	RCT	CRSwNP, small to medium size (by endoscopy); n = 142 (with and without ESS)	Fluticasone propionate: Arm 1. 400 μg BID; Arm 2. 400 μg daily; 12 weeks; nasal drop	1. Symptom scores; 2. Polyp score; 3. PNIF	Favor corticosteroid over placebo. Higher dose more effective for some outcomes
Holmstrom[986]	1999	1b	RCT	CRSwNP, small to medium size (by endoscopy); n = 104 (without ESS)	Fluticasone propionate; 400 μg daily; 12 weeks; nasal drop	Polyp score	No difference

(Continued)

TABLE VIII-7. Continued

Study	Year	LOE	Study design	Study groups	Type of corticosteroid, dose, duration, delivery method	Clinical endpoint	Conclusions
Lund[985]	1998	1b	RCT	CRSwNP (by endoscopy and CT); n = 34 (with and without ESS)	1. Fluticasone propionate, 400 μg BID; 2. Beclomethasone dipropionate, 400 μg BID; 12 weeks; spray	1. Symptom scores; 2. Polyp score; 3. Need for surgery; 4. Acoustic rhinometry and PNIF	Beclomethasone effective for some symptoms. Fluticasone more effective for polyp score. No difference in need for surgery. INCS improved nasal airway
Tos[984]	1998	1b	RCT	CRSwNP, medium to large size (by endoscopy); n = 138 (with ESS)	Budesonide: Arm 1. Spray 64 μg BID; Arm 2. Dry powder inhaler 100 μg per nominal dose/170 μg per delivered dose BID; 6 weeks; spray or dry powder inhaler	1. Symptom scores; 2. Sense of smell; 3. Overall efficacy; 4. Polyp score; 5. Number of polyps	Favor corticosteroid over placebo for all outcomes except number of polyps
Holmberg[983]	1997	1b	RCT	CRSwNP (by endoscopy); n = 55 (with ESS)	Arm 1. Fluticasone propionate, 200 μg BID; Arm 2. Beclomethasone dipropionate, 200 μg BID; 26 weeks; spray	1. Symptom scores; 2. Polyp score	Fluticasone reduced symptoms. Both INCS treatments improved polyps score
Mastalerz[982]	1997	1b	RCT	mixed CRS, with aspirin sensitivity (not stated); n = 15 (without ESS)	Fluticasone propionate, 400 μg daily; 4 weeks; spray	Symptom scores	Favor corticosteroid over placebo
Lildholdt[981]	1995	1b	RCT	CRSwNP (by rhinoscopy); n = 126 (without ESS)	Budesonide: Arm 1. 200 μg; Arm 2. 400 μg BID; 4 weeks; dry powder inhaler	1. Symptom scores; 2.Polyp score	Favor both doses of corticosteroid over placebo for both outcomes
Vendelo Johansen[980]	1993	1b	RCT	CRSwNP, small to medium size eosinophilic polyps (by pathology); n = 91 (without ESS)	Budesonide, 200 μg BID; 12 weeks; spray and aerosol	1. Symptom scores; 2. Sense of smell; 3. Polyp score	Favor corticosteroid over placebo for symptoms and polyp score. No difference for sense of smell
Ruhno[979]	1990	1b	RCT	CRSwNP; n = 36 (with ESS)	Budesonide, 400 μg BID; 4 weeks; spray	1. Symptom scores; 2.Polyp scores	Favor corticosteroid over placebo for both outcomes
Hartwig[978]	1988	1b	RCT	CRSwNP (by endoscopy); n = 73 (with ESS)	Budesonide, 200 μg BID; 24 weeks; aerosol	1. Symptom scores; 2.Polyp score	No difference in symptom scores. Favor corticosteroid over placebo for polyps score

(*Continued*)

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TABLE VIII-7. Continued

Study	Year	LOE	Study design	Study groups	Type of corticosteroid, dose, duration, delivery method	Clinical endpoint	Conclusions
Chalton[977]	1985	1b	RCT	CRSwNP (by endoscopy); n = 30 (without ESS)	Betamethasone, 100 μg BID; 4 weeks; nasal drop	Disappearance of NPs	Favor corticosteroid over placebo
Dingsor[976]	1985	1b	RCT	CRSwNP (by rhinoscopy); n = 41 (with ESS)	Flunisolide, 100 μg BID; 52 weeks; spray	1. Symptom scores; 2. Polyp number; 3. Polyp size	Favor corticosteroid over placebo for obstruction and both polyps outcomes
Lang[1004]	1983	1b	RCT	CRSwNP, small to medium size (by endoscopy); n = 32 (without ESS)	Beclomethasone dipropionate, 400 μg BID; 104 weeks; spray	1. Symptom scores; 2. Polyp size	No difference for both outcomes
Drettner[975]	1982	1b	RCT	CRSwNP; n = 25 (with ESS)	Flunisolide, 100 μg BID; 12 weeks; spray	1. Symptom scores; 2. Polyp size	Favor corticosteroid over placebo for symptoms. No difference for polyp size
Holopainen[974]	1982	1b	RCT	CRSwNP, small to medium size (by rhinoscopy); n = 19 (with ESS)	Budesonide, 200 μg BID; 16 weeks; spray	1. Symptom scores; 2. Polyp number; 3. Polyp size	No difference in symptom scores. Favor corticosteroid over placebo for polyp number and size
Mygind[972]	1975	1b	RCT	CRSwNP, medium to large size; n = 35 (with and without ESS)	Beclomethasone dipropionate, 100 μg QID; 3 weeks; aerosol	1. Symptom scores; 2. Change in symptoms; 3. Polyp size	INCS treatment had lower symptoms scores, but not greater reduction in symptoms. No difference for polyps size
Baradaranfar[1007]	2014	2b	Prospective nonrandomized matched	CRSwNP (by endoscopy); n = 60 (with and without ESS)	Fluticasone propionate, 400 μg BID; 8 weeks; spray	Effect of surgery on delivery of INCS to improve olfaction	Combined INCS and surgical treatment better than INCS alone
Jurkiewicz[1006]	2004	2b	RCT vs no treatment	CRSwNP; n = 86 (with ESS)	Fluticasone propionate, 400 μg BID; 52 weeks; spray	1. Symptom scores; 2. Endoscopy for polyps	Favor corticosteroid over placebo for both outcomes
el Naggar[1005]	1995	2b	RCT vs no treatment in the other nostril	CRSwNP (by endoscopy); n = 29 (with ESS)	Beclomethasone dipropionate, 100 μg BID in 1 nostril; 6 weeks; spray	1. Olfaction (UPSIT)	No difference in olfaction between nostrils
Karlsson[973]	1982	2b	RCT vs no treatment	CRSwNP, medium to large size; n = 40 (with ESS)	Beclomethasone dipropionate, 400 μg daily for 1 month then 200 μg daily; 30 weeks; intranasal	1. Polyp score	Favor corticosteroid over placebo

UPSIT = University of Pennsylvania Smell Identification Test.

Nasal biopsy studies after long-term administration of INCS do not show any evidence of damage to the nasal mucosa. Specifically, mucosal atrophy does not occur because the mucosa is a single layer of epithelium compared to keratin-producing multilayered skin and has cilia whose action is enhanced by the corticosteroid, facilitating its rapid removal.[1013–1015] Finally the systemic bioavailability of INCS varies from <1% to up to 40% to 50%, which will influence the risk of systemic adverse effects.[1016]

- Aggregate Grade of Evidence: A (Level 1b: 36 studies, Level 2b: 4 studies).
- Benefit: Improved symptoms, endoscopic appearances, polyp size, and QoL, objective tests of olfaction and airway and polyp recurrence.
- Harm: Epistaxis, nasal irritation, headache.
- Cost: Moderate depending on preparation
- Benefits-Harm Assessment: Benefit outweighs harm.
- Value Judgments: None.
- Policy Level: Recommended.
- Intervention: Topical nasal corticosteroids (sprays or drops) are recommended for CRSwNP before or after sinus surgery.

VIII.E.2.b. CRSwNP Management with Topical Corticosteroids: Nonstandard Delivery (Irrigation and Nebulizers). Nonstandard delivery of topical corticosteroids has been studied in addition to standardized delivery methods. In systematically reviewing this literature, only 1 RCT[1017] was identified and 5 further noncontrolled studies were included. Three of the 5 were prospective[719–721] but 2 were severely underpowered. The remaining 2 were retrospective.[1018,1019] Most trials included a mixed population of CRSwNP and CRSsNP, and 4 mentioned ASA-tolerance status.[719,721,1017,1018] There were 208 patients with CRSwNP and 1 mixed study of 9 individuals did not give the number of CRSwNP.

All 6 considered budesonide, either as irrigation or in 1 case in nebulized form.[1019] A commercially available preparation of budesonide was used off-label that is available in 2 doses of 250 μg/2 mL or 500 μg/2 mL. In the included studies, dosage varied from 128 μg to 1 mg. One study used either budesonide or beclomethasone, also 1 mg but the percentage of patients using 1 or the other is not given.[719] The volume of saline ranged from 5 to 240 mL or was not stated. For 4 trials all or most of the patients had undergone sinus surgery immediately prior to the administration of the corticosteroid or had undergone surgery in the past.[719,1017–1019]

Outcomes included individual and overall symptoms scores, endoscopic/polyp scores, QoL questionnaires (SNOT-20, SNOT-21, SNOT-22), CT scores, oral corticosteroid use, and tissue eosinophilia. Adrenal function was the primary outcome for 1 study.[720] Because of disparity of treatments and outcome measures, no meta-analyses are possible.

A summary of outcomes is provided in Table VIII-8. The single well-powered RCT showed no difference in outcome for patient-based (QoL) or objective (endoscopy and CT scores) assessments.[1017] The rest of the results varied from study to study, with some showing improvement and others no difference. Most are substantially undermined by their study design and there is a need for further well-conducted RCTs.

With regard to adverse effects, concern has centered on whether off-label utilization of budesonide might result in systemic absorption and adrenal suppression.[702,1020] No RCTs have been done to adequately address this issue but those studies that have considered this aspect have not shown any overt problem. Bhalla et al.[722] retrospectively considered 18 patients receiving budesonide irrigation and showed no reduction in morning cortisol, and in selected patients an adrenocorticotropic hormone (ACTH) stimulation test did not show hypothalamic-pituitary-adrenal (HPA) axis suppression. Similar findings were reported in a prospective study by Sachanandani et al.[720] involving 9 patients using 250 μg/nostril daily for 4 weeks. Welch et al.[723] considered 10 patients who prospectively used 500 μg/2 mL in 250 mL of saline twice daily and showed no change in serum or 24-hour urinary cortisol at this higher dose.

Another prospective study considered the effects of budesonide irrigation (500 μg/2 mL in 240 mL saline BID) on intraocular pressure in 18 patients.[1021] No significant elevation of pressure was shown with an average duration of use of 6.3 months in 10 of the patients. A relatively low dose of active drug is probably delivered to the mucosa using irrigation systems although the exact exposure is undetermined at present.[775,806,808] This may not be the case with small-volume, high-dose nebulized devices for which no safety data is as yet available. Longer-term adequately powered RCTs are needed on these safety issues.

- Aggregate Grade of Evidence: B (Level 1b:1 study, level 4: 5studies).
- Benefit: Overall not possible to statistically confirm therapeutic improvement on present evidence.
- Harm: No evidence of adrenal suppression but cannot be excluded with nonstandardized delivery and dosage regimes.
- Cost: Moderate.
- Benefits-Harm Assessment: Off-label use, likely negligible side effects compared with oral corticosteroids.
- Value Judgments: Only one level 1B study so insufficient data at present.
- Policy Level: Option.
- Intervention: Nonstandard delivery of topical corticosteroids is an option in CRSwNP, mainly after sinus surgery.

TABLE VIII-8. Evidence for CRSwNP management with topical corticosteroids (nonstandard delivery)

Study	Year	LOE	Study design	Study groups	Type of corticosteroid, dose, duration of treatment	Delivery method of corticosteroid	Clinical endpoint	Conclusions
Rotenberg[1017]	2011	1b	RCT	CRSwNP; Aspirin tolerant; n = 64 (with ESS)	Budesonide: Arm 1. 128 μg BID as spray; Arm 2. 500 μg BID in saline irrigation; 52 weeks	INCS plus saline; drug in saline; saline irrigation alone	1. SNOT 21; 2. Endoscopy score (Lund Kennedy); 3. LM CT score	No difference between groups ($p > 0.05$)
Jang[1018]	2013	4	Retrospective	CRSwNP (n = 30); AFRS (n = 13); AERD (n = 13); CRSsNP (n = 4) (with ESS)	Budesonide (with then without); 250 μg BID; 25 weeks mean overall (2–89); 13 weeks mean (1–80) on treatment; 12 weeks (1–76) without	Saline irrigation	1. SNOT-22; 2. Endoscopy (Lund Kennedy)	QoL better with corticosteroid, especially CRSwNP and AERD. Only CRSwNP had improved endoscopy
Snidvongs[719]	2012	4	Prospective	CRSwNP and CRSsNP; n = 111 (with ESS)	Budesonide or beclomethasone; 1 mg daily; 55.5 $\pm$ 40 weeks	High-volume saline irrigations	1. Symptom score; 2. SNOT-22; 3. Endoscopy (Lund Kennedy); 4. Tissue eosinophilia	Symptoms, QoL, and endoscopy improved with corticosteroids. Patients with high tissue eosinophilia did better for all outcomes
Sachanandani[720]	2009	4	Prospective pilot	CRSwNP and CRSsNP; n = 9	Budesonide; 250 μg; 4 weeks	Isotonic saline (5 mL) each nostril daily	1. Adrenal function; 2. SNOT-20	No adverse effect on adrenal function. Improved SNOT-20
Steinke[721]	2009	4	Prospective pilot	CRS (chronic hyperplastic and aspirin tolerant); n = 8	Budesonide; dose not stated; 12 weeks	High-volume saline irrigations	1. CT score; 2. Symptoms; 3. Endoscopy (Lund-Kennedy)	All measures improved
Kanowitz[1019]	2008	4	Retrospective	CRSwNP (n = 37) and CRSsNP (n = 7) (with ESS)	Budesonide; 250 μg; 31 weeks mean (8–80 weeks)	Nebulized (MAD)	1. Symptoms; 2. Endoscopy; 3. Oral corticosteroid use; 4. Global assessment; 5. Olfaction	Improvement in global assessment and oral corticosteroid use. No difference in other measures

VIII.E.3. CRSwNP Management: Oral Corticosteroids

Sixteen articles were identified that met criteria for oral corticosteroids in the management of CRSwNP. These studies examined different dosage, duration, and combination regimens. They all evaluated subjective and objective changes following corticosteroid courses of varying lengths, with all the studies showing positive changes in the majority of the parameters evaluated for patients treated with corticosteroids.

Kroflic et al.[1022] performed an RCT comparing 40 patients assigned to oral methylprednisolone or topical furosemide nebulizer for 7 days prior to sinus surgery. After 7 days, the oral corticosteroids significantly improved subjective scores for nasal obstruction, olfaction, and nasal secretions. Nasal endoscopy scores were significantly improved and eosinophils were significantly reduced in the polyp tissue after oral corticosteroids.

Van Zele et al.[1023] randomized 47 CRSwNP patients to receive oral methylprednisolone taper (20 days), doxycycline, or placebo. They reported a significant reduction of the size of the polyps on nasal endoscopy, a decrease in nasal congestion, PND, and loss of sense of smell. Polyp size was improved in the corticosteroid group up to 8 weeks, but was not found to differ from baseline at the 12-week follow-up. The corticosteroid group showed no significant improvement on rhinorrhea compared to placebo, but did demonstrate significant decreases in blood eosinophil counts, IgE, ECP, and IL-5. There was no difference in the matrix metalloproteinase (MMP)-9 levels between the corticosteroids and placebo groups. Almost one-half of the subjects reported at least 1 adverse event, but there was no significant difference in the number or type between the groups.

Hissaria et al.[1024] randomized 41 subjects to receive 50 mg of prednisolone or placebo daily for 14 days. At the completion of treatment, both groups showed significant improvement in symptoms based on the physician interview and the RSOM scores, with the corticosteroid group demonstrating a significant improvement over the placebo group in each of these categories. The objective measures, including nasal endoscopy and MRI, showed significant improvements in the corticosteroid group over the placebo. Insomnia was reported more frequently in the prednisolone group, but no significant adverse reactions to the corticosteroids were reported.

Vaidyanathan et al.[1025] reported their RCT in which 60 CRSwNP patients were randomized to receive 25 mg of prednisolone or placebo daily for 2 weeks. All patients received fluticasone propionate nasal drops (400 μg BID) for 8 weeks then fluticasone propionate nasal spray (200 μg BID) for 18 weeks. The authors reported significant improvements in nasal endoscopy, hyposmia VAS, Pocket Smell Test, total nasal symptom scores, mini Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), PNIF, serum EDN, and high-sensitivity CRP levels after the 2 weeks of oral corticosteroids. During their follow-up period, the polyp size showed statistically significant reduction at the 2-week ($p < 0.001$) and 10-week ($p = 0.001$) follow-ups. At 28 weeks, the reduction in size was not statistically significant ($p = 0.11$). The improvement in olfaction showed similar trends at the 2-week, 10-week, and 28-week follow-up. They also reported basal and dynamic adrenal function suppression after the 2-week treatment with oral corticosteroids. This returned to baseline after completion of the oral corticosteroids. The markers of bone turnover showed a similar trend with significant drops in the procollagen studies following the corticosteroids. Similar rates of adverse events were noted in each group, though none were considered serious as defined by the protocol.

Kirtsreesakul et al.[1026] included 109 patients, randomized to receive 50 mg of prednisolone or placebo daily for 14 days. The authors found that subjective symptoms improved in both groups, though the corticosteroid group had significantly greater improvements in all subjective measures over the placebo group. Only the corticosteroid group had significant improvements in the peak expiratory flows index and nasal endoscopy measures. Of note, the corticosteroid group had more patients report GI disturbances and dyspepsia than did the placebo group.

Finally, an evidence-based risk analysis of oral corticosteroid use in CRSwNP was performed by Leung et al.[733] Using published complications rates, QoL changes, and costs, their analysis simulated the economic impact of adverse events from a Medicare patient perspective, societal perspective, and a universal healthcare perspective. This analysis found that a breakeven threshold favored surgery over medical therapy when CRSwNP patients required oral corticosteroids more than once every 2 years.

These data support the infrequent use of oral corticosteroids in CRSwNP patients in the immediate and short-term period. The long-term efficacy of an oral corticosteroid taper, followed by maintenance with INCS is likely 8 to 12 weeks. Two studies found no difference in longer-term effect.[1023,1025] Vaidyanathan et al.[1025] found adrenal suppression and alteration of bone metabolism to be transient. Although no severe adverse events were reported in this study, the higher doses of corticosteroids (50 mg/day for 14 days) may exceed the thresholds reported for osteonecrosis (300 to 1000 mg of oral prednisone).[1027] Practitioners must be aware of the relative benefits vs risks when developing treatment plans with their patients (Table VIII-9).

- Aggregate Grade of Evidence: A (Level 1b: 5 studies; Level 3: 2 studies; Level 4: 11 studies).
- Benefit: Significant short-term improvements in subjective and objective measures in CRSwNP patients. Duration of improvement may last 8 to 12 weeks in conjunction with INCS use.
- Harm: More GI symptoms in corticosteroid group, no severe reactions reported. Transient adrenal suppression, insomnia, and increased bone turnover. All established

TABLE VIII-9. Evidence for CRSwNP management with oral corticosteroids

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Kirtsreesakul[1026]	2011	1b	DBRCT	1. Prednisolone 50 mg daily for 14 days; 2. Placebo	1. Nasal symptoms (Likert scale); 2. Nasal peak expiratory flow index; 3. Polyp size	Greater improvement in symptoms in corticosteroid arm. Polyp size and nasal patency were improved
Vaidyanathan[1025]	2011	1b	DBRCT	1. Prednisolone 25 mg/day × 14 days followed by INCS; 2. Placebo × 14 days followed by INCS	1 Polyp size; 2. Olfaction; 3. Total nasal symptom score; 4. mini-RQLQ; 5. PNIF; 6. EDN and CRP; 7. Adrenal suppression; 8. Bone turnover indices	Improvement in all outcomes (#1–#6) in corticosteroid arm. Benefits of oral corticosteroids faded by 28 weeks. Transient adrenal suppression and decrease in osteoblast activity was observed
Van Zele[1023]	2010	1b	DBRCT, multicenter	1. Methylprednisolone 32 mg × 5 days, 16 mg × 5 days, 8 mg × 10 days; 2. Oral doxycycline for 20 days; 3. Placebo	1. Nasal polyps grade by nasal endoscopy; 2. PNIF; 3. Nasal symptoms; 4. Serum eosinophil count; 5. Nasal secretion of IL-5, IgE, MMP-9, ECP	Improvement in polyp size, PNIF, nasal symptoms, and inflammatory markers in the corticosteroid arm. Return to baseline of clinical endpoints at the end of the study
Hissaria[1024]	2006	1b	DBRCT	1. Prednisolone 50 mg daily × 14 days; 2. Placebo	1. Nasal symptoms (VAS); 2. RSOM-31; 3. MRI; 4. Nasal endoscopy	Greater improvement in the corticosteroid arm. MRI and endoscopy showed improvement in corticosteroid arm
Kroflic[1022]	2006	1b	RCT	1. Methylprednisolone 1 mg/kg daily for 7 days prior to surgery; 2. Nasal furosemide for 7 days prior to surgery	1. Nasal symptoms; 2. Endoscopic grading of polyp size; 3. Histology; 4. Intraoperative bleeding	Improved nasal symptoms and polyp size in both groups with no difference between groups. Reduced NP size in corticosteroid group

corticosteroid risks exist, particularly with prolonged treatment.

- Cost: Low.
- Benefits-Harm Assessment: Preponderance of benefit to harm in small, short-term follow-up and with use less than once every 2 years.
- Value Judgments: Significant improvements in subjective and objective measures based on high-quality data, low risk, and low cost. Risks of oral corticosteroids outweigh benefits relative to surgery with use more than once every 2 years.
- Policy Level: Recommendation.
- Intervention: Oral corticosteroids are recommended in the short-term management of CRSwNP. Longer-term or frequent use of corticosteroids for CRSwNP is not supported by the literature and carries an increased risk of harm to the patient.

VIII.E.4. CRSwNP Management: Antibiotics

VIII.E.4.a. CRSwNP Management with Antibiotics: Oral Nonmacrolide Antibiotics for <3 Weeks. Antibiotics are prescribed in 26% of ambulatory visits for CRSwNP.[1028] This finding is based on a nationwide database in the United States, which does not differentiate between use in acute exacerbations of CRSwNP and the chronic phase of this condition. Despite the common use of antimicrobials in CRSwNP, surprisingly few studies address this practice.

In the EBRR on antimicrobials in CRS published in 2013, Soler et al.[752] found only 6 studies examining the short-term (<3 weeks) use of antibiotics in CRS. Only 1 of these, Van Zele et al.[1023] differentiated CRSwNP from CRSsNP patients. This study examined doxycycline 200 mg once followed by 100 mg daily for 20 days using a prospective RCT. The authors demonstrated a reduction in visible polyp size following treatment with doxycycline but no difference was seen in patient-reported nasal congestion scores, PNIF, rhinorrhea, or hyposmia. The authors pointed out that the intrinsic anti-inflammatory effects of doxycycline may have been responsible for the polyp size reduction in addition to or instead of the antimicrobial effect.

Since the Soler et al.[752] review identified this 1 study, only 1 additional clinical trial examining antibiotics in CRSwNP has been published. Hoza et al.[1029] examined the efficacy of erdosteine, a mucolytic agent with antibacterial, antioxidant, and anti-inflammatory effects. Erdosteine was administered alone or in combination with an INCS. There

was no placebo control. 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 other property of erdosteine was responsible for the improvement seen in this study.

In summary, despite the widespread use of antibiotics in CRSwNP, there is a paucity of evidence for their efficacy (Table VIII-10). Antibiotics have a number of potential harms so that their use in CRSwNP in a nonacute exacerbation should be discouraged.

- Aggregate Grade of Evidence: B (1 Level 1b study, 1 Level 4 study).
- Benefit: Reduction in polyp size with doxycycline; but no change in patient-reported outcomes; lack of placebo in erdosteine trial makes it impossible to determine a benefit for this therapy.
- Harm: GI upset and potential for resistance and for anaphylaxis.
- Cost: Variable, depending on antibiotic chosen.
- Benefits-Harm Assessment: Harm outweighs demonstrated benefits.
- Value Judgments: Unclear/limited benefits with significant harm and potentially significant cost
- Policy Level: Recommendation against.
- Intervention: Nonmacrolide antibiotics (<3-week course) should generally not be prescribed for CRSwNP in nonacute clinical situations.

VIII.E.4.b. CRSwNP Management with Antibiotics: Oral Non-Macrolide Antibiotics for > 3 Weeks. CRSwNP is thought to be primarily an inflammatory disease. Based on first principles, the potential benefit of >3-week duration of antibiotics may be limited, likely outweighed by the common risks of antibiotics, such as gastrointestinal upset, *Clostridium difficile* colitis, rash, and anaphylaxis, and the risk of antimicrobial resistance (both individually and societally).

No studies examining the use of nonmacrolide antibiotics for longer than 3 weeks in CRSwNP have been published. Therefore, no evidence-based recommendations can be made regarding this practice.

- Aggregate Grade of Evidence: not applicable.

VIII.E.4.c. CRSwNP Management with Antibiotics: Macrolide Antibiotics. The anti-inflammatory properties of macrolides have led many to examine their role in the treatment of CRSwNP. Numerous cohort studies have evaluated the impact of macrolides on polyp size and recurrence, specifically in a post-ESS setting. Recently, higher level evidence has also been published.

Macrolides have been pursued as treatment for CRS because of proposed antibacterial and immunomodulatory properties, as previously reviewed in Section VII.E.4.c. In addition to modulating NF-kB proinflammatory cytokine production,[744–748] studies suggest a non–allergy-mediated role for macrolides in reducing nasal fibroblast proliferation, differentiation, collagen production, and decreased eosinophilic infiltration into nasal epithelium and lamina propria.[1030–1032]

An EBRR by Soler et al.[752] addressed the utility of macrolide use in CRS. Neither of the 2 RCTs exclusively evaluated CRSwNP patients and just 3 of the remaining 15 retrospective studies specifically assessed CRSwNP patients. Results within these CRSwNP studies may be affected by differences in polyp composition, where racial and geographic factors have resulted in distinct neutrophilic and eosinophilic polyp phenotypes. Katsuta et al.[1033] treated CRSwNP patients with 3 months of roxithromycin 500 mg BID and found improvements in symptoms, endoscopy, and CT findings in greater than 50% of patients. Yamada et al.[1034] used clarithromycin 400 mg daily for 8 to 12 weeks and found improved polyp grade in 40% of patients. Moriyama et al.[1035] studied erythromycin 400 to 600 mg daily for 7 months in postoperative patients, showing improved rhinoscopy findings without significant side effects.

More recently, 1 RCT has examined macrolides specifically in CRSwNP patients. To evaluate the effect of macrolide dosing duration, Varvyanskaya and Lopatin[1036] evaluated 66 patients with bilateral NPs on nasal endoscopy and CT imaging after ESS. They were randomized to 3 treatment groups: clarithromycin 250 mg daily for 24 weeks (n = 22), clarithromycin 250 mg daily for 12 weeks (n = 22), and control (n = 22). All participants received mometasone furoate 400 μg daily and were evaluated at 6, 12, and 24 weeks after ESS. Both 12-week and 24-week durations of clarithromycin treatment resulted in improved SNOT-20 scores at each follow-up time point compared to control. Both macrolide treatment groups demonstrated significant reduction in polyposis as well. At the 24-week time point, the 24-week treatment and 12-week treatment groups had statistically significant 8-fold and 5.3-fold reductions in polyp burden, respectively, compared to just 1.8-fold reduction in the control group of mometasone furoate alone. Similarly, LM scores were significantly improved after 24 weeks in the extended-duration treatment group. Finally, levels of ECP were significantly reduced at 12 and 24 weeks post-ESS in both treatment groups, suggesting that macrolide reduction of eosinophilic inflammation may reduce polyp recurrence.

Haxel et al.[761] used a DBRCT to examine the efficacy of macrolide in both CRSwNP and CRSsNP patients following sinus surgery. Both CRSwNP and CRSsNP patients were found to have improved endoscopy scores following 3 months of erythromycin 250 mg daily compared to controls. Interestingly, CRSsNP patients had a more robust response than CRSwNP patients.

Additional lower-level evidence supports the use of macrolides, with most using clarithromycin in varying

TABLE VIII-10. Evidence for CRSwNP management with nonmacrolide oral antibiotics for <3 weeks

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Van Zele[1023]	2010	1b	RCT	1. Doxycycline; 2. Placebo	1. Polyp size; 2. Nasal obstruction; 3. Olfaction; 4. Rhinorrhea; 5. Postnasal drainage	Reduction in polyp size at week 12; reduction in postnasal drainage at week 2
Hoza[1029]	2013	4	Case series	1. Erdosteine; 2. Erdosteine with INCS spray	SNOT-22 score	Reduction in symptom score; better response seen without INCS

dosages and durations. A recent study by Dabirmoghaddam et al.[1037] in 40 patients with severe polyposis demonstrated a significant endoscopic response in 72% of patients treated with clarithromycin 500 mg twice daily. Peric et al.[1032] reported statistically significant reduction in polyp score in both allergic and nonallergic patients and reduction in levels of IL-8 after 8 weeks of treatment with clarithromycin 500 mg daily. Haruna et al.[755] suggest that macrolide treatment may be less efficacious in reducing symptoms in patients with predominant eosinophilic disease or severe polyp burden if polypectomy is not initially performed. Finally, Ichimura et al.[1038] determined that roxithromycin improved NPs in 52% of CRSwNP patients at a dose of 150 mg daily for at least 8 weeks.

Adverse effects and caution in using macrolides is reviewed in Section VII.E.4.c.

Limited data from 1 RCT of macrolides and CRSwNP as well as lower-level evidence demonstrate some benefit, particularly following ESS (Table VIII-11). Existing studies have utilized different drugs, dosages, and durations of therapy. Risks of adverse events are significant so that potential benefit must be balanced with potential harm.

- Aggregate Grade of Evidence: B (Level 1b: 2 studies; Level 2b: 5 studies; Level 3b: 1 study; Level 4: 1 study).
- Benefit: Macrolides appear to reduce polyp burden in post-ESS patients and improve CRS symptoms.
- Harm: Significant potential for medication interactions. Rare mild adverse events, particularly potential for severe cardiovascular complications.
- Cost: Low.
- Benefits-Harm Assessment: Benefits appear to outweigh harm, though data are limited.
- Value Judgments: Limited data to determine benefit-harm balance. Optimal drug, dosage, and duration of therapy are not known.
- Policy Level: Option.
- Intervention: In CRSwNP, macrolides may be beneficial after ESS to decrease recurrence of polyps.

VIII.E.4.d CRSwNP Management with Antibiotics: Intravenous Antibiotics. *Because of limited data, CRSwNP and CRSsNP are combined in Section VII.E.4.d.*

VIII.E.4.e CRSwNP Management with Antibiotics: Topical Antibiotics. *Because of limited data, CRSwNP and CRSsNP are combined in Section VII.E.4.e.*

VIII.E.5. CRSwNP Management: Antifungals

VIII.E.5.a CRSwNP Management: Antifungals: Oral Antifungals. The Cochrane review conducted by Sacks et al.[788] synthesized all RCTs investigating the use of oral antifungals in the management of CRS, of which only 1 met inclusion criteria (see Table VIII-12).[1039] In this study, 50 adult CRSwNP patients who were diagnosed with AFRS by clinical, radiologic, histopathologic, and laboratory workup and who subsequently underwent ESS were recruited and postoperatively randomized into 5 groups. This study was not blinded and there was no discussion of the method of randomization in the methods. In addition to conventional medical treatment (CMT) consisting of oral antibiotics and oral and topical corticosteroids, patients received oral itraconazole (group A), fluconazole nasal spray (group B), combined oral itraconazole and nasal fluconazole (group C), and irrigation with a fluconazole solution through the nasal fossa (group D); the control group (group E) received CMT only. A total of 41 patients were available for follow-up (9 months maximum). Recurrence rates in the 5 groups were as follows: group A 66.7%; group B 10.0%; group C 14.3%; group D 28.6%; and group E 75.0%. It was not mentioned whether these differences were statistically significant.

Kennedy et al.[379] examined use of oral antifungal treatment in CRS but did not delineate polyp status. They found no improvement with the use of oral terbinafine. No other RCTs using oral antifungals for CRSwNP have been published.

On the basis of this 1 small randomized but not placebo-controlled study in an AFRS subset of CRSwNP, there is no evidence to support the use of systemic antifungal treatment in the routine management of CRSwNP more generally.

- Aggregate Grade of Evidence: A (Level 1a: 1 study, Level 1b: 1 study).
- Benefit: No demonstrated benefit of oral antifungals in routine management of CRSwNP.

TABLE VIII-11. Evidence for CRSwNP management with macrolide antibiotics

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Haxel[761]	2015	1b	RCT	1. Erythromycin 250 mg daily (n = 29); 2. Placebo (n = 29)	1. ECP and MPO in nasal secretions; 2. Multiple other patient reported and clinical measures	Improved nasal endoscopy score. Duration or low-dose of this trial not efficacious. High chance of Type II error
Varvyanskaya[1036]	2014	1b	RCT	1. Clarithromycin 250 mg daily × 24 weeks (n = 22); 2. Clarithromycin 250 mg daily × 12 weeks (n = 22); 3. Control (n = 22)	1. SNOT-20; 2. Symptoms (VAS); 3. Olfaction; 4. Endoscopy; 5. Saccharin transit; 6. Acoustic rhinometry; 7. CT	SNOT-20, CT, and endoscopy were improved in both treatment groups compared to control. VAS scores improved, but nonsignificant
Dabirmoghaddam[1037]	2013	2b	Cohort study	1. Clarithromycin 500 mg BID (n = 40)	1. Symptoms (VAS); 2. NP size; 3. CT (LM score)	Improvement in nasal obstruction, hyposmia, rhinorrhea, NP size, and LM score
Peric[1032]	2012	2b	Cohort study	1. Clarithromycin 500 mg daily (n = 40)	NP score	Reduction in polyp score in both nonallergic and allergic patients
Haruna[755]	2009	2b	Cohort study	1. Roxithromycin 150 mg daily (n = 45); 2. Clarithromycin 200 mg daily (n = 23)	1. Change in CT score; 2. Subjective symptom score	Improvement of symptoms in most patients. Less efficacious in some patients if NPs not removed first
Katsuta[1033]	2002	2b	Cohort study	Roxithromycin 500 mg BID	1. Symptoms; 2. Endoscopy; 3. CT scores	More than 50% of patients demonstrated clinical improvement
Yamada[1034]	2000	2b	Cohort study	1. Clarithromycin 400 mg daily (n = 20); 2. Observation; nonconcurrent (n = 18)	1. NP size; 2. IL-8 levels in nasal lavage; 3. IL-4, IL-6, IL-10, and MCP-1 levels in nasal lavage	40% of patients showed reduction in polyp size; IL-8 levels reduced with treatment
Moriyama[1035]	1995	3b	Retrospective case-control	1. Erythromycin postoperatively (600 mg TID for 1–2 months, then 400 mg BID); 2. No erythromycin postoperatively	1. Symptoms; 2. Endoscopy	Erythromycin demonstrated a greater improvement in symptoms and endoscopy compared to no erythromycin
Ichimura[1038]	1996	4	Case series	1. Roxithromycin 150 mg daily (n = 20); 2. Roxithromycin 150 mg daily + Azelastine 1 mg BID (n = 20)	1. Subjective symptom score; 2. Serum IgE; 3. Serum eosinophil count; 4. CT scan score	Reduction in polyp size, with greater impact on smaller polyps

MCP-1 = monocyte chemoattractant protein 1; MPO = myeloperoxidase.

- Harm: Systemic side effects including derangement of liver function tests have been reported.
- Cost: Moderate.
- Benefits-Harm Assessment: Risk of adverse effects outweigh potential benefit because evidence for use of oral antifungal therapy is lacking.
- Value Judgments: Studies included are often a mix of CRSwNP and CRSsNP.
- Policy Level: Recommendation against.
- Intervention: Oral antifungal agents should not be given for the routine treatment of CRSwNP.

VIII.E.5.b. CRSwNP Management: Antifungals: Topical Antifungals. The Cochrane review conducted by Sacks et al.[788] synthesized all RCTs investigating the use of topical antifungals in the management of CRS. A systematic search for RCTs using the same search strategies as in the Cochrane database was conducted and 4 resulting studies were reviewed and categorized as either CRSsNP or CRSwNP depending on the major population.

Ebbens et al. recruited 116 adult patients with CRS (with and without NPs) who had undergone ESS. These patients from 6 European tertiary care otorhinolaryngology clinics

TABLE VIII-12. Evidence for CRSwNP management with oral antifungals

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Khalil[1039]	2011	1b	Nonblinded 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 statistical analysis was done)

had persistent clinical signs and symptoms for over 6 months.[381] More than 80% of the patients had CRSwNP (amphotericin B group 47/59 patients [80%] and placebo group 48/57 [84%]; personal communication Ebbens). These patients were randomized into 2 groups: 25 mL amphotericin B solution (100 μg/mL) to each nostril twice daily using a nasal irrigating device (daily amount of amphotericin B = 10 mg) (n = 59) or a yellow-colored placebo solution (n = 57) for 13 weeks. The primary outcomes were symptom scores (using a total VAS) and endoscopic scores. Secondary outcomes included change from baseline in disease-specific QoL using the RSOM-31 and individual VAS scores, change in QoL using the SF-36, change in PNIF, and change in polyp scores. Eight (13.6%) treatment patients and 9 (15.8%) control patients did not complete the study.

Gerlinger et al.[1040] studied 33 adult patients presenting with CRSwNP who had previous ESS. They were randomized into 1 group receiving amphotericin B nasal spray (5 mg/mL) (daily amount of amphotericin B = 4 mg, n = 16) or the other group receiving a placebo spray (n = 17), 2 sprays twice daily into each nostril for 52 weeks. The primary outcome measure was a modified LM CT score. Secondary outcomes included a nonvalidated sinonasal assessment questionnaire and endoscopic assessment. Two (12.5%) patients in the intervention group and 1 (5.9%) patient in the control group did not complete the study.

The study by Khalil et al.[1039] involved both topical and oral antifungal treatment. Fifty adult CRSwNP patients who were diagnosed with AFRS by clinical, radiologic, histopathologic, and laboratory workup and who subsequently underwent ESS were postoperatively randomized into 5 groups. This study was not blinded and there was no discussion of the method of randomization in the methods. In addition to conventional medical treatment consisting of oral antibiotics and oral and topical corticosteroids, patients received oral itraconazole (group A), fluconazole nasal spray (group B), combined oral itraconazole and nasal fluconazole (group C), and irrigation with a fluconazole solution through the nasal fossa (group D); the control group (group E) received CMT only. A total of 41 patients were available for follow-up (9 month maximum). Recurrence rates in the 5 groups were 66.7%, 10.0%, 14.3%, 28.6%, and 75.0%, respectively. It was not mentioned whether these differences were statistically significant.

Weschta et al.[377] studied 78 adult patients with CRSwNP presenting for ESS who were recruited and randomized into 2 groups. Thirty-three patients had previous sinus surgery, 17 (43.6%) in the intervention arm and 16 (41.6%) in the control arm. Following ESS, both groups were instructed to spray twice (200 mcL) in each nostril 4 times a day for 8 weeks. The intervention group (n = 39) received amphotericin B nasal spray (3 mg/mL, daily amount of amphotericin B = 4.8 mg) whereas the control group received a placebo nasal spray (n = 39). Primary outcomes included CT scores (modified LM), RS QoL scores (RQLQ), and endoscopy scores. Ten (25.6%) amphotericin B patients and 5 (12.8%) control patients did not complete the study.

Of note, Ponikau et al.[378] studied topical amphotericin and found a radiologic change, but no symptom or endoscopic change. They did not delineate polyp status.

Results of the 4 studies on CRSwNP patients are presented in Table VIII-13. The results of all studies showed no significant improvement in QoL questionnaire scores, or the radiographic scores when compared to placebo; 1 study favored the control group for symptoms[377] and another study favored the control group for the radiographic scores.[1040] In 1 study the amphotericin B group showed no significant improvement in nasal endoscopy scores.[381] Khalil et al.[1039] showed an improvement in recurrence rates in AFRS with fluconazole nasal spray but did not perform a statistical analysis on these patients. It is difficult to know how generalizable the Khalil et al.[1039] data are to CRSwNP patients overall. On the basis of the available studies there is no evidence to support the use of topical antifungal treatment in the routine management of CRSwNP.

- Aggregate Grade of Evidence: A (Level 1a: 1 study, Level 1b: 4 studies).*
- Benefit: No demonstrated benefit of topical antifungals in management of typical CRSwNP, but may have some benefit in certain CRSwNP subsets, such as AFRS.
- Harm: Main side effect reported is local irritation. Meta-analysis performed in the Cochrane Review did not demonstrate a statistically significant difference in adverse effects between treatment and placebo groups.
- Cost: Moderate.
- Benefits-Harm Assessment: With no benefit seen for CRSwNP patients generally, the benefits cannot outweigh the risks and costs.

TABLE VIII-13. Evidence for CRSwNP management with topical antifungals

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Sacks[788]	2011	1a	Systematic review with meta-analysis combining CRSwNP and CRSsNP	1. Topical antifungal therapy; 2. Placebo	1. Collated symptom scores; 2. QoL questionnaire; 3. Adverse events	No benefit of topical antifungal over placebo
Khalil[1039]	2011	1b	Nonblinded 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 statistical analysis was done)
Gerlinger[1040]	2009	1b	RCT	1. 4 mg daily amphotericin B (n = 16); 2. Placebo (n = 17)	1. LM CT score; 2. Questionnaire; 3. Endoscopic score	No benefit of topical antifungal over placebo
Ebbens[381]	2006	1b	RCT	1. 25 mL amphotericin B (n = 59); 2. Yellow-colored placebo (n = 57)	1. Total and individual symptom VAS; 2. RSOM-31; 3. SF-36; 4. PNIF	No benefit of topical antifungal over placebo
Weschta[377]	2004	1b	RCT	1. 4.8 mg daily amphotericin B (n = 39); 2. Placebo (n = 39)	1. CT score (modified LM); 2. RQLQ; 3. Endoscopic score	No benefit of topical antifungal over placebo

- Value Judgments: None.
- Policy Level: Recommendation against.
- Intervention: Topical antifungal agents should not be used in routine CRSwNP treatment.

*Studies included are often a mix of CRSwNP and CRSsNP.

VIII.E.6. CRSwNP Management: Topical Alternative Therapies

VIII.E.6.a CRSwNP Management with Topical Alternative Therapies: Surfactants. *Because of limited data, CRSwNP and CRSsNP are combined in Section VII.E.6.a.*

VIII.E.6.b. CRSwNP Management with Topical Alternative Therapies: Manuka Honey. *Because of limited data, CRSwNP and CRSsNP are combined in Section VII.E.6.b.*

VIII.E.6.c. CRSwNP Management with Topical Alternative Therapies: Xylitol. *Because of limited data, CRSwNP and CRSsNP are combined in Section VII.E.6.c.*

VIII.E.6.d. CRSwNP Management with Topical Alternative Therapies: Colloidal Silver. *Because of the limited data, CRSwNP and CRSsNP are combined in Section VII.E.6.d.*

VIII.E.7. CRSwNP Management: Distribution of Topical Medications and the Influence of Head Position, Device, Surgery, and Nasal Anatomy

Because of limited data, CRSwNP and CRSsNP are combined in Section VII.E.7.

VIII.E.8. CRSwNP Management: Immune Workup and Treatment

Because of limited data, CRSwNP and CRSsNP are combined in Section VII.E.8.

VIII.E.9. CRSwNP Management: Anti-LT Therapy

Upregulation of the cysLT pathway has been demonstrated in asthma, AR, and CRSwNP. CysLTs are inflammatory mediators synthesized by eosinophils and mast cells through the breakdown of arachidonic acid. Both increased cysLT production and upregulation of cysLT receptors have been seen in these conditions, particularly in AERD. Because of the known increase in cysLT activity in CRSwNP, anti-LT therapy has been used in CRSwNP. Few studies have examined the effectiveness of anti-LT therapy in CRSwNP and these were recently summarized by Wentzel et al.[1041] and Smith and Sautter.[1042]

Wentzel et al.[1041] 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 antagonist, to placebo[1043,1044]; 2 compared montelukast to INCS[1045,1046]; and 1 compared montelukast and INCS to INCS alone following a course of oral corticosteroids.[1047] Wentzel et al.[1041] were able to combine 2 of the RCTs into a meta-analysis. Their systematic review and meta-analysis 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[1042] confined itself to English-language studies that addressed the efficacy of montelukast in CRSwNP. They identified 5 such studies. Three were RCTs (level 1b),[1043,1046,1047] with 1 each of a nonrandomized, noncontrolled study (level 3)[1048] and a basic science study (level 5).[1049] Overall, they found moderate evidence of efficacy as an adjunctive treatment, used in conjunction with corticosteroids. Interestingly, they cited 1 ex vivo basic science study that showed montelukast combined with zileuton, a selective 5-lipoxygenase enzyme inhibitor, better prevented mast cell activation in CRSwNP tissue than montelukast alone.[1049]

Finally, 1 double-blinded placebo-controlled study has examined zileuton as an addon therapy to inhaled and/or oral corticosteroids in AERD patients.[1050] Dahlen et al.[1050] 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.

In summary, 2 reviews have demonstrated a limited benefit to anti-LT therapy (Table VIII-14). The risks of LT therapy vary with the specific drug chosen. Montelukast has a relatively limited adverse reaction profile, but other anti-LT medications such as zileuton have been associated with significant liver concerns.

- Aggregate Grade of Evidence: A (Level 1a: 2 studies).
- Benefit: Improvement in symptoms, comparable to INCS. May have limited benefit as an adjunct to INCS.
- Harm: Limited risks. Montelukast has been associated with rare neuropsychiatric events in postmarketing reports. Zileuton and other medications are associated with elevated liver enzymes.
- 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.

VIII.E.10. CRSwNP and AERD Management: Aspirin Desensitization

ESS today still is the treatment of choice for NP removal in individuals suffering from AERD. However, in this particular subset of patients, recurrence of inflammatory mucosal changes and ultimately NPs are seen early on, often within months, and a high percentage of patients have to undergo revision surgeries.[960,961] 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 diverse adaptive aspirin desensitization protocols, the respective impact on LT and prostaglandin (PG) release, and their clinical results.[1051,1052] Some of these protocols vary in aspirin intake route, especially with regard to oral vs IV application during the initial desensitization phase.[1053–1055] 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 calm down the inflammatory situation and have the best possible impact on polyp relapse and QoL. One caveat before initiating desensitization is a thorough evaluation of the pulmonary function, which should not be worse than 75% of the expected functional expiratory volume within 1 second (FEV1) for the individual.

In several publications, including a level 1b trial in the early 1980s, Stevenson et al.[1053,1056] 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 of sinus infections, revision surgeries, and INCS use during this high-dose aspirin desensitization. However, severe aspirin-related side effects like gastric bleeding and gastric pain were observed as well as impaired renal function, nausea, and blood-clotting disorders.[950,1056] These adverse effects led to high dropout rates around 50% after just several months. This is unfavorable, because desensitization only offers a potential causative therapeutic option if given long enough to normalize the pathologic shift in the arachidonic acid pathway. Earlier clinical observations were able to demonstrate that in most patients this effect takes 6 to 9 months to become measurable in vitro.[947] Even so, it is uncertain whether any interruption of the maintenance dose for longer than 48 hours might end the refractory state of the metabolism and jeopardize the beneficial effect. Therefore, successful long-term desensitization should be continued over years, potentially decades, if benefits are to remain.

Data in the literature with regard to dosage during long-term desensitization have been as variable as the respective LOE. Rozsasi et al.[1057] recommended a maintenance dose of 300 mg daily to reduce NP recurrence and to improve

TABLE VIII-14. Evidence for CRSwNP management with antileukotriene therapy

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Smith[1042]	2014	1a	Systematic review of RCTs	CRSwNP	1. Symptom improvement; 2. Other clinical parameters	Moderate evidence for montelukast improving symptoms as an adjunct to INCS
Wentzel[1041]	2013	1a	Systematic review and meta-analysis of RCTs	CRSwNP	1. Symptom improvement; 2. Other clinical parameters	Montelukast shows improvement in symptoms over placebo, similar to that seen with INCS
Dahlén[1050]	1998	1b	DBRCT using zileuton 600 mg QID	AERD	1. PFTs; 2. Symptoms scoring; 3. PNIF	Zileuton resulted in improved PFTs as well as nasal symptoms and PNIF

PFT = pulmonary function test.

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.[947,1052] The most suitable protocol to establish efficacious and well-tolerable desensitization with the lowest possible maintenance dose of oral aspirin still remains yet to be determined. Lee et al.[1058] recommend an aspirin intake dose of at least 325 mg twice daily for optimal symptom control, but current reports showed that even aspirin doses of 650 mg/day are associated with a considerable risk of gastrointestinal bleeding.[1059,1060]

In 2013, the first double-blind placebo-controlled clinical trial was published, investigating adaptive aspirin desensitization with an initial challenge-dose reaching 800 mg aspirin over 1 day followed by a maintenance dose of just 100 mg daily. This low-dose protocol was revealed to be safe, with less than 3% of patients in the treatment group complaining about gastric irritations, all of which could continue the treatment after adding a PPI.[1061] With this unprecedented LOE it was shown that 100 mg as a maintenance dose could significantly reduce the clinical key symptoms such as nasal obstruction, discharge, and headache ($p = 0.001$). QoL was also significantly improved over a 3-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 level 1b evidence on a 100-mg protocol are that low-dose desensitization leads to a significant decrease in underlying inflammatory activity and therefore helps reduce the need for systemic corticosteroids in this group of patients, leading to a reduced need for surgical revisions.

In a recent review, Klimek et al.[1062] concluded that based on the currently available clinical and pathophysiological data, aspirin desensitization has been proven to be efficacious and safe and suitable to reduce the need for other medications in AERD patients. Parikh and Scadding[1054,1063] have reported on the use of topical nasal lysine in aspirin-sensitive patients. Interestingly, with only 75 mg applied intranasally, they were able to provide level 1b evidence for alterations of cysLT receptors and weaker evidence levels for improved clinical outcomes using this regimen[1054,1063] (Table VIII-15).

In future trials, potential differences or clinical benefits of 100 mg vs 300 mg of aspirin or vice versa should be evaluated by randomized double-blind prospective dose-finding trials because 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 practicable dosing. One of the few reasons why patients with AERD fail desensitization is that with their impaired pulmonary function they cannot tolerate high doses. However, with more recently elaborated evidence, low-dose desensitization has been proven to be an effective therapeutic pathway and should be recommended in patients with uncontrolled AERD.

- Aggregate Grade of Evidence: B (Level 1b: 4 studies; Level 2a: 3 studies; Level 2b: 6 studies; Level 2c: 2 studies; Level 3b: 1 study; Level 5: 1 study).
- 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: GI bleeding, increased morbidity in renal disease, and blood clotting issues at high maintenance doses. Less than 3% GI side effects with low-dose protocols.
- Cost: (1) Initial cost of desensitization. (2) Minimal direct costs for 100 mg aspirin daily. (3) Potentially costs 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 is 1 of the very few causative medical treatment options available to patients with CRSwNP.
- Policy Level: Recommendation.
- Intervention: Aspirin desensitization should be considered in AERD patients after surgical removal of NPs to prevent recurrence.

VIII.F. CRSwNP: Complications

Complications from CRSwNP fall into 2 broad pathophysiologic categories: (1) erosion and compression of the orbit

TABLE VIII-15. Evidence for CRSwNP with AERD management with aspirin desensitization

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Fruth[1061]	2013	1b	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
Lee[1058]	2007	1b	RCT	137 AERD patients randomized to different high-maintenance doses for desensitization	Symptom and medication scores after 1 year	Recommendation to start at 650 mg twice daily and subsequently decrease to 325 mg twice daily
Parikh[1054]	2005	1b	Randomized placebo-controlled crossover trial	22 AERD patients undergoing desensitization with intranasal lysine aspirin	1. Clinical improvement; 2. Improvement of in vitro parameters	Improvement only in tissue studies, no clinical benefit after 6 months
Stevenson[1053]	1984	1b	DBRCT	Patients with AERD undergoing oral desensitization	Nasal and pulmonary symptom- and medication scores during desensitization	CRS symptoms significantly reduced, asthma symptoms in one-half of patients
Baker[950]	2011	2a	SR	Patients with AERD undergoing high-dose desensitization	GI side effects	GI symptoms are the primary risk in high-dose desensitization
Lanas[1059]	2011	2a	SR	Patients with AERD and low-dose desensitization	GI symptoms and bleeding	Increased risk for GI bleeding in low-dose desensitization, decreased by PPI
Pfaar[1055]	2006	2a	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
Mendelsohn[960]	2011	2b	Large retrospective cohort study	Patients undergoing ESS for NP (n = 549)	Recurrence (measured by Kaplan-Meier curves)	Revision rates significantly higher in AERD
Rozsasi[1057]	2008	2b	Comparative cohort study	Patients with AERD undergoing low-dose desensitization with 100-mg 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
Gosepath[947]	2002	2b	Long-term cohort study	Patients with AERD undergoing long-term low-dose desensitization	Recurrence of NPs and need for surgical revisions	Long-term low-dose desensitization is clinically effective and can be monitored in vitro
Gosepath[1052]	2001	2b	Prospective cohort study	Patients with AERD undergoing low-dose desensitization after surgery	Effectiveness of low-dose desensitization and in vitro monitoring after 1 year	Clinical success after 1 year with 100 mg; correlation between clinical symptoms and in vitro monitoring
Stevenson[1056]	1996	2b	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, corticosteroid use
Lumry[1051]	1983	2b	Cohort study	Patients with incomplete AERD	Improvement after aspirin desensitization	77% of patients without asthma showed clinical improvement after desensitization
Klimek[1062]	2014	2c	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

(*Continued*)

TABLE VIII-15. Continued

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Parikh[1063]	2014	2c	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
Amar[961]	2000	3b	Case-control study	1.AERD; 2.CRS with/without asthma	1. Clinical effect of ESS; 2. Recurrent CRS; 3. Number of surgical interventions	Surgery is less effective long term in patients with AERD
Moberg[1060]	2011	5	Online questionnaire	1. Primary CV prevention; 2. Secondary CV prevention	Adherence to low-dose ASA in patients with GI problems	Poor adherence in patients with GI problems

CV = cardiovascular.

and skull base; and (2) sinus obstruction with mucocele formation. Complications from CRSwNP can also be categorized in anatomic terms: (1) orbital complications that manifest as loss of vision, proptosis, diplopia, and epiphora; and (2) intracranial complications that manifest as meningitis, altered mental status, and other neurologic deficits.

Although erosion of the lamina papyracea and skull base can occur with longstanding polyp growth, compression of the orbit and brain directly by polyps is rare. In a series of 82 patients with AERD, 2 patients developed encroachment and subsequent infections of the lacrimal apparatus, and 2 patients had erosion of the medial orbital wall, leading to orbital cellulitis in 1 and proptosis in the other. No intracranial complications were reported.[1064] Reports of intracranial involvement in the setting of NPs, with subsequent meningitis or intracranial abscess, are rare.

AFRS, which includes nasal polyposis as a hallmark finding, poses a unique situation. Substantial involvement of the skull base and lamina papyracea occurs in up to 50% of cases. [1065,1066] The role of gender and ethnicity is unclear, but African-American males have been reported to have a higher incidence of erosion.[1067] Compressive noninfective optic neuropathy with visual loss is less common (about 4%) but can also occur, with the possibility of partial or complete recovery of vision.[1068] Whether a CRSwNP case is AFRS-related or not, orbital and skull-base involvement in the absence of an acute infection is an insidious process characterized by smooth expansion without dural or periorbital invasion.

NPs can also cause sinus outflow obstruction, leading to mucocele formation. In 1 large study of NP patients, the incidence of mucocele in unoperated CRSwNP cases was 0.6%, whereas the incidence of mucocele in surgically-treated patients was 2.5% per year.[1069] The frontoethmoid region was the most commonly affected, and patients with AERD were at higher risk. In the same aforementioned series of 82 patients with AERD,[1064] 3 of the 7 orbital complications involved mucoceles encroaching on the orbit. Of these 3, two developed blindness as a result of optic nerve ischemia. A control group of aspirin-tolerant patients did not have any orbital complications.[1064] Overall, mucocele formation in CRSwNP is rare, but prior surgery and aspirin sensitivity seem to be risk factors.

VIII.G. CRSwNP and AFRS: Differences in Pathophysiology

AFRS is a subset of CRSwNP. It is a noninvasive, eosinophilic, recurrent form of polypoid RS that, based upon certain characteristics, is distinct from other forms of CRSwNP.[1070–1072] AFRS was originally described as the sinonasal corollary to allergic bronchopulmonary aspergillosis, which involves Gell and Coombs type I and III reactions to *Aspergillus*.[1073,1074] In AFRS, inhaled fungal spores are believed to trigger an escalating immunologic reaction of the sinonasal cavities.[1075,1076] The 1994 Bent-Kuhn AFRS diagnostic criteria include: type I hypersensitivity, nasal polyposis, characteristic CT findings, eosinophilic mucus without fungal invasion, and positive fungal stain.[358,1077] Aside from NPs, these criteria collectively help to differentiate AFRS from other forms of CRSwNP. Some authors describe alternate AFRS criteria, specifying positive fungal culture instead of fungal stain, and noting that not all AFRS patients have fungal allergy.[359,1078] This has stirred debate regarding AFRS pathophysiology.[370,1072,1076]

CRSwNP, including AFRS, often involves a Th2-predominant immune response with eosinophilic inflammation.[1071,1079,1080] Theoretically, the primary stimulus in AFRS is a Type I IgE-mediated hypersensitivity to ubiquitous fungal allergens. AFRS patients have elevated serum total and fungal-specific IgE compared to CRSwNP patients, and serum-specific IgE levels (to both fungal and nonfungal allergens) have been shown to correlate with clinical severity and recurrence.[917,1073,1074,1077,1081,1082] Eosinophilic mucin, which is not present in all forms of CRSwNP, is a byproduct of inflammation and contributes to disease persistence or progression. Eosinophilic mucin characteristic of AFRS is thick, tenacious, and consists of necrotic and degranulating eosinophils in a background of mucin, Charcot-Leyden crystals, and fungal

hyphae.[1077,1083] Dematiaceous fungi and *Aspergillus* are commonly identified, but fungi are diverse and vary based on geographical region.[1073,1075,1076,1081,1083,1084] Interestingly, correlation between fungal species in mucin and systemic fungal allergy was poor in 1 Australian study.[370]

Clinically, AFRS tends to be a more severe form of CRSwNP. Characteristic CT scan findings include increased density of material within sinus cavities and expansion or erosion of paranasal sinus bony walls. Unlike CRSwNP, greater than 30% of AFRS patients have skull-base or orbital expansion/erosion on presentation,[1066,1077,1082,1085–1088] potentially causing visual disturbance or facial deformity.[1070,1072,1083] Compared to CRSwNP overall, AFRS patients are younger, atopic, and often have unilateral disease.[925,1073,1079,1089] In the United States, associations with lower socioeconomic status, Southern geographic region, and African-American ethnicity have been identified.[925,1085,1090–1092]

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.[1071,1073,1074] Elevated IgG3 levels specific to *Alternaria alternata* and *Aspergillus fumigatus* distinguished eosinophilic RS, including AFRS, from control groups.[370] *Staphylococcus aureus* is a common organism in polypoid RS, and may modify these disease processes as a direct pathogen or via superantigen production.[903,925,1084,1093,1094] *S. aureus* colonization is more prevalent in AFRS vs other CRSwNP subtypes.[925] Vitamin D_3 levels are also decreased in CRSwNP and AFRS, with levels inversely correlating with bone erosion.[426] Additionally, genetic analysis has demonstrated differential gene expression and allelic variations in AFRS vs other CRS subtypes.[634,1095,1096]

A local mucosal response also likely contributes to AFRS pathogenesis. Respiratory epithelial cells can initiate a local Th2 immune response.[1094] NPs contain elevated levels of dendritic cells, mast cells, eosinophils, and Th2 cytokines.[538,1079,1080,1094,1097,1098] AFRS mucosa has a predominance of CD8+ T cells vs CRSwNP mucosa, which has elevated CD20+ B-cells.[1086] Various studies demonstrate elevation of fungal and nonfungal IgE within AFRS mucosa, and local IgE correlates with sinonasal eosinophilia.[917,1079,1080,1093,1099,1100] Most AFRS patients also have detectable fungal-specific IgE in their mucin.[1077]

AFRS is a distinct, often more severe, subclass of CRSwNP. Although the precise AFRS pathophysiology remains unclear, type I hypersensitivity, eosinophilic inflammation, and Th2 cytokine profiles are important. Environment, socioeconomic factors, and genetic predisposition also likely contribute.

- Aggregate Grade of Evidence: Level 2b: 16 studies; Level 3a: 1 study; Level 4: 14 studies; Level 5: 10 studies (Table VIII-16).

VIII.H. CRSwNP and AFRS: Differences in 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.[1094] 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.

Antifungal Therapy

Several studies support the role of fungi in the pathophysiology of AFRS. Although several clinical trials have addressed the role of oral antifungals in CRS, only a small number of studies have specifically included AFRS. A recent systematic review by Gan et al.[1101] on the medical management of AFRS evaluated studies on oral and topical antifungals. This review only included studies that strictly included AFRS patients that met the Bent and Kuhn diagnostic criteria. For oral antifungals, 5 clinical studies were identified. Two studies, Chan et al.[1102] and Khalil et al.,[1039] were excluded for failure to specifically include fungal type I hypersensitivity in the criteria for AFRS. These studies were included in the review by Gan et al.[1101] and are included in this review and in Table VIII-17, but failure to require type I hypersensitivity may bias the recommendations and results.

Rains and Mineck,[1103] in a noncontrolled case series of AFRS patients (n = 137) treated with an oral antifungal (itraconazole 400 mg/day tapered to 200 mg/day for 3 to 6 months depending on response) found that the addition of itraconazole to their usual postoperative low-dose corticosteroids reduced reoperation rate from a range of 48% to 56% to 20.5%.

Kupferberg et al.[1104] and Seiberling and Wormald[1105] published 2 case series with small numbers. In Kupferberg et al.'s study,[1104] oral antifungals alone improved symptoms in only 1 of the 3 patients who received them. Seiberling and Wormald[1105] reported on management of postoperative recurrent NPs in AFRS patients treated with 6 months of itraconazole. Of the 9 AFRS patients included in the study, 7 responded positively to itraconazole alone but 2 experienced another recurrence that required another course of itraconazole to clear.

Chan et al.[1102] and Khalil et al.[1039] defined AFRS by the Bent and Kuhn criteria except for demonstration of fungal Type I hypersensitivity. Chan et al.[1102] reported a case series with 32 recurrent patients postoperatively who failed to respond to other medical therapies including prednisone and topical antifungals. Eighteen of the 32 patients had subjective significant or moderate improvement and 12 had endoscopic improvement. The subjective and endoscopic improvements did not correlate. Khalil et al.[1039] performed

TABLE VIII-16. Evidence for differences in pathophysiology between CRSwNP and AFRS

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Clinical description						
Han[1079]	2013	2b	Prospective case-control study	1. AERD; 2. AFRS; 3. Asthmatic RS with allergy; 4. Asthmatic RS without allergy; 5. Nonasthmatic RS with allergy; 6. Nonasthmatic RS without allergy; 7. CF	1. Clinical data; 2. 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
Chakrabarti[1083]	2009	3a	Consensus panel/review article	N/A	N/A	Suggested terminology for various forms of fungal RS. Consensus to call mucus in AFRS eosinophilic mucin
Uri[1072]	2013	4	Retrospective case series	1. AFRS; 2. EMRS	Clinical data	AFRS and EMRS have similar clinical presentations, but follow different clinical courses. Unilateral disease and orbital involvement are more common in AFRS than EMRS
Marfani[1087]	2010	4	Retrospective case series	Patients diagnosed with AFRS	Clinical data	The majority of patients were young, male, and of low socioeconomic status. Unilateral disease present in over 59% of patients
Ghegan[1066]	2006	4	Retrospective case series	Patients undergoing ESS for inflammatory disease	Clinical data	AFRS patients were >12 times more likely to have bony erosion than CRS. Patients with AFRS were younger. Bony erosion was more common in males and African American patients
Saravanan[1078]	2006	4	Prospective comparative study	Patients with CRS	Clinical and pathologic data	Reviewed diagnostic findings in patients with AFRS
Ferguson[1089]	2000	4	Literature review and retrospective case series	1. AFRS; 2. EMRS	Clinical and immunologic data	Unilateral disease, and elevated IgE levels were more common in AFRS. Adult-onset asthma and AIT were more frequent in EMRS
Ferguson[1092]	2000	4	National survey; literature review	Patients with AFRS	Clinical data	AFRS prevalence varied geographically, with no correlation to environmental mold counts
Mukherji[1088]	1998	4	Retrospective review	Patients with AFRS	Clinical data	AFRS was more common in males and in those from southern U.S. states
deShazo[359]	1995	4	Retrospective case series	Patients diagnosed with AFRS	Clinical data	Proposal of 5 diagnostic criteria for AFRS
Bent[358]	1994	4	Prospective case series	Patients diagnosed with AFRS	Clinical and pathologic data	Defined diagnostic criteria for AFRS
Histopathologic evaluation						
Laury[1098]	2014	2b	Prospective case-control study	1. AFRS; 2. CRSsNP; 3. Control group	Semiquantitative reverse-transcription PCR and immunofluorescence of sinus tissue	Periostin was significantly elevated in AFRS compared to CRSsNP and controls; correlated with bone erosion
Bakhshaee[1081]	2013	2b	Prospective cohort study	Patients with >1 year history of CRSwNP	Clinical and histopathological data	Prevalence of AFRS among patients with NPs was 9.45%

(*Continued*)

TABLE VIII-16. Continued

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Ragab[1086]	2013	2b	Prospective case-control study	1. AFRS; 2. Mycetoma; 3. CRSwNP; 4. CRSsNP	Histopathologic and IHC of sinonasal mucosa	$CD8^+$ T cells were the most common cell type in AFRS. $CD20^+$ B cells were most common in CRSwNP and CRSsNP
Ayers[538]	2011	2b	Prospective case-control study	1. CRSwNP; 2. CRSsNP; 3. AFRS; 4. Control group	IHC of mucosa from the OMC	Dendritic cells and associated chemokines are significantly increased in the mucosa of AFRS and CRSwNP
Ahn[1100]	2009	2b	Prospective case-control study	1. CRSsNP; 2. AFRS; 3. 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[1097]	2009	2b	Prospective case-control study	1. CRS; 2. AFRS; 3. AFRS-like (fungal allergy, but no fungi in EM); 4. Nonallergic fungal eosinophilic RS; 5. Nonallergic nonfungal eosinophilic RS	IHC and flow cytometry of polyp, nonpolyp tissue, and peripheral blood; 2. 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
Wise[1099]	2008	2b	Prospective case-control study	1. Control group; 2. AFRS; 3. CRSsNP	Immunohistochemistry 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
Carney[1080]	2006	2b	Prospective case-control study	1. Control group; 2. AFRS; 3. Nonallergic eosinophilic fungal RS (those patients with NPs and positive fungal culture or stain, but without fungal allergy); 4. CRS	Immunohistochemistry of infundibular mucosa	AFRS, nonallergic eosinophilic fungal RS, and CRSsNP patients have elevated local mast cells, eosinophils, and IgE^+ cell numbers compared to controls. There was 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						
Matsuwaki[917]	2013	2b	Prospective case-control study	1. AFRS; 2. CRSwNP; 3. Control group	Immunohistochemistry 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, with fungal-specific IgE more strongly correlated compared to nonfungal IgE
Hutcheson[1082]	2010	2b	Prospective case-control study	1.AFRS; 2. CRS	1.Serum total IgE and IgG anti-*Alternaria*–specific antibodies; 2. Serum antifungal IgE by Western immunoblotting	Mean serum total IgE was significantly higher in AFRS compared to CRS. Mean serum IgG anti-*Alternaria* antibodies were significantly elevated in AFRS compared to CRS. Statistically significant increase in mean number of IgE antifungal bands from AFRS compared to CRS

(*Continued*)

TABLE VIII-16. Continued

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Pant[370]	2005	2b	Prospective case-control study	1. EMCRS; 2. AFRS; 3. AFRS-like; 4. Nonallergic fungal eosinophilic RS; 5. Nonallergic, nonfungal eosinophilic RS; CRS; 6. AR with fungal allergy; 7. Control	1. IHC of sinonasal mucosa; 2. Serum Ig levels; 3. Clinical data	Fungal-specific IgG3 levels were elevated in all EMCRS patients, irrespective of the presence of fungal allergy or fungi within eosinophilic mucin
Other immune mechanisms						
Seiberling[903]	2005	2b	Prospective case-control	1. CRSwNP; 2. CRSsNP; 3. Control group	1. Presence of SEA, SEB, SEC, SED, and TSST-1; 2. Pathologic evaluation of tissue	Association between toxin detection and CRSwNP. Higher eosinophil counts in CRSwNP
Clark[925]	2013	4	Retrospective case-series	1. CRSwNP; 2. AFRS	Sinus culture	There is a higher prevalence of *S. aureus* in patients with AFRS vs patients with other types of CRSwNP
Mulligan[426]	2011	4	Retrospective case-series	1. AFRS; 2. CRSwNP; 3. CRSsNP; 4. Control group	1. VD_3 deficiency; 2. Circulating levels of immune cells; 3. Degree of bone erosion on sinus CT scan	CRSwNP and AFRS, but not CRSsNP, have insufficient vitamin D_3 levels. Vitamin D_3 levels inversely correlate with circulating dendritic cells
Gene expression						
Ebert[1095]	2014	2b	Prospective case-control study	1. AFRS; 2. CRSwNP; 3. Control group	Gene expression profiles in mucosal tissue assessed by microarray analysis	Protease-activated receptor 3 gene expression was elevated compared to controls. No difference between AFRS and controls
Orlandi[1096]	2007	2b	Prospective case-control	1. AFRS; 2. EMRS	Gene expression profiles in NP tissue using microarray analysis	38 genes were overexpressed or underexpressed in AFRS; 10 were differentially expressed in EMRS
Schubert[634]	2004	2b	Prospective case-control	1. AFRS; 2. Hypertrophic sinus disease	HLA DNA genotyping	66% of AFRS patients carried at least 1 HLA-DQB*03 allele. Allelic variants differed between CRSwNP and AFRS patients
Demographic and socioeconomic factors						
Miller[1091]	2014	4	Retrospective case-series	Patients who met 3 of 5 AFRS Bent-Kuhn diagnostic criteria	1. Demographic and socioeconomic factors; 2. Measures of disease severity	Majority of patients were African American. Higher prevalence of bone erosion in males. Lower socioeconomic status was associated with more severe disease
Wise[1090]	2008	4	Retrospective chart review	1. AFRS; 2. CRSwNP; 3. 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 compared to CRSsNP, but not CRSwNP
Ghegan[1085]	2007	4	Retrospective chart review	AFRS	Demographic and socioeconomic factors	Majority of patients were African American. Higher prevalence of bone erosion in males. Socioeconomic factors did not significantly correlate with bone erosion

AIT = aspirin intolerant; AScA = asthmatic sinusitis with allergy; EMCRS = eosinophilic mucus chronic rhinosinusitis; SEA, SEB, SEC, SED = staphylococcal enterotoxin A, B, C, D.

TABLE VIII-17. Evidence for AFRS management with oral antifungal therapy

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Khalil[1039]	2011	1b	Nonblinded 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 statistical analysis was done)
Seiberling[1105]	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)	1. RS symptoms; 2. Endoscopy	83% had improved symptoms and endoscopy (7/9 with AFRS); 3/19 who responded had to stop due to elevated liver enzymes
Chan[1102]	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[1107]	2004	4	Pilot study	Patients with "a history of AFRS" with progression of symptoms treated with fluconazole spray (n = 16)	1. Nasal endoscopy; 2. Symptoms	75% had stabilization or decrease in mucosal edema and symptoms
Rains[1103]	2003	4	Case series	AFRS (n = 137)	Recurrence	50.4% recurrence and reoperation in 20.5%
Kupferberg[1104]	1997	4	Case series	Postoperative AFRS patients receiving: 1. No treatment (n = 9); 2. Oral corticosteroids (n = 100); 3. Oral corticosteroids and oral antifungals (n = 2); 4. Oral antifungals only (n = 3)	Symptoms	1 of 3 patients receiving only oral antifungals reported improvement in symptoms

an unblinded randomized clinical trial evaluating both oral and topical antifungals in 41 patients divided into 5 arms postoperatively: (1) itraconazole; (2) topical fluconazole spray alone; (3) itraconazole and topical fluconazole together; (4) fluconazole irrigations; and (5) no antifungal. All patients received conventional medical therapy which consisted of high-dose oral corticosteroid tapered over 6 weeks, 14 days of amoxicillin-clavulanate, and 2 weeks of saline irrigations. The primary outcome in this study was recurrence of disease. The lowest recurrence rates were in the groups treated with either topical fluconazole spray or irrigation (10.0% to 28.6% vs 66.7% to 75%). However, there are a number of limitations of this study, including risk of bias from the unblinded nature of the study and unclear definition of the primary outcome of recurrent disease.

Although not designed to evaluate oral antifungals specifically, and hence not formally included in Table VIII-17, Rupa et al.[1106] conducted a randomized controlled study comparing 2 groups of AFRS patients. One group (n = 12) was treated with oral itraconazole (200 mg/day for 12 weeks) and the other group (n = 12) had oral itraconazole plus oral corticosteroids (50 mg prednisone × 6 weeks and then tapered off over 6 additional weeks. Rupa et al.[1106] found that although partial relief of initial sinus symptoms was reported in all 12 patients randomized to 12 weeks of oral itraconazole alone, the nasal endoscopic evaluation revealed that only 1 of the 12 patients had no evidence of disease. This finding contrasted with 8 of the 12 patients having no evidence of disease if oral corticosteroids were added to the oral itraconazole.

Topical antifungals have been studied minimally in AFRS patients. As mentioned above, Khalil et al.[1039] found beneficial effects of fluconazole sprays and irrigations on recurrence rates. Jen et al.[1107] performed an open-label pilot study using topical fluconazole spray in patients with history of AFRS. They did not define the inclusion criteria, nor did they detail the outcomes measures used. They reported that mucosal edema and patient symptoms stabilized or improved in 75% of patients and worsened in 25%. These 2 studies, both with significant methodologic flaws, provide the only evidence for topical antifungals in the treatment of AFRS.

Overall, only a few studies examine oral or topical antifungal therapy for AFRS and most are low-level, have few subjects, and/or contain methodological flaws. Some studies show promising results, but these are balanced by significant numbers of nonresponders and adverse events. At this point, there is insufficient evidence to recommend for or against antifungal therapy in AFRS.

- Aggregate Grade of Evidence: C (Level 2b:1 study; Level 4: 5 studies).

Immunotherapy

Type I hypersensitivity to fungi is a criterion for AFRS diagnosis and may represent a significant component of the pathophysiology of AFRS. As such, immunotherapy (IT)

TABLE VIII-18. Evidence for AFRS management with immunotherapy

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Gan[1101]	2014	3a	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

IT = immunotherapy; N/A = not applicable; SR = systematic review.

represents a reasonable treatment option. Gan et al.[1101] performed an evidence-based review with recommendations regarding IT for AFRS. They identified 2 level 3b studies and 3 level 4 studies that showed some value in treating AFRS with IT. Unfortunately, there were again 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. The authors concluded that there was an equal degree of benefit and harm, with IT as an option for postoperative AFRS patients. Given the limited current evidence, additional clinical trials are needed to examine this question (Table VIII-18).

- Aggregate Grade of Evidence: C (Level 3a: 1 study).

Anti-IgE

No studies have been performed evaluating anti-IgE (omalizumab) in AFRS patients specifically. Given the Type I fungal hypersensitivity and typical extremely elevated serum IgE levels, anti-IgE may represent a treatment option for AFRS patients but current evidence is lacking.

IX. Acute Exacerbation of Chronic Rhinosinusitis (AECRS)

IX.A. AECRS: Incidence/Prevalance

There are no consistent data about the incidence of AECRS in literature review. However, there are studies suggesting that the underlying immunologic activity of the chronic disease may directly correlate to the rate of acute exacerbations and infections. For instance, clinical follow-up in a subgroup of patients with AERD showed markedly less frequent acute exacerbations after successful desensitization (average of 4 episodes per year before vs 2 after desensitization).[1052]

IX.B. AECRS: Pathophysiology

Rank et al.[1108] performed a pilot study that investigated immunological changes in nasal secretion of CRSwNP patients during clinical worsening of their CRS symptoms. Interleukin (IL)-6, major basic protein, myeloperoxidase, EDN, and uric acid were significantly elevated during CRS exacerbation. However, this study was limited to the immunology changes in patients suffering from CRSwNP. The elevated IL-6 levels might suggest viral infection[1109] or might be related to the altered IL-6 pathway described in patients with CRS.[526]

Bacterial infection also contributes 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.[1110] However, the low number of studies, the diversity of the different study cohorts, and the missing 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 exacerbation of AECRS. This again points to some role for bacteria in AECRS.

Brook[1111] compared isolated organisms of the maxillary sinus of patients with CRS with those suffering from an AECRS. 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. *S. pneumoniae* and *H. 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. [1112]

Substantiated studies focusing on the identification of risk factors leading to an exacerbation of patients with CRS are rare because the emphasis of prior studies was to investigate the pathophysiology of the development of CRS.

Rank et al.[1113] performed a retrospective cohort study in 2010. Exacerbation of CRS was identified based on diagnosis coding and at least 1 of the following: prescription for systemic antibiotics, systemic corticosteroids, plans for surgical intervention, emergency department or urgent care visit, or hospitalization for CRS.[1113] After investigating 800 patients, 1 of the main observations was that AECRS is more likely to occur during winter months, suggesting a pattern similar to ARS without underlying chronic disease. 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.

Although there are many contributing factors, CRS is characterized by a dysfunctional host-environment interaction.[7] One might assume that the tissue changes

associated with CRS predispose to AECRS. Therefore, it could be concluded that AECRS is due to an imbalance of host defense and environmental factors similar to the pathophysiology of any ARS.

Besides immunologic changes at the level of receptors, cytokines, interleukins, and other mediators, MCC is considered crucial for the basic "first line of defense" of respiratory mucosa. It has 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.[1114] 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.

Last, atrophic rhinitis in combination with CRS has been hypothesized to be another predisposing factor for AECRS.[1115]

IX.C. AECRS: Diagnosis

Though the diagnosis of CRS is well codified in rhinology, literature on the diagnosis of AECRS is scant, often extrapolated from studies with a range of subjective and objective measures with varied endpoints, and often in post-ESS patients. Section IV.D defines AECRS as a sudden worsening of symptoms in a patient previously diagnosed with CRS, with a return to baseline symptoms after treatment. There are no comparative studies of different definitions or criteria.

Several studies have defined AECRS by worsened sinonasal symptoms with accompanying presence of purulence corroborated by endoscopically-derived bacterial cultures. Walgama et al.[1116] based the diagnosis of AECRS on acute worsening of sinonasal symptoms for at least 1 week and evidence of purulent secretions on nasal endoscopy. Bhattacharyya and Kepnes[1117] diagnosed AECRS based on 1 major or minor symptom of CRS in conjunction with presence of mucopurulent secretions that predominantly demonstrated gram-positive cocci. Solares et al.[1118] identified 24 AECRS patients based on worsened sinus symptoms, purulence on nasal endoscopy and positive culture of methicillin-resistant *Staphylococcus aureus*.

Rather than defining AECRS based on purulence, Chaudhry et al.[1119] defined 130 post-ESS patients with AECRS based on an increase in SNOT-22 score and recurrent NPs on endoscopic exam. These acute exacerbations did not present with purulent drainage, and may represent a separate subset of acute exacerbations.[1119] Ikeda et al.[1120] evaluated 42 subjects with AECRS and asthma post-ESS and found that 38% of these patients developed a decline in peak expiratory flow.

In summary, there exists a paucity of data on the diagnostic criteria of AECRS. Further, the data that does exist suffers from a lack of consistency in reporting of endpoints. Presumably, patients with established diagnosis of CRS have symptoms at baseline. If history suggests an abrupt worsening of these preexisting symptoms, diagnosis of AECRS should be considered. Subjective features of AECRS may include: (1) nasal blockage, congestion, or stuffiness; (2) nasal discharge or PND; (3) facial pain, pressure, or headache; and (4) reduction or loss of smell. Endoscopy represents an important modality in the diagnostic algorithm demonstrating presence of purulence, crusting, edema, or polyps, thus providing supportive evidence. CT imaging is reserved for select cases with equivocal diagnosis based on endoscopy or concern for potential complications of AECRS. Additional prospective studies are required to better formalize definitive diagnostic criteria for AECRS.

IX.D. AECRS: Management

There are no trials to endorse an evidence-based treatment of AECRS, though there is a tendency to treat AECRS like an episode of ARS or RARS. Treatments are principally extrapolated from ARS, whereas there is recognition of the need to treat the underlying CRS as well. The inflammation in CRS may impact the natural evolution of an acute exacerbation, such that type of therapy, duration of therapy, mode of delivery, and outcomes of therapy may all differ in AECRS compared to ARS or RARS. There is a significant gap in evidence for this topic and more robust data to guide medical decision-making is needed.[7,812]

IX.E. AECRS: Complications

The orbital, intracranial, and osseous complications related to AECRS are rare, but usually related to a chronic refractory untreated or misdiagnosed CRS. These complications are described elsewhere in this document (Sections VII.F and VIII.F).

Mucoceles are relatively rare and grow slowly unless AECRS produces a mucopyocoele. They occur most often in the frontoethmoid region and the symptoms presented in AECRS are related to an orbital complication of ARS. The treatment usually includes antibiotics and, in the majority of cases, ESS to promote drainage and marsupialization.[7,228,229,234,1121–1123]

The most common osseous complication in adults is osteomyelitis of the frontal sinus, usually associated with the progress of inflammation. It may be present as Pott's puffy tumor or frontocutaneous 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. Early diagnosis and aggressive surgery treatment are essential to avoid severe local or systemic complications.[1124]

X. Surgery for CRSwNP and CRSsNP

X.A. Surgery for CRSwNP and CRSsNP: General Concepts

Surgery for CRS is generally indicated when symptoms persist despite medical therapy, although what constitutes

an appropriate trial of medical therapy remains ill-defined (see Section X.B). Surgical techniques have evolved over the last 3 decades, transitioning from open approaches to microscopic approaches to endoscopic surgery, and more recently to more minimal tissue-sparing techniques such as balloon dilation.

The advent of the Hopkins rods in the 1960s paved the way for more widespread use of nasal endoscopes and helped revolutionize sinus surgery, offering more accurate visualization of the natural drainage pathways of the sinuses and associated sinonasal anatomy. The techniques and discussions of Messerklinger and Wigand in the 1970s further shaped the way sinus surgery was performed, with an evolving surgical strategy away from radical removal of all sinus mucosa toward more methodical, targeted approaches. In the 1980s and 1990s, open surgical approaches, such as Caldwell Luc surgery of the maxillary sinus and obliteration of the frontal sinus, continued to have their advocates, but their popularity waned as endoscopic techniques became more broadly accepted.

Today, endoscopic approaches have become the standard for surgical treatment of CRSsNP and CRSwNP. The tenets of contemporary sinus surgery emphasize mucosal preservation and enlargement of natural sinus drainage pathways. The degree to which the sinuses should be opened and the extent of tissue removal have been a matter of significant debate (see Section X.D.1).

Surgical treatment for CRSwNP places a greater emphasis on tissue removal compared to surgery for CRSsNP. In CRSwNP, the primary surgical aims are the following: (1) to establish a patent nasal airway and relieve sinus outflow obstruction; (2) to decrease the overall inflammatory load; and (3) to open the sinuses for postoperative topical drug delivery.[1125] Although ESS has become the mainstay for achieving these aims, it is notable that strong evidence for the superiority of ESS over simple polypectomy is lacking.[7,1126] Moreover, for CRSwNP specifically (as opposed to CRS overall), there is a similar lack of high-level evidence for the superiority of surgery over medical therapy for nasal polyposis.[1127] To be clear, evidence can be extrapolated from some studies, especially lower levels of evidence, to support the superiority of surgery in CRSwNP. Nonetheless, as in many cases of surgical treatments, RCTs for the surgical treatment of CRSwNP are not available.

Nevertheless, a formal ESS using mucosal-preserving technique addresses the aims of CRSwNP treatment, and is generally advocated for patients with polyposis. A complete ESS also allows for postoperative surveillance and the ability to perform in-office polypectomy if polyps recur, without needing to return to the operating room. One study has shown that more aggressive, but mucosal preserving, surgery in the frontal sinus leads to lower polyp recurrence.[1128] Although not widely utilized, a radical approach to ethmoidectomy involving removal of ethmoid mucosa and the MTs ("nasalization") has also been shown to have favorable outcomes. In 1 retrospective 5-year study, patients who received nasalization ethmoidectomy experienced better symptom relief and reduced polyp recurrence than patients who underwent mucosal-preserving ethmoidectomy.[1129]

Surgical interventions for CRSsNP encompass a wider range of strategies. Mucosal-preserving endoscopic techniques have largely replaced open approaches, although outcomes comparisons between ESS with open sinus surgery are limited. The 2012 EPOS guidelines[7] found 3 studies comparing ESS with various conventional sinus surgery techniques, such as Caldwell-Luc maxillary sinus surgery and inferior meatal antrostomy with antral irrigation, and found that ESS was superior. Currently, open approaches may still have utility to augment endoscopic exposure or access in complex frontal or maxillary cases, via frontal trephination or canine fossa puncture, respectively.

Although there are abundant level 4 studies asserting the efficacy of ESS, well-conducted RCTs are less common. Challenges of surgical study design include the difficulty of completely blinding patients and assessors to the interventions, thus introducing the potential for bias. Developing a suitable control group is also a challenge, because incorporation of "sham" procedures may challenge ethical standards. In addition, variances of technique for a particular procedure may undermine the generalizability of these trials. A Cochrane review, updated in 2009, reviewed the evidence for ESS vs medical treatment and conventional sinus surgery, and found only 3 RCTs. They concluded from the pooled evidence that ESS was not superior to either medical treatment or an inferior meatal antrostomy as performed by traditional sinus surgery techniques, although importantly admitted that the small sample sizes could not exclude a type II error.[1130] However, RCTs are not always practical or ethical to perform, nor do they always reflect daily practice. A recent multi-institutional prospective study compared medical vs surgical therapy for CRS in patients who had failed initial medical therapy. Patients were followed for 1 year and were grouped in nonrandomized fashion into 3 cohorts: medical therapy, surgical therapy, or crossover from medical to surgical treatment. Results from this study showed that patients in the surgical cohort reported significantly higher levels of symptomatic improvement than the medical cohort. Additionally, patients in the crossover group had stagnant or worsening QoL, which improved after ESS.[1131]

Balloon catheter dilation of the paranasal sinuses is a relatively new surgical technique that aims for ostial dilation without tissue removal. Current balloon technologies are applicable to the maxillary, frontal, and sphenoid sinuses, although there is some evidence that anterior ethmoid disease may respond to dilation of the ethmoid infundibulum which occurs in the course of maxillary ostial dilation.[285,286,1132] There have been many studies looking at the safety and efficacy of this technology, but few RCTs. The earliest RCT compared balloon dilation of the frontal recess vs ESS and found no significant difference in outcome.[1133] A more recent study compared Draf 2a frontal sinusotomy to a "hybrid" frontal approach

combining balloon dilation of the frontal recess and traditional endoscopic techniques; the study found comparable rates of ostial patency up to 1 year postoperatively, with the hybrid technique having a slightly shorter surgical time and less mean blood loss volume vs conventional ESS.[1134] A third RCT looked at maxillary sinus balloon dilation vs ESS in patients with chronic maxillary sinusitis with or without anterior ethmoid disease. Both techniques were found to be equally effective in improving SNOT-20 scores, maintaining ostial patency, reducing RS episodes, and improving work productivity at 1-year follow-up.[1132] More recently, balloon dilation has been studied for in-office treatment of CRS and RARS. A nonrandomized prospective case series showed a high catheterization success rate of 93% to 98% with satisfactory patient tolerance of the procedure. Clinical outcomes showed significant improvements in SNOT-20 scores sustained through 1 year, as well as reduced episodes of ARS.[285]

As evidenced by the plethora of treatment methods for CRS and the varied associated literature, it is difficult to recommend 1 standard therapy for all patients. Treatment often has to be customized to the individual patient, depending on disease severity, patient comorbidities, and surgeon expertise. As new techniques emerge, critical assessment of outcomes is essential to understand the role of these newer approaches in the surgical armamentarium.

X.B. Surgery for CRSwNP and CRSsNP: Appropriate ("Maximal") Medical Management

Statements regarding indications for sinus surgery invariably cite "failure of maximal medical therapy" (MMT) as a prerequisite; surgery without a prior trial of medical treatment is uncommon. However, although there is a high level of consistency between guidelines regarding the need for such a trial, there is much less consensus on what MMT entails.

Recent work has examined how prolonging the time between diagnosis and surgery for CRS may negatively impact outcomes.[1135–1137] The term "maximal" medical therapy may thus not be entirely appropriate, inasmuch as it implies surgery should be delayed until all available options have been exhausted. Therefore, instead of using the term "maximal medical therapy," this ICAR:RS document will use the term "appropriate" medical therapy (AMT). 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.)

What is AMT?

Although there are numerous studies evaluating the efficacy of individual drug classes in the treatment of CRS, discussed elsewhere in this ICAR:RS document (see Sections VII.E and VIII.E), there are no clinical trials evaluating the optimal combination of drugs. There are several guidelines where recommendations are made, and these demonstrate consistency with regard to inclusion of oral antibiotics, INCS, and selective use of oral corticosteroids (Table X-1).[7,1138,1139] A recent systematic review 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.[1140]

While incorporating the best available evidence into a recommendation for AMT, including evidence from this ICAR:RS 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 all of the above 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 this best available evidence.

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. Interestingly, however, this modality was reported in 62% of MMT protocols, with inclusion in previous MMT protocols not differentiated based on NP status.

For CRSwNP, the best available evidence and balance of benefits and harm appear to favor a single, short course of oral corticosteroids. Section VIII.E.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[733] recent 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.

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 VII.E.3). In comparing the risks and benefits of surgery to medical therapy including oral corticosteroids, it is evident that they may be considered as an option in CRSsNP, particularly in those patients displaying characteristics of an eosinophilic

TABLE X-1. Maximal medical therapy defined by published guidelines

Guideline	Antibiotics	INCS	Systemic corticosteroids	Saline irrigation	Other
AAOA Guidelines (2009)[1138]	Yes	Yes	Yes for CRSwNP or CRSsNP if initial 2-week treatment fails	Not specified	Oral or topical decongestants
AAO-HNS Guidelines (2015)[4]	Yes, culture-directed	Optional	Optional	Optional	Treatment of AR
Canadian Guidelines (2011)[671]	Yes, culture-directed	Yes	Yes in CRSwNP; Optional in CRSsNP	Optional	Leukotrienes optional in AERD patients
EPOS (2012)[7]	Macrolides for selected CRSsNP; doxycycline for selected CRSwNP	Yes	Yes in moderate/severe CRSwNP; no for CRSsNP	Yes	
BSACI (2008)[202]	Macrolide antibiotics	Yes	Yes in moderate/severe CRSwNP; no for CRSsNP	Yes	Leukotrienes optional in AERD patients; antihistamines for AR

phenotype. Clearly more work is needed to elucidate the balance of potential benefit and harm in CRSsNP.

Oral Antibiotics. Although oral antibiotics were used in approximately 88% of MMT regimens, robust evidence to support a clear indication for their use is lacking. It is not clear what role bacteria play in CRS and, interestingly, in ARS, where they are known to play a role, antibiotic use is not recommended but instead is an option (see Section V.D.1). 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 VII.E, 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 VIII.E 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 results, a broad-spectrum antibiotic such as amoxicillin-clavulanate. In contrast, EPOS recommends antibiotic choice to be primarily linked to associated anti-inflammatory effects; macrolides are recommended for CRSsNP for their antineutrophilic effects, whereas doxycycline is recommended in CRSwNP, where eosinophilic inflammation predominates. This ICAR:RS statement finds insufficient evidence to recommend 1 class of antibiotics over another in an AMT protocol. Further trials are urgently required to rationalize the appropriate indications and agents in the face of increasing antibiotic resistance.

Surveys of prescribing habits of both U.S. and U.K. ENT specialists (Table X-2) reveal broad adherence to combination treatment recommendations. This does not confirm the effectiveness of such regimens, but does suggest acceptance of the published guidelines.

In summary, the evidence for what should constitute appropriate medical therapy prior to surgical intervention is very much lacking. Recommendations are given based on available evidence, but the grade of evidence is D, leading to weak strength of recommendation.

- Aggregate Grade of Evidence: D.
- Benefit: Symptomatic improvement and avoidance of risks of surgical intervention.
- Harm: Risks of corticosteroids, GI side effects of antimicrobials, risk of cardiovascular toxicity with macrolide antibiotics, potential for increasing antibiotic resistance.
- Cost: Direct cost of medications.
- Benefits-Harm Assessment: Differ for particular therapy and clinical scenario.
- Value Judgements: Perceived lower risk of antibiotic treatment vs risks of surgery, although recent evidence has shown a low breakeven threshold for surgery vs 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.
- Intervention:
    - 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. Antibiotics are an option.
    - For CRSsNP: Appropriate medical therapy prior to surgical intervention should include INCS, saline

TABLE X-2. Results of surveys to establish medical therapy trial prior to surgery prescribing habits

Survey	Antibiotics	INCS	Systemic corticosteroids	Saline irrigation	Other
ENT UK Survey (2013) (n = 159)[1141]	92%	61% always, 27% sometimes	4% always, 30% sometimes	23% always, 42% sometimes	3% antihistamines, 4% topical decongestants
AAO-HNS Survey (2006) (n = 80)[1142]	94%	94%	34%		47% oral decongestants, 47% mucolytics
ARS Survey (2007) (n = 308)[1143]	51% always, 30% almost always		10% always, 20% almost always		

irrigations, and antibiotics. Oral corticosteroids are an option.

How long should appropriate medical management last?

There is 1 randomized trial currently listed on the U.S. NIH website, clinicaltrials.gov (Identifier NCT01825408), that intends to determine the optimal duration (3 vs 6 weeks) of oral antibiotics as part of a medical therapy trial prior to surgery. There are no completed RCTs addressing the optimal duration of a medical therapy trial prior to surgery. One published nonrandomized uncontrolled study suggests 6 weeks of culture directed oral antibiotics to be more effective than 3 weeks.[741] However, the 38% improvement in CT staging from the 3-week to 6-week scan has questionable clinical value and may have still occurred without ongoing treatment.

Guidelines again diverge in recommendations, with European guidelines recommending a prolonged course of low-dose macrolides, whereas North American guidelines recommend a longer course than would be prescribed in ABRS, but up to a maximum of 4 weeks (Table X-3). This is reflected in clinical practice, with 1 in 4 specialists using a course of 6 weeks or more in the United Kingdom, compared with less than 1 in 30 among U.S. rhinologists (Table X-4).

There are multiple RCTs evaluating the benefits of INCS in CRS. Studies where treatment duration is less than or equal to 3 weeks show no benefit over placebo, whereas studies of 4 weeks or more consistently favor INCS.

- Aggregate Grade of Evidence: D.
- Benefit: Symptomatic improvement and avoidance of risks of surgical intervention.
- Harm: Risks of corticosteroids, GI side effects of antimicrobials, risk of cardiovascular toxicity with macrolide antibiotics, potential of increasing antibiotic resistance.
- Cost: Direct cost of medications.
- Value Judgements: Low risk of treatment and delay of surgery vs risks of surgery considered in recommending a 3-week to 4-week trial.
- Policy Level: Recommendation
- Intervention: A trial of 3 to 4 weeks of AMT should be considered as the minimum.

When should AMT be deemed to have failed?

Success of AMT should be defined by a symptomatic response, such that symptoms are not sufficiently bothersome to merit surgery. Although persistent radiological and endoscopic evidence of disease do not itself define failure, they may be predictive for subsequent relapse. Failure is thus defined by insufficient symptomatic response to AMT, in the presence of radiological or endoscopic evidence of CRS.

What is the response rate and long-term control rate after MMT/AMT?

The response rate to previous trials of MMT varies between 30.4% and 90% (Table X-5).[728,729,1144–1146] It is accepted that CRS has a chronic relapsing course, but the long-term fate following a successful trial of medical therapy is not well reported. Subramanian et al.[729] found a relapse rate of 47.5% in those initially responding to medical therapy trial prior to surgery, requiring a further course of medical treatment. CRSwNP and previous sinus surgery were predictors of relapse. In contrast, Young et al.[1146] found no significant deterioration in the symptom scores of medical responders from the end of a 3-month treatment period to 5 months (mean) of further follow-up. Ongoing medical treatment was not defined in either study. Baguley et al.[1145] identified a group of medical responders with persistent radiological disease on completion of medical therapy but resolution of symptoms. Despite ongoing INCS and saline rinses, 43% suffered a symptomatic relapse between 3 and 23 months of further follow-up and 29% required surgery.

Continued medical therapy following a failed trial of 1 MMT protocol (>3 weeks of antibiotics and INCS) has been assessed in a nonrandomized multi-institutional cohort study.[1131] Ten percent of a cohort initially electing continued medical therapy failed to receive continued benefit and opted to cross-over and receive sinus surgery. The crossover group of patients suffered from deterioration in their QoL, which prompted the choice for surgery. The 90% of patients who continued within the medical therapy cohort had significant better baseline QoL scores and reported stable QoL over a 6-month period, but failed to report reductions in the use of rescue medication or days of missed work/school.

TABLE X-3. Duration of medical therapy trials prior to surgery recommended by major guidelines

Guideline	Antibiotics	INCS	Systemic corticosteroids	Saline irrigation
AAOA Guidelines (2009)[1138]	3–4 weeks	At least 1 month	8–12 days	Not specified
AAO-HNS Guidelines (2015)[4]	2–4 weeks	Not specified	Not specified	Not specified
Canadian Guidelines (2011)[671]	"Slightly longer than for ABRS"	Not specified	2 weeks in CRSwNP; optional in CRSsNP	Not specified
EPOS (2012)[7]	12 weeks macrolides; 3 weeks doxycycline	3 months, except 1 month in severe CRSwNP	"short course"	Yes
BSACI (2007)[202]	12 weeks of macrolide antibiotics	Not specified	5–10 days	Yes

TABLE X-4. 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)[1141]	<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)[1143]	0–2 weeks: 12%; 2.1–3 weeks: 37%; >6 weeks: 3%	Not specified	0–5 days: 7%; 6–14 days: 67%
AAO-HNS Survey (2006) (n = 80)[1142]	Mean duration >5 weeks	Mean duration 6 weeks	Mean duration 1 week

TABLE X-5. Reported response rates to medical therapy trials prior to surgery

Study	Intervention	Outcome measured	Response rate
Lal[728]	4 weeks amoxicillin-clavulanate, 12 days oral corticosteroid, 4 weeks INCS, 4 weeks saline rinse	Complete resolution of symptoms Partial response	51.03% 17.8%
Dilidaer[1144]	Not specified	Complete control	30.4%
Young[1146]	3 weeks oral prednisolone, antibiotics, INCS, and saline rinses	Improvement in symptoms sufficient to avoid surgery	37.5%
Subramanian[729]	4 weeks antibiotics, INCS, saline rinses, 10 days prednisolone	Improvement in symptoms sufficient to avoid surgery	90%
Baguley[1145]	3 weeks prednisolone, 4–6 weeks INCS, saline rinse, optional 20 days antibiotics	Control = symptoms resolved or no longer bothersome	38%

Smith and Rudmik[1147] evaluated the impact of continuing medical therapy in patients with large reductions in baseline QoL who chose sinus surgery but had to wait for a mean of 7 months because of surgical waitlists. They found that patients with large reductions in baseline QoL who continued medical therapy failed to receive QoL improvements and had increased absenteeism. It is worth noting that all clinical outcomes improved after this cohort received sinus surgery.[1148]

Data from a prospective cohort study and from 2 independent electronic health records reviews[1135–1137] suggest that benefit from surgery, both in terms of symptomatic response and ongoing healthcare utilization, is reduced if surgical intervention is delayed. Therefore, surgery should be considered once AMT has been deemed to have failed, and further repeated courses should be avoided.

X.C. Surgery for CRSwNP and CRSsNP: Preoperative Management

ESS has become the standard treatment modality for patients who do not respond to AMT. Since the introduction of ESS, the technique has improved and been standardized. Preoperative management is an essential part of ESS, and optimal perioperative management including preoperative, intraoperative, and postoperative care should be offered to patients to help assure a positive surgical outcome.

The objective of preoperative management is not to cure CRS, but rather to create the best conditions for ESS. The outcome of ESS depends on several factors, and a clean surgical field, especially a bloodless one, is the most important factor.[1149] Impaired visibility due to a bloody field can impair surgical dissection, prolong the length of the procedure and increase the rate of complications.[1149,1150] Accordingly, it could be said that the substantive objective

of preoperative management is to create a unobscured endoscopic view during ESS.

Preoperative disease extent appears to be a predictive factor for bleeding during ESS. In a cohort study of 40 patients, preoperative LM CT scan score was significantly correlated with intraoperative bleeding in primary cases, and there was no correlation in revision cases. [1151] Similarly, another study of 230 RS patients found that extent of disease was a consistent predictor for intraoperative bleeding.[1152]

In addition to disease extent, corticosteroid and antibiotic treatment are both commonly discussed as preoperative treatment measures. Corticosteroids (systemic or topical) and antibiotics have been proposed to decrease inflammation and vascularity of the sinus mucosa, leading to improved visibility in the preoperative setting. However, there is no uniform protocol for preoperative management before ESS, mostly because of the paucity of available evidence.

X.C.1. CRSsNP: Preoperative Corticosteroids

There are no clinical trials investigating the role of preoperative systemic or topical corticosteroid use in CRSsNP patients alone. Several studies have included both CRSsNP and CRSwNP patients. Albu et al.[1150] reported a double-blinded randomized, placebo control trial of 70 patients, of which 37 were CRSsNP and 33 were CRSwNP. The treatment group received a 4-week course of intranasal mometasone furoate 200 μg twice daily. The treatment group had significantly less intraoperative blood loss, a better surgical field, and shorter operation time. Subgoup analysis was carried out on the CRSsNP patients, with preservation of statistical significance of the above findings (despite the study not being powered for the smaller subgroup sample size). No studies regarding preoperative systemic corticosteroid administration in CRSsNP patients were identified. In a national survey of U.S. surgeons on the use of preoperative systemic corticosteroids in ESS, only 26% of respondents prescribed them in CRSsNP cases. [65] It is well known that corticosteroid treatment has potential morbidity. Although uncommon, oral corticosteroids are associated with side effects such as Cushing's disease, blood sugar dyscrasias, gastrointestinal tract ulcer, and avascular necrosis.[1106] Topical corticosteroid use is also related with mild adverse effects, such as nasal dryness, bleeding, burning sense, and throat irritation.[1153] In conclusion, topical corticosteroid can be used as preoperative treatment for better surgical field. In case of oral corticosteroid, there is no study to evaluate its efficacy as a preoperative agent for CRSsNP. Therefore, there is not enough benefit to outweigh the known risks (Table X-6).

- Aggregate Grade of Evidence: C (Level 1b: 1 study, Level 5: 1 study).
- Benefit: Objective improvement in surgical field, objective decrease in intraoperative bleeding, and objective decrease in operation time seen with INCS. Subjective improvement in surgical difficulty.
- Harm: Possible side effects of topical or systemic corticosteroids are known.
- 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 in oral corticosteroids.
- Intervention: INCS are recommended in the preoperative management of CRSsNP.

X.C.2. CRSsNP: Preoperative Oral Antibiotics

No studies were identified addressing the preoperative use of systemic antibiotic treatment. Several studies did describe short-term antibiotic use in CRSsNP patients. Short-term (9 to 14 days) use of antibiotics improved clinical symptoms such as nasal discharge and nasal blockage, and there was no difference in the clinical efficacy of several kinds of antibiotics.[737–739] Although there has been no trial directly investigating preoperative antibiotics and intraoperative condition, patient-reported symptoms have been shown to be correlated with intraoperative bleeding and longer surgery time.[1155] Therefore, preoperative oral antibiotics may be beneficial in patients presenting with acute exacerbation of symptom and purulent discharge on endoscopic examination. Oral antibiotics are relatively safe with very few side effects; however, like any medication, adverse effects related to oral antibiotics may occur. Skin rashes, drug fever, and gastrointestinal troubles such as abdominal pain, diarrhea, and nausea/vomiting may occur. In rare cases, patients may experience more serious side effects, such as renal toxicity or liver toxicity.[1156] In conclusion, short-term, culture-directed, oral antibiotic treatment for acute exacerbations of CRSsNP may be beneficial before surgery. Because no studies examine this issue directly, no recommendations are given.

- Aggregate Grade of Evidence: not applicable.

X.C.3. CRSwNP: Preoperative Corticosteroids

There have been many clinical trials about the effect of corticosteroids on CRSwNP, but only a few of these studies have tried to elucidate the role of corticosteroid treatment as a preoperative measure in CRSwNP patients (Table X-7). As described above in "CRSsNP: Preoperative Corticosteroids," there were 2 studies of preoperative corticosteroid use in both CRSsNP and CRSwNP.[65,1150] In addition, Wright and Agrawal[65] performed a randomized, placebo-controlled trial comparing 26 patients randomly assigned to receive 30 mg of oral prednisone or placebo for 5 days, preoperatively. The results demonstrated a significantly higher percentage of severely inflamed mucosa in the placebo group, which was associated with a technically more difficult surgery. Sieskiewicz et al.[1149] reported their open-label controlled trial in which 36 CRSwNP patients

TABLE X-6. Evidence for preoperative corticosteroid administration in CRSsNP

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Albu[1150]	2010	1b	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
Gonzalez-Castro[1154]	2013	5	Survey, expert opinion			Only 26.17% of respondents prescribed corticosteroid

TABLE X-7. Evidence for preoperative corticosteroid administration in CRSwNP

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Albu[1150]	2010	1b	Individual 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[65]	2007	1b	Individual 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
Atighechi[1157]	2013	2b	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[1149]	2006	2b	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[1155]	2014	4	Case series	Treatment with systemic or topical corticosteroid	Intraoperative blood loss	INCS use was associated with increased blood loss during surgery
Gonzalez-Castro[1154]	2013	5	Survey, expert opinion			96.64% of respondents prescribed oral corticosteroids

were assigned to 30 mg of oral prednisone or no treatment. Although total blood loss was only slightly less in the corticosteroid-treated group, the visual condition of the surgical field improved significantly. In a national survey on the use of preoperative systemic corticosteroids in ESS, 96.64% of respondents prescribed them in CRSwNP patients.[1154] In conclusion, preoperative treatment with topical or oral corticosteroids is recommended to ensure better intraoperative conditions in the absence of comorbidities that are aggravated with systemic corticosteroids.

- Aggregate Grade of Evidence: B (Level 1b: 2 studies; Level 2b: 2 studies; Level 4: 1 study; Level 5: 1 study); 1 study shows contradicting results.
- Benefit: Objective improvement in surgical field, decrease in intraoperative bleeding, and decrease in operation time. Subjective improvement in surgical difficulty.
- Harm: No specific reports about side effect as preoperative treatment, but possible risks of corticosteroids are known.
- 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. In case of oral corticosteroids, medium dose (30 to 40 mg) for 4 to 7 days is the most commonly prescribed regimen. Other techniques (eg, use of concentrated epinephrine) may be used to diminish bleeding intraoperatively.
- Policy Level: Recommendation.
- Intervention: Recommendation for the use of oral and topical corticosteroids in the preoperative management of CRSwNP.

X.C.4. CRSwNP: Preoperative Oral Antibiotics

As with preoperative antibiotics in CRSsNP patients, no studies regarding preoperative antibiotic use before ESS in CRSwNP patients were identified. No recommendation is therefore given.

- Aggregate Grade of Evidence: not applicable.

X.D. Surgery for CRSwNP and CRSsNP: Surgical Principles

X.D.1. Surgical Principles/Techinques: Extent of Surgery

Since the introduction of endoscopic techniques for the surgical treatment of CRS in the 1980s, the goal of ESS

has been to reestablish ventilation and drainage of the paranasal sinuses through enlargement of the natural ostia.[1158] Conventional ESS involves opening of the OMC with enlargement of the maxillary sinus otium[1159] as well as concurrent clearance of disease in the anterior and/or posterior ethmoid cells to provide secondary drainage of obstructed frontal and/or sphenoid sinuses. Direct enlargement of frontal and sphenoid ostia are performed as needed.

Modifications of conventional ESS techniques have been described to match the extent and location of a patient's sinus disease, including 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. It is proposed that sinus surgery should address the clearance of these transition spaces, rather than the enlargement of sinus ostia. MIST addresses the ethmoid infundibulum as the transition space where maxillary sinus outflow obstruction occurs. Like conventional ESS, MIST involves removal of the uncinate process in order to open the infundibulum and expose the maxillary ostium, but MIST does not include direct enlargement of the natural ostium itself.[1160] The contrasts between conventional ESS and more conservative approaches, such as MIST, have been studied in patients with chronic maxillary sinusitis, and these findings have been interpreted to generally translate to the other paranasal sinuses as well.[1160–1163]

MIST and traditional maxillary antrostomy each have their own set of potential advantages and disadvantages. Because MIST involves less manipulation of mucosa and bone, the likelihood for postoperative scar formation in the region of the maxillary ostium may be reduced. On the other hand, maxillary antrostomy not only eradicates disease in the infundibulum, but also provides direct enlargement of the natural maxillary sinus ostium. This latter step may be beneficial in cases of more severe inflammatory disease with ostial stenosis or anatomic variants, such as an infraorbital ethmoid (Haller) cell. Ostial enlargement may also be advantageous when the surgeon wishes to clear disease within the maxillary sinus, such as in AFRS.

Limited evidence in an animal model suggests that the creation of an antrostomy that is too large may be lead to detrimental effects such as osteitis and diminished MCC.[1161] On the other hand, clinical studies have shown that a mega-antrostomy for recalcitrant chronic maxillary sinusitis is effective in reducing sinonasal symptomatology, objective endoscopic and radiographic evidence of CRS, and corticosteroid and antibiotic use.[1162,1163] Enlargement of the maxillary ostium may also be associated with decreased NO levels in the maxillary sinus,[1164] but the clinical impact of this decrease remains unknown.

The primary concerns regarding MIST are whether it will provide adequate ventilation of diseased sinuses and the same clinical outcomes as traditional ESS. These issues have been studied with respect to the maxillary sinus. Previous work, utilizing xenon ventilation in a cadaveric sheep's head model,[1165] has reported no significant difference in maxillary sinus ventilation for sinuses that underwent small antrostomies (approximated as 2 to 3 times the natural ostium size) or large antrostomies (approximated as 6 times the natural ostium size). Although it is unclear whether this finding extends to simple removal of the uncinate process without enlargement of the maxillary ostium, these results do suggest diminishing returns from the standpoint of ventilation with increasing maxillary antrostomy size.

Cohort studies of CRS patients undergoing MIST have demonstrated postoperative improvements in sinonasal symptoms.[1166,1167] In 1 prospectively studied cohort, 78.8% of CRS patients (including those with and without NPs) who underwent MIST maintained improvement in their baseline CSS scores 2 years after surgery. Only 5.9% of patients required revision MIST during that same period.[1166] Postoperative improvement in sinonasal symptoms were found to be greater in patients who underwent concomitant nasal polypectomy at time of MIST,[1167] calling into question the extent that MIST-specific sinus ventilation contributed to the observed clinical improvement.

Two RCTs have been reported with patients undergoing a MIST procedure on 1 randomly-chosen side and traditional ESS, including maxillary antrostomy, performed on the other.[1168,1169] Nine months after surgery no significant difference in radiographic LM score was detected between the MIST or ESS sides,[1168] although maxillary sinuses with smaller postoperative ostia were associated with maxillary sinus opacity or OMC obstruction.[1168] Additionally, there was greater endoscopic evidence of maxillary sinus obstruction in the MIST group at 3 months, but not at 6, 9, or 12 months after surgery.[1169] 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.[1170] The creation of a small or large maxillary antrostomy was not found to be associated with symptomatic improvement in facial pain, nasal obstruction, or rhinorrhea.[1170]

The necessary extent of ESS has also been addressed through a recent study of balloon dilation for RS.[1132] In this prospective randomized trial, patients with chronic maxillary sinusitis with or without concomitant anterior ethmoid sinus disease who failed medical therapy received either in-office balloon dilation of the maxillary sinus ostium or ESS. For patients who had anterior ethmoid disease, no further procedural intervention was performed in the balloon dilation group, whereas concurrent ethmoidectomy was performed in the sinus surgery group. At 1 year, no statistically significant differences were found between the 2 cohorts with respect to study endpoints, which included SNOT-20 scoring, maxillary ostium

patency based on CT scan, reduction in RS episodes, and improvement in work productivity and daily activity. The applicability of this study's results are limited, however, because of the (1) exclusion of patients with posterior ethmoid, frontal, or sphenoid sinus disease, and (2) exclusion of patients needing other sinonasal procedures such as septoplasty for deviated septum. The additional expense of new technology must also be considered with the utilization of balloon technology for treatment of CRS.[1171]

As delivery of topical medications has become an increasingly important treatment modality in the management of CRS, the impact of sinus surgery to enhance such delivery must be considered. Postoperative distribution of topical medications to the paranasal sinuses may be limited by utilization of more conservative ESS techniques, such as MIST or balloon dilation. Studies have suggested that maxillary antrum size correlates with airflow rates into the maxillary sinuses,[1172] as well as intrasinus delivery of topical medications.[1173] Recent evidence suggests that unoperated sinuses receive little topical therapy compared to sinuses which have been surgically opened. More extensive enlargement could, in fact, result in increased distribution of topical medications in general.[812] These findings have been summarized in an extensive EBRR, which suggests that sinus surgery may be an effective means to increase delivery of topical medications to the paranasal sinuses.[806]

Currently available data suggest that MIST may be reasonable for some CRS patients, particularly those with limited disease burden. The current evidence supports the use of balloon dilation for patients with minimal and focal sinus disease. Because of the lack of long-term outcomes data and the potential for greater risk of sinus (e.g. maxillary sinus) obstruction, which may lead to either recurrent sinus disease or poor penetration of topical medications, current evidence does not support the routine application of limited techniques, such as MIST or balloon sinus dilation, for all CRS patients (Table X-8).

- Aggregate Grade of Evidence: C (Level 1b, 3 studies; Level 2b, 3 studies; Level 5, 1 study).
- 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 reduced postoperative scar formation and surgical time.
- Harm: Potential harm of more conservative techniques includes insufficient removal of obstructing sinonasal disease, leading to persistent inflammation, faster relapse of symptoms, and reduced delivery of topical medications.
- 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, which needs to be considered in an environment of limited healthcare resources.
- Benefits-Harm Assessment: Over the short term (up to 1 year postoperatively), 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 has the potential for improved long-term sinus ventilation and delivery of topical medications. There is no significant argument 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.

X.D.2. Surgical Principles/Techniques: Concurrent Septoplasty

Rhinologic surgeons may perform septoplasty as an adjunctive procedure in patients who are undergoing ESS. The septal procedure may be performed to provide access to the paranasal sinuses, or to address severe nasal obstruction due to NSD. Because the 2 procedures are often performed together, it may difficult to separate the benefits of 1 procedure from the other. Similarly, although some risks are clearly related to the septoplasty (eg, 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.[1174] Most authors describe techniques for endoscopic septoplasty (ES) and report limited outcomes data in these case series.[1175–1178] Giles et al.[1179] compared cohorts of patients undergoing ESS alone, ESS and CS, and ESS and ES and noted good outcomes in the ESS/ES group. Bothra and Mathur[1180] performed a similar comparison of ES and CS in patients undergoing ESS and noted no differences between groups.

In a prospective, multi-institutional study, Rudmik et al.[1181] compared ESS with septoplasty to ESS without septoplasty, and noted no differences in various QoL measures for CRS. Based upon these data, the authors concluded that patients undergoing concurrent septoplasty

TABLE X-8. Evidence for extent of surgery in CRSsNP and CRSwNP

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Bikhazi[1132]	2014	1b	RCT	Patients with chronic maxillary sinusitis (with or without chronic anterior ethmoid sinusitis) that have failed medical therapy who received: 1. In-office maxillary sinus balloon dilation; 2. Maxillary antrostomy with or without anterior ethmoidectomy	At 1 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 2 groups
Myller[1168]	2011	1b	RCT	CRSsNP patients in whom: 1. Wide maxillary antrostomy was performed on 1 side (2× natural ostium size); and 2. Uncinectomy alone was performed on the other side	1. Postoperative CT scan findings at 9 months; 2. Postoperative maxillary sinus ostium cross-sectional area	Improvement in overall ipsilateral LM for both surgical treatments. No difference in postoperative overall ipsilateral LM score between surgical treatments
Wadwongtham[1169]	2003	1b	DBRCT	In patients with bilateral and symmetric CRSwNP: 1. Wide maxillary antrostomy was performed on one side; and 2. Uncinectomy alone was performed on the other side	Maxillary sinus ostium obstruction at 3, 6, 9, and 12 months	Less maxillary sinus obstruction in the large antrostomy group compared to the uncinectomy group at 3 months but not at 6, 9, or 12 months after surgery
Salama[1167]	2009	2b	Prospective cohort study	A consecutive series of patients presenting with CRS and undergoing uncinectomy but not antrostomy to address the maxillary sinuses	1. Symptoms (VAS); 2. 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 postoperatively
Albu[1170]	2004	2b	RCT (nonvalidated means of measuring symptoms and 45% follow-up)	Surgical CRS patients who underwent: 1. Small maxillary antrostomy (mean diameter 6 mm); 2. Large maxillary antrostomy (mean diameter 16 mm)	Patient-reported change in symptoms of obstruction, facial pain, and rhinorrhea	Maxillary antrostomy size is not associated with postoperative changes in patients' symptoms of obstruction, facial pain, and rhinorrhea
Catalano[1166]	2003	2b	Prospective cohort study	Patients undergoing minimally invasive sinus surgery for CRS	1. CSS; 2. Need for revision surgery	Postoperative CSS scores were improved: 78.8% of patients had improved CSS score; 5.9% of patients required revision MIST
Setliff[1160]	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%

MIST = minimally invasive sinus technique.

should not be excluded from studies evaluating the impact of ESS on CRS.[1181]

In a large retrospective case series, Chang et al.[1182] compared ESS with septoplasty and ESS without septoplasty and noted a lower revision rate in patients who underwent both procedures. This is the only study that demonstrates a clear benefit of performing septoplasty and ESS concurrently, but this conclusion is limited by the retrospective study design[1182] (Table X-9).

- Aggregate Level of Evidence: D (Level 2a: 1 study; Level 4: 8 studies; Level 5: 1 study).
- Benefit : Reduction in nasal obstruction, improved access for ESS.

TABLE X-9. Evidence for concurrent septoplasty with ESS in CRSsNP and CRSwNP

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Rudmik[1181]	2011	2a	Prospective, multi-institutional cohort study	ESS with septoplasty (n = 108); ESS without septoplasty (n = 113)	1. Rhinosinusitis Disability Index; 2. Chronic Sinusitis Survey	No statistically significant differences between groups
Chang[1182]	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[1180]	2009	4	Case series	ESS with CS (n = 40); ESS with ES (n = 40)	1. Symptoms; 2. Physical examination; 3. Complications	No statistically significant differences between groups
Chung[1176]	2007	4	Case series	ESS with ES (n = 96); ES alone (n = 20)	1. Symptoms; 2. Physical examination; 3. Complications	ES is an alternative to CS, especially in patients undergoing ESS
Su[1178]	2004	4	Case series	ESS with ES (n = 81); ESS alone (n = 152)	1. Symptoms; 2. Complications	No statistically significant differences between groups
Castelnuovo[1177]	1999	4	Case series	ESS with CS (n = 89); ESS with ES (n = 155); Rhinoplasty with ES (n = 15)	Complications	ES facilitates less extensive manipulation of the septal framework
Hwang[1175]	1999	4	Case series	ESS with ES (n = 108); ES alone (n = 3)	1. Physical examination; 2. Complications	ES is an adjunctive procedure
Giles[1179]	1994	4	Case series	ESS without septoplasty (n = 496); ESS with CS (n = 144); ESS with ES(n = 38)	1. Symptoms; 2. Physical examination	Good healing and no obstruction in the endoscopic septoplasty group
Cantrell[1174]	1997	5	Report of technique	ESS with "limited" septoplasty (n = 100)	Not specified	"Limited" septoplasty may be performed with ESS

CS = conventional septoplasty; ES = endoscopic septoplasty.

- Harm: Bleeding, postoperative discomfort/pain, septal hematoma, septal perforation, persistent obstruction, intranasal scarring.
- 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 NSD and CRS may experience reduced nasal obstruction when septoplasty is performed at the time of ESS. Correcting an NSD has an unknown impact on sinus disease.
- Policy Level: Option in patients with NSD undergoing ESS.
- Intervention: Septoplasty (either ES or CS) is an option to be performed at the time of ESS. Because the impact on sinus inflammation is unknown, the decision to perform a septoplasty should be determined by anticipated reduction in nasal obstruction or the need to access the sinuses for ESS.

X.D.3. Surgical Principles/Techniques- MT Preservation or Resection

Whether to routinely preserve or resect the MT during sinus surgery has been a topic of debate for decades. Proponents of preservation point to the MT's role in sensation of airflow, direction of airflow, humidification, and olfaction. Risk of CSF leak and frontal sinus obstruction from a lateralized MT stump as well as the loss of a landmark for future revision surgery are also given as reasons for preservation. Advocates for resection cite better access during surgery, with better maxillary ostial patency and reduced incidence of synechiae postoperatively.

These various arguments have been examined in the literature over the last 2 decades and have shown limited effects of both preservation and resection.

QoL. Two prospective nonrandomized cohorts have used validated outcome metrics to compare QoL after MT resection and preservation. Byun and Lee[1183] studied

CRSwNP patients and found no difference in SNOT-20 scores or symptoms using a VAS. Soler et al.[1184] found that although MT resection was associated with improved endoscopy scores vs MT preservation, there was no difference in RSDI, CSS, and SF-36 scores in CRS patients with or without NP. Importantly, in both nonrandomized cohorts, MT resection was associated with greater disease burden preoperatively, assessed by endoscopy, CT, olfaction testing, and symptom surveys. As a result, it is difficult to fully assess the possible benefit of MT resection.

Postoperative Frontal Sinusitis. Five studies looked at this issue from different perspectives and came to varying conclusions. In 1995, Swanson et al.[1185] studied patients presenting to a tertiary rhinologic practice with continued CRS following previous surgery. They found a higher risk of frontal sinusitis if the MT had been previously resected. In their sample of 110 patients, 75% of MT resection sides had frontal sinusitis compared to 45% of MT preservation sides. Subsequent studies examined this issue in samples of patients undergoing MT resection and found a 10% to 18% rate of frontal sinusitis.[1186,1187] Two other studies compared MT resection to preservation and found no difference in the rate of frontal sinusitis, although both had rather small sample sizes.[1188,1189] These results cast doubt on MT resection's significance as a risk for postoperative frontal sinusitis.

Recurrence of Nasal Polyps. Four studies have examined the effect of MT resection on recurrence of nasal polyposis. Brescia et al.[1190] found MT preservation to be associated with lower endoscopy scores 12 months after ESS. The authors reported, however, that the study was too small (n = 48) to confidently conclude a true effect and called for a larger study. Shortly thereafter Marchioni et al.[1191] found a trend toward a beneficial effect of MT resection in their prospective cohort of 56 patients with CRSwNP, though the effect was not statistically significant in this small sample ($p = 0.0589$). Subsequently, Wu et al.[1192] retrospectively reviewed 299 CRSwNP patients who underwent ESS and found that those who had MT resection had a longer median time to recurrence of NPs (4.56 vs 3.93 years, $p = 0.048$). Interestingly the beneficial effect disappeared after 8 years. In a nonrandomized prospective study, Byun and Lee[1183] found MT preservation patients to have better endoscopy scores at 12 months postoperatively. They noted, however, that MT resection patients had a greater burden of disease preoperatively, based on endoscopy, CT, and VAS assessment of symptoms. MT resection appears to have a limited beneficial effect in CRSwNP patients. This advantage may be due to better topical medication access; future studies will need to examine the impact of corticosteroid irrigations following MT resection.

Olfaction. Four studies have examined the effect of MT resection on postoperative olfaction. Two prospective cohort studies using objective testing have shown no effect.[1193,1194] Two additional studies have shown a beneficial effect on olfaction following MT resection.[1184,1195] Based on these studies, it appears the concern that MT resection reduces olfactory ability is unwarranted, and partial MT resection may in fact be associated with improved olfactory outcomes.

Maxillary Ostial Stenosis. MT resection has been studied as a method of preserving antrostomy patency following ESS. One RCT, 1 prospective nonrandomized cohort study, and 1 retrospective analysis have all shown no effect on maxillary patency.[1188,1196,1197] One retrospective study in 1992 initially found no effect, but when synechiae that might lead to maxillary stenosis were included, there was a positive effect for MT resection.[1198] It appears from these data that MT resection has no significant effect on middle meatal antrostomy patency following ESS.

MT Synechiae. Two retrospective reviews from 1995 reviewed the effect of MT resection on synechiae formation between the MT and the lateral nasal wall.[1199,1200] Both found no effect.

Loss of a Landmark for Revision Surgery. One retrospective review in 1992 examined this issue and found that MT resection is associated with an increased risk of CSF leak, nasolacrimal duct stenosis, lamina papyracea injury, and orbital hematoma.[1201]

Atrophic Rhinitis. One study has examined this issue in 1106 matched patients with and without MT resection and found that none of the 509 patients who underwent MT resection had postoperative atrophic rhinitis.[1202] The authors did note, however, that the median length of follow-up was 4.2 years and may be too short to definitively rule out this risk.

Summary. Rigid adherence to MT preservation or routine MT resection is not supported by the cumulative evidence. Even staunch preservationists must acknowledge the role of conservative and/or partial resection in cases of a concha bullosa, paradoxical curvature of the MT, extremely narrow nasal cavity, or extensive polyp involvement of the MT. On the other hand, routine MT resection without consideration of alternatives, such as complete uncinectomy and MT suture medialization to prevent synechiae, must also be discouraged. At present, management of the MT requires a thoughtful approach with considerations of all potential risks, benefits, and alternatives (Table X-9).

- Aggregate Grade of Evidence: C (Level 1b: 2 studies; Level 2b: 6 studies; Level 3b: 1 study; Level 4: 11 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.
- Cost: No additional cost beyond those associated with ESS.
- Benefits-Harm Assessment: Most of the potential risks and benefits postulated for MT resection are not supported in the literature.
- Value Judgments: MT resection may improve access to the ethmoid cavity during ESS. Thoughtful consideration must be given alternatives to 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.
- Policy Level: Option.
- Intervention: MT resection may be employed during ESS, especially in cases of CRSwNP.

X.D.4. Surgical Principles/Techniques: Image Guidance

Image-guided surgery (IGS) technology has found support among sinus surgeons seeking to improve clinical outcomes. In addition to preoperative imaging review, IGS incorporates surgical navigation, which permits surgeons intraoperatively to localize specific points in the operating field against preoperative imaging data sets.[1203] Since 2002, the AAO-HNS'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.[1204]

It must be remembered that the use of IGS is often associated with more extensive surgery, presumably due to the benefits of using the technology.[1205,1206] 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.

IGS does seem to increase operative time.[1205,1207–1210] This increase may reflect the time for IGS setup. Alternatively, case selection bias may adversely influence operative time. In contrast, IGS does not seem to be associated with increased intraoperative blood loss.[1206,1207]

Numerous publications include complication rates. 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[1205] showed comparable complication rates, despite more extensive surgery in the IGS patients. Fried et al.[1206] 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. A more recent publication also associated reduced rate of complications with IGS.[1209] Most authors have not detected differences in complications with IGS.[1211,1212] A 2013 systematic review, by Ramakrishan et al.[1212] 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. Smith et al.[1213] have estimated that such a study designed to detect differences in complication rates would require as many 35,000 enrolled patients. Dalgorf et al.,[1214] in an extensive meta-analysis, concluded that IGS is indeed associated with fewer complications.

Although improvements in clinical outcomes associated with the use of IGS have been difficult to confirm, Javer and Genoway[1215] were able to show improved RSOM-31 scores in patients whose ESS was performed with IGS. Masterson et al.[1216] found a reduction in revision surgery among patients whose ESS was performed with IGS. Other studies have not demonstrated similar benefits of IGS.[1217–1220]

Strauss et al.[1221] 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. Presumably, the information provided by IGS, as captured in this study, translates to more complete/effective surgery and greater operative efficiency.

IGS has also been combined with intraoperative fluoroscopy,[1222] CT-MR fusion,[1223,1224] and 3D CT angiography.[1225] These reports emphasize technical feasibility of these adaptations and explore potential clinical applications. Furthermore, IGS also has specific uses for skull-base surgery,[1226] pediatric ESS,[1227,1228] trephination procedures, [1229] orbital surgery,[1219] and osteoplastic frontal sinus surgery.[1230]

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. [1231–1233] These data are consistent with the theme of surgeon acceptance of IGS.

IGS technology entails incremental costs. One study has proposed that IGS may reduce the overall cost of care, by reducing the need for revision surgery.[1216] From a medicolegal perspective, IGS has not been implicated as a factor in litigation for ESS-related complications[1234] (Table X-11).

- Aggregate Grade of Evidence: D (Level 2a: 1 study; Level 3b: 6 studies; Level 4: 33 studies; Table X-11).
- Benefit: Potential for reduction of complications and more complete surgery.
- Harm: None identified.
- Cost: Moderate. Cost is due to additional equipment, time for setup.
- Benefits-Harm Assessment: Benefits outweigh risks, potentially outweigh costs.
- Value Judgments: Benefit is likely achieved in more difficult cases, with a higher risk of complication. Achieve-

TABLE X-10. Evidence for middle turbinate resection with ESS in CRSsNP and CRSwNP

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Gulati[1196]	2010	1b	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[1202]	2000	1b	RCT (n = 1106)	Patients undergoing ESS: 1. MT resection; 2. MT preservation	Atrophic rhinitis, synechia, and need for revision surgery	MT resection was associated with less synechia and need for revision surgery. Patients with MT resection had no atrophic rhinitis after a mean of 4.2 years
Byun[1183]	2012	2b	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[1197]	2010	2b	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[1184]	2010	2b	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 2 groups postoperatively
Federspil[1193]	2008	2b	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[1191]	2008	2b	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[1189]	2006	2b	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
Friedman[1194]	1996	3b	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 2 groups
Wu[1192]	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[1190]	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[1188]	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

(*Continued*)

TABLE X-10. Continued

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Fortune[1186]	1998	4	Retrospective review (n = 115)	Patients with CRS undergoing MT resection	Frontal sinusitis after surgery	Patients with MT resection had a 10% rate of frontal sinusitis postoperatively
Saidi[1187]	1998	4	Retrospective review (n = 33)	Patients with CRS undergoing MT resection	Frontal sinusitis after surgery	Patients with MT resection had a 18% rate of frontal sinusitis postoperatively when not present preoperatively
Jankowski[1195]	1997	4	Retrospective review (n = 78)	CRSwNP patients undergoing surgery: 1. Nasalization, including MT resection; 2. Ethmoidectomy, with MT preservation	Olfaction (VAS)	Patients who underwent nasalization, including MT resection, had better olfaction than patients who underwent traditional ethmoidectomy, with MT preservation
Kinsella[1199]	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[1200]	1995	4	Retrospective review (n = 337)	CRS patients undergoing ESS: 1. MT resection; 2. MT preservation	Middle turbinate synechiae	Patients who had MT resection had the same rate of synechiae formation as those who had MT preservation
Swanson[1185]	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[1198]	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[1201]	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

SIT = Smell Identification Test.

ment of high levels of evidence are complicated by the need for very large sample sizes and possible ethical issues involving clinical equipoise.

- Policy Level: Option.
- Intervention: Image guidance is an option for ESS for CRSsNP and CRSwNP.

X.D.5. Surgical Principles/Techniques: Use of Packing

Absorbable and nonabsorbable materials are commonly used to pack the sinus cavities in the perioperative period. Proponents of their use suggest that they facilitate hemostasis and improve wound healing, whereas 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. [1268–1271] Three RCTs comparing packing to no-packing reported no evidence of significant postoperative bleeding requiring intervention in their unpacked arms.[1268–1270] This is further supported by a large retrospective series by Orlandi and Lanza[1271] of 165 patients undergoing ESS. This study observed that only 11.2% of patients required packing at the end of their sinus procedure, with no reports of significant postoperative 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.[1272–1275] Both Floseal® (Baxter Inc, Deerfield, IL), an absorbable matrix of bovine-derived gelatin with human-derived thrombin, and HemoStase® (CryoLife Inc, Kennesaw, GA), a purified plant polysaccharide, resulted in complete cessation of intraoperative bleeding within 5 minutes of application.[1272,1273] Although Jameson et al.[1274] 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, FL), a nonabsorbable, highly porous polyvinyl acetyl sponge, Floseal® did not

TABLE X-11. Evidence for use of image guidance with ESS in CRSsNP and CRSwNP

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Dalgorf[1214]	2013	2a	Meta-analysis	14 controlled cohorts (including 1 randomized trial)	Complications	IGS reduces major complication rates
Tschopp[1235]	2008	3b	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[1236]	2006	3b	Prospective case series	ESS procedures: with IGS (n = 80); without IGS (n = 15)	RSOM-31	IGS usage associated with greater improvement in QoL after ESS
Woodworth[1237]	2005	3b	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[1238]	2002	3b	Prospective case series	34 consecutive patients	Calculated TRE	Laser surface registration TRE was 2.4 ± 1.7 mm
Metson[1239]	1999	3b	Prospective case series	121 patients undergoing ESS: no IGS (n = 42)	TRE; operative time; EBL; costs; complication rates	IGS is associated with greater costs and operative time
Fried[1240]	1997	3b	Prospective case series (multicenter)	55 patients undergoing ESS	Technical description of new technology; calculated TRE; surgeon satisfaction; case descriptions	Autoregistration TRE was 2.28 ± 0.91 mm. IGS is an important new technology for ESS
Sunkaraneni[1241]	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 postoperative period; IGS does not appear to reduce complication rates
Eloy[1242]	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[1358]	2013	4	Database query	62,823 patients undergoing ESS	Complication rates	Major ESS complications seem to be decreasing; impact of IGS is unclear
Masterson[1216]	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
Mueller[1211]	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
Al-Swiahb[1209]	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
Parikh[1243]	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

(*Continued*)

TABLE X-11. Continued

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Crawley[1244]	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
Benoit[1245]	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
Dubin[1246]	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
Brown[1247]	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
Zacharek [1248]	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
Tabaee[1249]	2006	4	Case series	ESS procedures: with 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
Strauss[1221]	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 at specific subsites
Stelter[1250]	2006	4	Case series	ESS with IGS (n = 368)	TRE; surgeon satisfaction; complications	Risks associated with inaccurate IGS are minimal
Leong[1224]	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
Knott[1251]	2006	NA	Simulation laboratory	Comparison of contour-based registration and paired-point registration	TRE	Distribution of points for contour-based registration influences TRE
Tabaee[1252]	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
Orlandi[1233]	2006	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

(*Continued*)

TABLE X-11. Continued

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Leong[1225]	2005	4	Case series	Patients undergoing ESS with IGS and 3D-CTA (n = 18)	Feasibility; indications; surgeon satisfaction	IGS with 3D-CTA offers advantages over conventional IGS in more complex cases
Chiu[1253]	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
Von Buchwald[1254]	2005	4	Case series	42 patients undergoing endoscopic inverted papilloma resection with IGS	Recurrence rates, complications	Endoscopic inverted papilloma resection with IGS is safe
Chiu[1255]	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
Rombaux[1256]	2003	4	Case series	32 patients undergoing ESS	Clinical accuracy; complications; preparation time	IGS accuracy is adequate for ESS
Rassekh[1257]	2003	4	Case series	22 procedures in 21 patients	TRE; completion of setup; complications	IGS carries a learning curve for surgeons
Metson[1258]	2003	4	Case series	1000 IGS procedures performed by 42 surgeons	Case volume; surgeon satisfaction	IGS offers both benefits and pitfalls
Eliashar[1259]	2003	4	Case series	ESS procedures: with IGS (n = 34); without IGS (n = 131)	Operative time; surgeons satisfaction; complications	IGS is associated with longer operative time and greater surgeon satisfaction
Reardon[1260]	2002	4	Case series	ESS procedures: with IGS (n = 400); without IGS (n = 400)	Extent of surgery; complications	IGS usage is associated with more extensive surgery
Fried[1261]	2002	4	Case series	Consecutive patients undergoing ESS: with IGS (n = 97); without IGS (n = 61)	Patient comorbidities; extent of surgery; complications; EBL; operative time; repeat surgery	IGS may reduce complications and reduce the need for revision surgery
Olson[1262]	2000	4	Case series	62 ESS with IGS cases	Indications for surgery; surgeon satisfaction; TRE	IGS is helpful at specific subsites, especially in the setting of anatomic complexity
Metson[1263]	2000	4	Case series	754 IGS procedures performed by 34 physicians	TRE; operative time; surgeon satisfaction	IGS can be deployed in a multisurgeon OR
Fried[1264]	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

(*Continued*)

TABLE X-11. Continued

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Roth[1265]	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
Klimek[1226]	1995	4	Case series	14 pediatric patients undergoing skull-base surgery	Technical description; completion of procedure	IGS has promise for skull-base surgery
Ramakrishnan[1212]	2013	5	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
Fried[1266]	2008	5	Literature review	NA	Abstracted observations and data from published reports	Almost all experts agree that IGS is a significant advance for ESS
Smith[1213]	2007	5	Systematic review	5 peer-reviewed publications	Complications	Studies intended to confirm the impact of IGS on complication rates are not feasible
Justice[1232]	2012	NA	Survey	Physician survey (n = 337)	IGS usage; surgeon satisfaction	IGS technology is increasingly available, and surgeons favor its use for specific surgical challenges
Knott[1251]	2006	NA	Simulation laboratory	Comparison of contour-based registration and paired-point registration	TRE	Distribution of points for contour-based registration influences TRE
Hepworth[1231]	2006	NA	Survey	Survey of practicing ENT surgeons (n = 672)	IGS usage; surgeon satisfaction	IGS usage is increasing; surgeons favor usage for more complex ESS cases
Hardy[1267]	2006	NA	Cadaveric dissection	1. Fiducial registration; 2. Landmark registration; 3. Contour registration	Time for registration; TRE	TRE was best for fiducial and worst for landmark

3D-CTA = Three-dimensional CT angiography; EBL = estimated blood loss; NA = not applicable; OR = operating room.

appear to achieve significantly faster hemostasis.[1275] Other absorbable agents that have been evaluated include chitosan-dextran (CD) gel, a biopolymer derived from the treatment of crustaceans; Sepragel®, a hyaluronan-derived gel (Genzyme Co, Cambridge, MA); Quixil®, a fibrin-based glue (OMRIX Biopharmaceuticals Ltd, Nes-Ziona, Israel); and Surgiflo® hemostatic matrix (Johnson & Johnson, Ethicon Division, Somerville, NJ) used in combination with thrombin (King Pharmaceuticals, Bristol, TN).[1268,1269,1276,1277] An RCT by Valentine et al.[1268] showed CD gel 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.[1269] Vaiman et al.[1276] showed Quixil® to be significantly superior to Merocel® in the control of intraoperative bleeding and bleeding on pack removal, but no significant difference was observed in postsurgical bleeding >30 hours after the procedure. Although Surgiflo® with thrombin was shown in 1 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.[1277]

Postoperative Hemostasis. For situations where packing is necessary, a number of trials have compared various materials. Vaiman et al.[1276] reported significantly less bleeding in sinus cavities treated with fibrin sealant

(Quixil®) compared to Merocel®, within the first 24 hours postsurgery, but not beyond. Yu et al.'s study[1278] 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. Floseal®,[1275] Surgicel®,[1279] Cutanplast®[1280] (Mascia Brunelli S.p.A., Milan, Italy), and oxidized cellulose[1281] 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[1281] study also showed oxidized cellulose to be associated with significantly less bleeding than Merocel®, immediately after surgery and on postoperative days 4, 6, and 7. Kim et al.[1282] investigated whether gloving Merocel® prior to its insertion had any effect on posthemostasis and found that sinus cavities packed with the gloved Merocel® had 40 g less bleeding on removal than sides packed with ungloved Merocel®.

Nasopore® (Stryker, Hamilton, ON, Canada), a fully synthetic absorbable dressing, has also been studied extensively. Two different RCTs comparing Nasopore® to Merocel® have shown contrasting results. Although Verim et al.[1283] showed a benefit of Nasopore® in all areas of postoperative morbidity including bleeding on packing removal, this was not replicated in Shoman et al.'s RCT.[1284] More recently a DBRCT by Kastl et al.[1285] showed no postoperative hemostatic benefit of Nasopore® over not packing at all. There is some evidence to suggest that presoaking Nasopore® with lidocaine may improve its hemostatic effect within the first 24 hours after surgery,[1286] without causing adverse hemodynamic effects, but studies comparing this treatment to no packing have not yet been performed.

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®[1287] and absorbable materials such as Floseal®,[1274] HemoStase®,[1288] carboxymethylcellulose (CMC),[1289] Merogel® (Medtronic ENT, Jacksonville, FL),[1290] Sepragel®,[1291] and CD gel.[1268] Only CD gel, 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.[1268,1287] CD gel 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.[1292] A small noncontrolled study by Kim et al.[1282] suggests that gloving the Merocel® pack prior to insertion may further reduce its postoperative adhesion rate; however, this finding has yet to be validated in a controlled study. Given the perceived benefits of Merocel® in reducing adhesion formation, several RCTs have evaluated different packing materials directly against Merocel®. Floseal®,[1275] fibrin sealant,[1278] oxidized cellulose,[1281] and Nasopore®[1283,1284] 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. Although an RCT by Berlucchi et al.[1293] suggested better early and long-term wound healing for Merogel®, no difference between these agents was observed in 2 other independent RCTs.[1294,1295] Interestingly an RCT by Shi et al.[1296] evaluating a similar hyaluronan-based gel, PureRegen Gel® (BioRegen Biomedical, Changzhou, China), observed improved wound healing in terms of adhesion formation, edema, and crusting when the gel was applied to Merocel® prior to packing. 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.[1274] and Baumann and Caversaccio[1275] 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 its possible proadhesion properties. Two studies by Chandra et al.,[1297,1298] 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.[1298] Like Floseal®, CMC has not been shown to confer any significant benefit on wound healing compared to leaving a cavity unpacked.[1289] Two separate RCTs do suggest, however, that CMC dressings may be associated to a lower rate of adhesion formation when compared to commonly used nonabsorbable dressings.[1299,1300]

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®,[1285] HemoStase®,[1270] Sepragel®,[1291] and Floseal®[1274] are not associated with any increased pain, compared to unpacked cavities. In fact, in the studies that evaluated Sepragel® and Floseal®, patients reported less subjective discomfort on the treated side.[1274,1291] Both studies were small in number, however, and did not use validated pain scoring systems. Bugten et al.[1287] 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 nonabsorbable materials. Nasopore® and Merogel® have both been found to better tolerated than nonabsorbable Merocel® while in situ,[1283,1284,1293] with Merogel® causing less discomfort on removal.[1293] 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® intraoperatively and 8 hours postsurgery

appeared to significantly reduce immediate postoperative pain for up to 16 hours after surgery,[1286] whereas gloved Merocel® packs were found to cause less discomfort on removal than standard Merocel® packs.[1282]

Summary. 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 (Table X-12).

- Aggregate Grade of Evidence:
    - Intraoperative Hemostasis: A (Level 1b: 5 studies; Level 3b: 1 study; Level 4: 2 studies);
    - Postoperative Hemostasis: A (Level 1b: 11 studies; Level 3b: 1 study; Level 4: 1 study);
    - Wound Healing: A (Level 1b: 21 studies; Level 3b: 1 study);
    - Patient Comfort: A (Level 1b: 13 studies).
- Benefit: Rapid control of intraoperative bleeding. Potential reduction in adhesion formation with some materials. CD 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 postoperative 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.

X.D.6. Surgical Principles/Techniques: Drug Eluting Packing, Stents, and Spacers

Although ESS is extremely 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, osteoneogeneiss, MT lateralization, and recurrent polyposis.[1302–1306] These complications are currently mitigated by saline irrigations to reduce crusting, postoperative debridement, adhesion lysis, and 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 are limited by patient compliance due to the requirement for multiple applications, and effectiveness may be impacted by postoperative edema, discharge, and crusting within the sinus cavity.[1307]

In order to improve postoperative healing, a wide variety of techniques have been developed and include 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 are drug eluting, they can also potentially provide local medical therapy to the sinus mucosa, independent of patient compliance with minimal systemic side effects.[1308]

Non–drug-eluting stents can act as spacers to prevent adhesion formation and provide a scaffold for mucosal regrowth. However, there has been conflicting evidence on their effectiveness.[1305,1309] Controversy remains regarding their effectiveness, when they should be placed, duration of placement, and type of stent employed.[1308] Silastic stents have been associated with biofilm formation postoperatively, which maybe counterproductive in the treatment of CRS.[1310]

In an "off-label" use, nonbiodegradable spacers such as the Relieva Stratus Microflow Spacer™ (Acclarent, Irvine, CA) have been used as an drug-eluting stent by filling the spacer with triamcinolone.[1308,1311] However, these can be difficult to remove, with a case report of retained spacers leading to inflammation and infection 7 months after initial insertion.[1312,1313] There has also been a case report of orbital violation leading to pain and a permanently dilated pupil.[1314]

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.[1315] Unlike nonbiodegradable stents, they may not require potentially painful postoperative removal. Currently, the only drug-eluting stent approved by the FDA is the Propel™corticosteroid-releasing implant (Intersect ENT, Palo Alto, CA). It consists of a self-expanding, bioabsorbable, drug-eluting stent with the active ingredient of 370 μg mometasone furoate embedded in a polymer matrix composed of polylactide-co-glycolide that degrades over 30 days. Once inserted, its springlike action helps maintain the patency of the middle meatus allowing continued sinus irrigation. In animal studies, this stent showed minimal mucosal inflammatory reaction.[1316]

The Propel™ stent has been investigated in 1 cohort and 2 RCTs, which have demonstrated its efficacy and safety. All 3 studies found similar outcomes in 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.[1307,1317,1318] A

TABLE X-12. Evidence for use of packing with ESS in CRSsNP and CRSwNP

Study	Year	LOE	Study design	Materials	Outcome measure	Findings
Intraoperative hemostasis						
Beyea[1273]	2011	1b	RCT: 18 patients; 36 sides	Floseal® vs HemoStase®	Total blood loss	No significant difference
Valentine[1268]	2010	1b	DBRCT: 40 patients; 80 sides	CD gel vs no packing	Time to hemostasis	Statistically significant difference: CD gel 2 minutes; no packing 10 minutes
Jameson[1274]	2006	1b	DBRCT: 45 patients; 90 sides	Floseal® with patties vs patties alone	Time to hemostasis	Statistically significant difference with Floseal® added to patties (16.4 minutes vs 30.8 minutes)
Vaiman[1276]	2005	1b	RCT: 91 patients undergoing ESS; 48 sides Merocel; 43 sides Quixil	Merocel® vs Quixil®	1. All types of bleeding; 2. Bleeding after removal; 3. Late bleeding >30 hours	Quixil significantly better in #1 and #2. No significant difference in #3
Frenkiel[1269]	2002	1b	RCT: 20 patients; 40 sides	Sepragel® vs no packing	Intraoperative hemostasis	No significant difference in total blood loss
Baumann[1275]	2003	3b	Individual case-control: 50 patients; 100 sides	Floseal® vs Merocel®	Hemostasis	No significant difference (mean 3 minutes)
Woodworth[1277]	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[1272]	2002	4	Cohort study: 18 patients; 30 sites	Floseal®	Time to hemostasis	Average time 2 minutes. Unable to stop bleeding 18 sites
Postoperative hemostasis						
Al-Shaikh[1281]	2014	1b	RCT: 47 patients, 94 sides	Oxidized cellulose powder vs Merocel®	Postoperative bleeding	Oxidized cellulose use had significantly less bleeding than Merocel®
Kastl[1285]	2014	1b	DBRCT: 47 patients; 94 sides	Nasopore® vs no packing	Postoperative bleeding	No significant difference
Verim[1283]	2014	1b	Partly blinded RCT: 56 patients, 112 sides	Nasopore® vs Merocel®	Postoperative hemostasis	Significantly better for Nasopore®
Yu[1278]	2014	1b	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[1280]	2013	1b	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[1286]	2013	1b	DBRCT: 63 patients, 123 sides	Nasopore® soaked in lidocaine vs Nasopore®	Postoperative bleeding as determined by the number of gauze changes	The number of gauze changes at 1, 4, 16, and 20 hours was not significantly different between the 2 groups
Kim[1282]	2012	1b	RCT: 15 patients, 30 sides	Gloved Merocel® vs Merocel®	Bleeding on pack removal	Gloved Merocel® had 40 g less blood loss than ungloved Merocel®

(Continued)

TABLE X-12. Continued

Study	Year	LOE	Study design	Materials	Outcome measure	Findings
Antisdel[1270]	2009	1b	Single-blinded RCT: 40 patients, 80 sides	Microporous polysaccharide hemospheres vs no packing	Postoperative hemostasis	Only significant difference on postoperative day 1
Shoman[1284]	2009	1b	RCT: 30 patients, 60 sides	Nasopore® vs Merocel®	Postoperative hemostasis	No significant difference
Vaiman[1276]	2005	1b	RCT: 91 patients undergoing ESS; 48 sides Merocel; 43 sides Quixil	Quixil® vs Merocel®	1. All types of bleeding; 2. Bleeding after removal; 3. Late bleeding >30 hours	Quixil® significantly better for all types of bleeding and bleeding upon removal. No difference in late bleeding
Shinkwin[1279]	1996	1b	RCT: 60 patients,120 sides	Surgicel® vs Merocel® or petroleum ointment gauze	Postoperative hemostasis	Surgicel® use had less bleeding on pack removal compared to Merocel® or petroleum ointment gauze
Baumann[1275]	2003	3b	Individual case-control: 50 patients, 100 sides	Floseal® vs Merocel®	Hemostasis	Removal of Merocel® associated with increased bleeding
Orlandi[1271]	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						
Akiyama[1299]	2014	1b	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[1281]	2014	1b	RCT: 47 patients, 94 sides	Oxidized cellulose powder vs Merocel®	Crusting, adhesions, infection	No significant difference
Verim[1283]	2014	1b	Partly blinded RCT: 56 patients, 112 sides	Nasopore® vs Merocel®	Edema, crusting, secretions, synechiae, granulation tissue, percentage reepithelization	No significant difference in wound healing at any time point in the first 6 months after surgery
Yu[1278]	2014	1b	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 at 1 week compared to Merocel®
Ngoc[1292]	2013	1b	Single-surgeon DBRCT: 26 patients, 52 sides	CD gel vs no packing	1. Wound healing including adhesion rate; 2. Ostial size at 3 months for maxillary, frontal, and sphenoid	No significant difference in wound healing. Significantly larger ostial sizes for CD-treated cavities
Shi[1296]	2013	1b	RCT: 54 patients, 108 sides	PureRegen® gel plus Merocel® vs Merocel® alone	Reepithelization, adhesions, edema, and crusting	PureRegen® gel had better % reepithelization, Incidence of nonobstructing adhesions, edema, and crusting
Kim[1282]	2012	1b	RCT: 15 patients, 30 sides	Gloved Merocel® vs Merocel®	1. Adhesion rate; 2. Postoperative Lund-Kennedy endoscopic score	Higher adhesion rate for ungloved pack. Significantly better endoscopic score at 4 weeks but no difference later

(Continued)

TABLE X-12. Continued

Study	Year	LOE	Study design	Materials	Outcome measure	Findings
Antisdel[1288]	2011	1b	RCT: 40 patients, 80 sides	Microporous polysaccharide hemospheres vs no packing	1. Synechiae; 2. Edema; 3. Infection	No significant difference in any outcomes.
Szczygielski[1300]	2010	1b	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[1268]	2010	1b	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[1293]	2009	1b	RCT: 66 patients, 88 sides	Merogel® vs Merocel®	1. Adhesions; 2. % Reepithelization; 3. Granulation; 4. Edema; 5. Crusting	Merogel showed superiority in most outcomes and at some time points
Kastl[1289]	2009	1b	RCT: 26 patients, 52 sides	CMC mesh vs CMC gel vs nothing	Wound healing	No significant difference among the groups
Shoman[1284]	2009	1b	RCT: 30 patients, 60 sides	Nasopore® vs Merocel®	Postoperative edema	No significant difference
Franklin[1295]	2007	1b	RCT: 35 patients, 70 sides	Merogel® vs Merocel®	Lund-Kennedy endoscopic score	No significant difference
Bugten[1287]	2006	1b	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[1274]	2006	1b	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[1290]	2006	1b	Blinded RCT: 42 patients, 84 sides	Merogel® vs nothing	Adhesion, edema, infection	No difference at 2, 4, and 6–8 weeks for any parameter
Chandra[1298]	2005	1b	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[1297]	2003	1b	RCT: 20 patients, 40 sides	Floseal® vs thrombin-soaked gelatin foam	Granulation and adhesions at 6 weeks	Floseal® had significantly more adhesions
Miller[1294]	2003	1b	RCT: 37 patients, 74 sides	Merogel® vs Merocel®	Postoperative edema at 8 weeks	No significant difference
Kimmelman[1291]	2002	1b	RCT: 10 patients, 20 sides	Sepragel® vs nothing	Synechiae, middle meatus stenosis, mucosal status	All significantly better in Sepragel®-treated sides at week 2
Baumann[1275]	2003	3b	Individual case-control: 50 patients, 100 sides	Floseal® vs Merocel®	Middle meatal synechiae and stenosis	No significant difference
Patient comfort						
Kastl[1285]	2014	1b	DBRCT: 47 patients, 94 sides	Nasopore® vs nothing	1. Pain, breathing, sleep disturbance, headache, well-being; 2. Pressure; 3. Subjective assessment of which side felt better	1. No significant difference in any of these parameters. 2. Packing showed slightly less on days 2 and 3. 3. No significant difference

(Continued)

TABLE X-12. Continued

Study	Year	LOE	Study design	Materials	Outcome measure	Findings
Verim[1283]	2014	1b	Partly blinded RCT: 56 patients, 112 sides	Nasopore® vs Merocel®	Pain, bleeding, facial edema, nasal obstruction	All significantly less with Nasopore®
Yu[1278]	2014	1b	Nonblinded RCT: 41 patients, 82 sides	Aerosolized fibrin sealant vs Merocel®	VAS score	No significant difference while pack in situ but greater pain and nasal bleeding during removal of pack
Cho[1280]	2013	1b	RCT: 100 patients, 200 sides	Cutanplast® vs Merocel®	Pain on pack removal	Cutanaplast® had significantly less pain on removal
Mo[1286]	2013	1b	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[1301]	2012	1b	DBRCT: 37 patients, 74 sides	Gloved Merocel® vs Merocel®	Discomfort on removal	Ungloved pack had more discomfort on removal than gloved pack
Antisdel[1270]	2009	1b	Single-blinded RCT: 40 patients, 80 sides	Microporous polysaccharide hemospheres vs no packing	Pain, obstruction, and nasal discharge	No significant difference
Berlucchi[1293]	2009	1b	RCT: 66 patients, 88 sides	Merogel® vs Merocel®	Pain on packing removal	Significantly decreased in Merogel® group
Shoman[1284]	2009	1b	RCT: 30 patients, 60 sides	Nasopore® vs Merocel®	1. Postoperative pain; 2. Pain on packing removal	1. Significantly decreased pain with Nasopore®; 2. No significant difference
Bugten[1287]	2006	1b	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[1274]	2006	1b	DBRCT: 45 patients, 90 sides	Floseal® with patties vs patties alone	Pain in first week	Significantly less in Floseal® group
Kimmelman[1291]	2002	1b	RCT: 10 patients, 20 sides	Sepragel® vs nothing	Postoperative subjective pain and congestion	Significantly less in packed group
Shinkwin[1279]	1996	1b	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

CD = chitosan-dextran; CMC = carboxymethylcellulose.

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.[1319] An economic evaluation also demonstrated that Propel™ is cost-effective in decreasing postoperative intervention.[1320]

Concerns raised regarding the data to date have included the lack of a nonstented arm in these studies, which might show that the stenting material without the corticosteroid is proinflammatory. Previous work in biomaterials in the sinuses has shown the potential for some materials to induce inflammation.[1321,1322] Additional work is needed to clarify this issue.

Corticosteroid eluting materials appear to have promise in the postoperative period. Additional indications are on the horizon.[1323] Clinical experience with this device is relatively narrow at this point and evidence, though at a high level, is limited to short-term outcomes (Table X-13).

- Aggregate Grade of Evidence: A (Level 1b: 2 studies; level 2b: 1 study).
- Benefit: Reduction in polyposis and adhesions formation, which translates to a reduction in postoperative interventions.
- Harm: Potential for misplacement and local reaction.

TABLE X-13. Evidence for use of drug-eluting stents with ESS in CRSsNP and CRSwNP

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Han[1319]	2012	1a	Meta-analysis	2 RCTs of outcomes at postoperative day 30	1. MT lateralization; 2. Adhesions; 3. Frank polyposis; 4. Need for postoperative intervention; 5. Need for postoperative corticosteroids	Relative reduction of adhesions and polyposis. 35% reduction in postoperative intervention. 40% reduction in oral corticosteroid usage
Marple[1307]	2012	1b	Prospective, multicenter, DBRCT using intrapatient control design (n = 105)	ESS for CRS	1. Postoperative interventions at 30 days; 2. Endoscopy; 3. Safety	Decrease in postoperative intervention. Decreased adhesions and polyposis. No safety concerns
Murr[1318]	2011	1b	Prospective multicenter intrapatient DBRCT (n = 43)	ESS for CRS	1. Endoscopic assessment at day 21; 2. Safety	Decreased polyposis and adhesions, no difference in MT lateralization. No device-related adverse effects. No systemic absorption
Forwith[1317]	2011	2b	Prospective multicenter single-cohort study (n = 50)	Unilateral (n = 10) or bilateral (n = 40) stent placement	1. SNOT-22 and RSDI at 6 months; 2. Safety; 3. 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
Lavigne[1324]	2014	4	Prospective, multicenter nonrandomized cohort study (n = 12)	Recurrent NP following ESS treated with non–FDA-approved stent	1. Safety of device; 2. 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[1325]	2014	4	Prospective, single-center, nonrandomized cohort study using Propel™	20 patients post-ESS had stent inserted within 7 days postoperatively	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[1326]	2014	4	Prospective single-center nonrandomized cohort study	5 patients with recurrent NP treated with non–FDA-approved stent	Safety of device	No systemic absorption or adrenal suppression. 10/10 successful implant insertion

- Cost: Variable depending on stents and medication. The Propel™ system is estimated at US$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 and 1 study has shown them to be cost-effective in preventing additional postoperative interventions. Experience is early and the amount of evidence is small, though high-level. Specific usage should be at the clinician's discretion taking into consideration various important patient-specific factors.
- Policy Level: The authors could not come to a consensus on the subject of corticosteroid-eluting stents. They were divided between recommendation (due to the high LOE) and option (due to the limited amount of evidence and experience, as well as cost considerations).
- Intervention: Corticosteroid-eluting stents can be considered in the postoperative ethmoidectomy cavity.

X.E. Surgery for CRSwNP and CRSsNP: Postoperative Management

In 2011, Rudmik et al.[1020] published an EBRR on postoperative care after ESS and divided the types of postoperative care into several distinct categories, which are followed in this update. Additional evidence was identified for many of these categories and also on the use of Mitomycin C, so that category was added.

X.E.1. Saline Irrigation

One new study was identified that partially addressed this intervention. Farag et al.[791] reported a single-blinded RCT comparing hypertonic saline irrigation with surfactant (1% baby shampoo) irrigation after ESS, and the primary

outcomes were olfaction and disease-specific QoL, with secondary outcomes of patient-reported side effects. The authors enrolled 40 patients, and found no differences in QoL or olfaction between the 2 groups. The patients prepared the irrigations themselves and were not blinded to treatment, and they reported a higher proportion of side effects with surfactant irrigation than hypertonic saline irrigation. The authors did not report a power analysis, so it is possible that the lack of statistical significance in QoL or olfaction outcomes could be due to a Type 2 statistical error.

In the 2011 review,[1020] the evidence supporting the use of saline irrigations was grade B, and the group made a recommendation for normal saline irrigations, beginning 24 to 48 hours after ESS.

X.E.2. Sinus Cavity Debridements

There were 2 new RCTs reported.[1327,1328] One study[1327] used a within-subject design with 1 side randomized to receive outpatient debridement at 2, 4, and 6 weeks, and the other side received no debridement. A surgeon blinded to which side was debrided assessed the endoscopic appearance at 3 months after surgery and assigned a modified endoscopic score. There were no significant differences in overall endoscopic findings or score; however, a subgroup analysis found that debridement significantly reduced adhesions ($p = 0.048$). The sample was statistically adequate to achieve the power desired based on a priori calculations; however, it was still a small study (24 subjects). Examination of the raw data showed the modified Lund-Kennedy mean endoscopic score was 1.50 on the debridement side and 2.94 on the control side. This did not achieve statistical significance, but it does not appear to be a trivial difference. Furthermore, the within-subject study design restricted the ability to obtain patient-reported outcomes such as symptoms or QoL, which have been shown to be positively affected by early postoperative debridement after surgery.

The other study[1328] was a between-subject design in which groups were randomized to no debridement for 4 weeks, or to outpatient endoscopic debridement at 2 and 4 weeks after surgery. Importantly, all patients received a dissolvable spacer at surgery (no medication added) and high-flow saline lavage and 3-week tapering dose of oral prednisone after surgery. The authors found no significant difference in endoscopic score or patient-based QoL at 6 months between the 2 groups. The authors also reported on a new postoperative patient inconvenience questionnaire, and found that the debridement group reported more pain and more overall inconvenience. The authors noted that their postoperative regimen was fairly aggressive, with 3 weeks of corticosteroids and high-flow saline irrigation, which might account for reduction in synechiae, granulation, and other undesirable postoperative outcomes in both groups.

The 2011 review[1020] found grade B evidence on this topic, which generally identified improved postoperative appearance and reduced postoperative complications such as synechiae if debridement was performed. The authors made a recommendation for sinus cavity debridements after ESS. In 2014, there was 1 new study showing limited benefit, and 1 study showing no benefit of debridement. Although both studies are RCTs, the methodology is still different, with multiple variables differing between studies, so that the evidence grade is still grade B, and compiling all the evidence on this topic the recommendation for postoperative outpatient debridement remains.

X.E.3. Topical Corticosteroids

There was a systematic review and meta-analysis of topical corticosteroids reported in 2013.[1009] The methodology was excellent, and the authors found that, pooling the results of several RCTs comparing topical corticosteroids with placebo, there was significant improvement in the corticosteroid group in the following outcomes: endoscopic score at 6 and 12 months, symptoms score, and recurrence rate of polyps.

The 2011 review[1020] found grade A evidence supporting the use of topical corticosteroids, and made a recommendation for standard INCS. A subsequent review article by some of the same authors[1329] stated, "Topical steroid therapy is integral for control of postoperative mucosal inflammation and should be started following ESS." A strong recommendation is made for INCS following ESS.

X.E.4. Oral Antibiotics

No new studies were identified which addressed oral antibiotics. However, there was a systematic review and meta-analysis on this topic.[1330] The review found a small number of eligible trials, and concluded that the data were unable to demonstrate clear evidence of complication reduction or outcome improvement. The 2011 review had concluded that the evidence supporting the use of antibiotics was level B, and the group made a recommendation of option for use of antibiotics, citing both benefits and potential side effects.[1020]

X.E.5. Topical Decongestants

No new studies were identified that addressed topical decongestants. In the 2011 review,[1020] there was insufficient evidence to support the use of topical decongestants, and the group made a recommendation against topical decongestants, because of potential side effects and no clear benefit.

X.E.6. Packing/Spacers Without Medication Impregnation

There was a systematic review and meta-analysis addressing the use of packing vs no packing after ESS.[1331] The review identified 8 studies with significant heterogeneity of design, and materials used, and reported a nonsignificant trend (risk ratio = 0.40; 95% CI, 0.14 to 1.12) toward reduction in synechiae formation when packing was used, and found that nonabsorbable spacers might have

improved outcomes compared to absorbable spacers. However, overall the data were too heterogeneous to make definitive recommendations. Another systematic review and meta-analysis[1332] compared dissolvable vs nondissolvable packing after ESS. They also found significant heterogeneity between studies and calculated a nonsignificant trend (risk ratio = 0.33; 95% CI, 0.04 to 2.78) toward better outcomes with dissolvable packing.

One new RCT was reported[1283] comparing dissolvable vs nondissolvable packing after ESS, and that trial found no significant differences in postoperative endoscopy scores at 6 months, but found increased pain while the nondissolvable packing was in place.

This evidence on whether to pack is grade B, but based on the lack of clear outcome difference and the heterogeneity of studies, it appears packing is an option. If packing is chosen, there appears to be grade A evidence of its safety and efficacy (see Section X.D.5).

X.E.7. Drug-Eluting Spacers/Stents

There have been several new studies on this topic, which are addressed in Section X.D.6.

X.E.8. Systemic Corticosteroids

There was 1 new RCT related to this topic, in which every patient received a corticosteroid-eluting middle meatus spacer, and then the groups were randomized to receive either systemic corticosteroids (prednisone 30 mg daily for 7 days) or placebo.[1333] Eighteen subjects were enrolled in each group, which satisfied the authors' a priori power analysis calculation. They found no significant difference in endoscopic outcome or patient-based QoL outcome between the 2 groups, and concluded there was no additional benefit of systemic corticosteroids when a corticosteroid-eluting stent was used.

The 2011 review[1020] also found limited evidence on this topic, but concluded that the use of systemic corticosteroids was an option. The current LOE also supports the recommendation of option.

X.E.9. Mitomycin C

This drug, an antifibroblast chemotherapy agent, has been used topically to prevent stenosis, scar formation, and synechiae formation. In other areas of the head and neck (airway, nasal choanae, lacrimal apparatus, etc.), the evidence from controlled studies is generally lacking; either studies have not been performed, or comparative studies show no clear benefit of mitomycin C. However, many clinicians believe their outcomes are improved with its use, and they use it for revision or high-risk cases. The topical use of mitomycin C is off-label.

There were 2 new studies on topical mitomycin C,[1334,1335] and a systematic review with meta-analysis.[1336] The new studies were RCTs with similar design: within-subject trials in which 1 side was randomly assigned to medication application, and the opposite side was the control. Mitomycin C was placed for 5 minutes after surgery was complete. Objective endoscopic outcomes were assessed, including synechia formation, granulation tissue, and maxillary ostium narrowing; 1 study also assessed subjective nasal obstruction.[1335] Outcomes were assessed about 1 week after surgery, and then at intervals from 1 to 3 months. Both studies found no significant long-term outcome differences, either in endoscopic outcomes or symptomatic outcomes. One study[1335] found a statistically significant increase in adhesions at 1 week in the control group, but there was no long-term outcome difference. The studies enrolled 37 (Baradaranfar et al.[1334]) and 50 (Venkatraman et al.[1335]) patients, but neither study reported a power analysis. The lack of difference might have been a type 2 statistical error, but in fact the raw data indicated little difference between the groups, so even a larger sample would likely not have made a difference.

The systematic review[1336] found methodologic problems with many of the individual studies, but when pooling the data found some benefit (risk ratio = 0.34; 95% CI, 0.18 to 0.65) in short-term synechia formation, and in maxillary sinus ostium stenosis (risk ratio = 0.26; 95% CI, 0.12 to 0.54). The authors did not pool long-term results, however, which tended to show small or no difference in outcome, and the authors cautioned that their pooled data were potentially questionable.

These data lead to a recommendation against the use of mitomycin C in following typical ESS, because there are potential side effects and there are no clear long-term benefits.

X.E.10. Other Treatments

There was 1 study comparing Chinese herbal medicine with oral antibiotics and with placebo.[1337] because this is nonstandard treatment, and because oral antibiotics (the comparison) are only an option for treatment, this study was not analyzed further.

X.E.11. Summary

Overall, the LOE and the study methodology on this topic has improved significantly since the 2011 evidence-based review. There were 12 RCTs on different topics, and there were several systematic reviews/meta-analyses, whereas when the literature was searched in 2010, there were many more case series and only a handful of RCTs, many with methodological issues. It is encouraging that the methodologic quality of studies is improving. The potential postoperative interventions and the treatment recommendations are summarized in Table X-14.

X.F. Surgery for CRSwNP and CRSsNP: Outcomes

Literature evaluating both clinician based ("objective") and patient-based ("subjective") outcomes of surgery in CRS, regardless of polyp status, broadly demonstrates that ESS provides clinically significant QoL (overall and disease-specific) as well as objective endoscopic improvements in

TABLE X-14. Evidence for postoperative care after ESS in CRSsNP and CRSwNP

Intervention	LOE	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	Recommendation for standard INCS
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. Reduced risk of synechia and turbinate lateralization	Pain, inconvenience, potential for creating synechia or granulation	Moderate to high, depending on material	Balance of benefit and harm. Potential small benefit of absorbable vs nonabsorbable packing.	Option for packing or spacer
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.	Consensus regarding recommendation cannot be reached at this point (see Section X.D.6)
Systemic corticosteroids	N/A	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

N/A = not applicable.

patients that have failed AMT.[75,77] In addition, cardinal symptoms[1338] and most symptoms classically ascribed to CRS[1339] substantially improve, and patient rating of health utility increases to that of the normal population after ESS.[1340] Patients undergoing revision surgery, regardless of polyp status, also experience significant improvement, though the magnitude of improvement is slightly less than primary surgery patients, likely because of a selection bias of more severe inflammatory disease in those requiring revision surgery.[77,1341,1342]

Health utility measurements (how patients value their current state of health) of CRS with and without polyposis demonstrate substantial reduction in health utility comparable to those with moderate asthma, end-stage renal disease, or Parkinson's disease.[46,49] Significant health utility improvements are seen with ESS and are comparable

to those seen with joint replacement surgery and coronary angioplasty.[46,49,1340,1343]

Comparative effectiveness studies of patients treated medically vs surgically can be divided into RCTs and real-world, nonrandomized observational comparison studies. A Cochrane Review in 2006[1130] based on 3 RCTs suggested that ESS did not offer additional benefit when compared to medical therapies.[751,1344] However, the included trials evaluated patients who had not failed a trial of appropriate medical therapy prior to randomization. Smith et al.[1131,1148,1342] published subsequent nonrandomized, real-world, multicenter observational studies and have demonstrated significant benefits of ESS over continued medical therapy in patients who have failed an initial trial of appropriate therapy. This AMT typically included at least culture-directed or broad spectrum antibiotics, INCS, and in most cases, a trial of oral corticosteroids.[1131,1148,1342,1343,1345] 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.[43,1131,1148,1342,1343,1345] Finally, a modeling based economic evaluation demonstrates 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.[1346] The most recent Cochrane review highlights the lack of high-quality RCTs, which are insufficient to draw firm conclusions.[1127]

ESS Outcomes Differences Between CRSwNP and CRSsNP

Clinicians have typically divided CRS into those with and those without polyps in an effort to further subclassify the disease and better understand outcome differences, recognizing that this is a gross and insufficient categorization, but one which has been traditionally applied in clinical practice and clinical research.

Patients with CRSwNP have worse objective (endoscopic and CT) disease severity both preoperatively and postoperatively relative to their CRSsNP counterparts.[75,1347] Despite this, clinicians see significant improvement in objective findings regardless of polyp status, indicating that ESS is important in bringing the objectively measured inflammatory processes under control.[69,75,1347] Patients with CRSwNP tend to have better baseline QoL relative to patients with CRSsNP; however, specific symptoms such as nasal airway obstruction and olfactory disturbance tend to dominate CRSwNP.[75,77,868,1347,1348] Interestingly, patients with CRSwNP have the greatest improvement in QoL following ESS despite their relatively better baseline QoL.[75,77]

Future Directions in ESS Outcomes Research

QoL instruments are currently considered critical to the evaluation of ESS outcomes in both CRSwNP and CRSsNP. In addition, the degree of baseline QoL impairment tends to drive patient decision-making for ESS[1349] and can help predict postoperative outcomes.[1350,1351] Future research needs to evaluate how incorporating patient-reported outcome measures into clinical decision-making can improve the outcomes after ESS. In addition, further study is needed in relation to 3 recent publications which have suggested that early intervention with ESS for patients with refractory CRS is associated with reduced long-term healthcare utilization and improved long-term clinical outcomes.[1135–1137]

X.G. Surgery for CRSwNP and CRSsNP: Complications

There are several studies that evaluate the rate of complications in ESS as well as give recommendations for prevention and treatment. It is clear that complications during ESS still occur; however, it is reassuring to note that the most severe complications are very uncommon and appear to be equivalent across studies. There are a number of well-performed analyses of complications that are of significant interest to those performing ESS.

May et al.[1352] performed a systematic review of studies covering complications in ESS. They found the overall rate of complications to be 0.85%. The rate of CSF rhinorrhea (most common complication) was 0.4%, the rate of orbital hematoma was 0.15%, and the rate of severe bleeding requiring transfusion was 0.2%. Other miscellaneous complications (adhesions, orbital penetration, etc.) occurred in 6.9% of patients.

Stankiewicz et al.[1353] reviewed their experience involving ESS in 3402 patients and noted an overall complication rate of 3.1%. These complications were subdivided into 14 different varieties of medical and surgical complications. The most frequent complication was hemorrhage (41/3402 or 1.2%), which was primarily postoperative in nature. Orbital hematoma was the second most common (20/3402 or 0.6%), and the third most common complication was CSF rhinorrhea (19/3402 or 0.6%). Other less common complications included meningitis, deep vein thrombosis, toxic shock, permanent blindness (2/3402 or 0.06%), temporary blindness (2/3402 or 0.06%), cardiac shock, and diplopia. Factors felt to be associated with an increased risk of these complications included age, revision surgery, polyps, and anatomic variations. Hopkins et al.[1354] reported a similar rate (0.4%) of major complications in 3128 patients prospectively evaluated in 87 National Health Service hospitals in England and Wales. Minor complications were defined as any other untoward event, and this occurred at an overall rate of 6.6% (207/3128). As with the review by Stankiewicz et al.,[1353] Hopkins et al.[1354] found the presence of polyps to be a risk factor for complications; moreover, LM score, QoL scores, and medical comorbidities were also found to be risk factors. Interestingly, the extent of surgery, use of microdebriders, and surgeon experience were not identified to be factors.

Surgeon experience has been felt by several authors to be a factor in complications. Both Stankiewicz[1355] and Soyka and Holzmann[1356] discuss whether risk is commensurate with surgeon experience. After reporting on an initial incidence of complications, Stankiewicz[1355] demonstrated that after the experience of an additional 300 ethmoidectomies, the overall complication rate went from 29% down to 9.3%, suggesting that as experience with the procedure increased, the likelihood of complications decreased. Using the Rombout and de Vries[1357] criteria, Soyka and Holzmann[1356] retrospectively evaluated 421 endoscopic procedures of varied complexity as performed by surgeons of varied skill levels and found that there was an overall complication rate of 39.7%, which included both minor and major complications. However, there was no significant correlation between the experience of the surgeon and the incidence of complications. Extent of surgery was not found to be correlated with complications either. These latter 2 findings appear to support the experience of Stankiewicz et al.[1353] and Hopkins et al.,[1354] and although conflicting, do remind the reader that complications occur even with experienced surgeons.

In a broader review, Ramakrishnan et al.[1358] reviewed a nationwide database of 40,638 patients undergoing ESS from 2003 to 2007. The overall rate of complications was 1.00%. The authors found that the rate of CSF leak was 0.17% and the rate of orbital injury was 0.07%. Most CSF leaks were recognized the day of surgery, and 76% were recognized within 30 days. CSF leaks were less common in the pediatric population, but orbital complications were more likely to occur in this group. The authors were unable to make any definitive conclusions about the influence of IGS on complication rates. This review is limited in its collection of data, as it has been noted to be difficult to assess how severe complications were and what possible other surgical and/or medical or health-related QoL factors may have contributed to the complications.

Similarly, Krings et al.[1359] used a larger set of healthcare data to determine the rates of complications in 78,944 patients undergoing primary ESS as well as 4151 patients undergoing revision ESS during the years 2005 to 2008. The overall complication rates in patients undergoing primary ESS and revision ESS were 0.36% (288/78,944) and 0.46% (19/4151), respectively. The rate of skull-base complications in patients undergoing primary ESS and revision ESS was 103 (0.13%) and 10 (0.25%), respectively. The rate of orbital complications in patients undergoing primary ESS and revision ESS was 178 (0.23%) and 12 (0.29%), respectively. The authors found that complications were significantly more common in patients aged 41 to 65 years, in patients age >65 years, in patients insured with Medicaid, and in those undergoing frontal sinus surgery. There were no differences in skull-base complications in surgeons who utilized IGS compared to those who did not; however, the overall rate of complications was higher in surgeries where IGS was utilized.

Asaka et al.[1360] performed a prospective study on 706 patients undergoing ESS for CRS. The overall complication rate in this group of patients was 5.8% (41/706). The rate of CSF rhinorrhea in this group was 0.14% (1/706); orbital complications occurred in 2.0% (14/706). Factors that were significantly correlated with complications included higher LM score, asthma and higher polyp score. Revision surgery was not associated with a higher complication rate in this series. The authors recommended evaluation for lower airway disease as well as deploying preoperative measures to reduce polyp scores in order to mitigate complications. Because polyps widely appear to correlate with an increased rate of complications, Devars du Mayne et al.[1361] compared polypectomy to ethmoidectomy in patients with CRS. Although both groups enjoyed a similar success rates (and recurrence rates), the group receiving polypectomy alone did incur fewer complications. This may be an expected result if the ethmoid is not completely dissected, but it may serve as an alternative procedure when indicated for the management of CRSwNP.

Armengot-Carcellar et al.[1362] reported a 0.39% incidence of intracranial complications in 763 patients; 3 patients developed CSF rhinorrhea, 1 of which developed a brain abscess requiring incision and drainage. Hou et al.[1363] reviewed their series of ESS and found 19 cases of intracranial complications. The intracranial complications included 14 CSF leaks, 3 direct frontal lobe injuries, 1 incident of subarachnoid hemorrhage, 2 cases of meningitis, and 3 cases of pneumocephalus. Pneumocephalus is a rare neurological complication of ESS, and other than those reviews[1362,1363] previously described, other case reports[1364,1365] of pneumocephalus after ESS seem to imply that this complication is sufficiently managed with endoscopic closure.[1366]

Microdebriders or tissue shavers have revolutionized the manner in which ESS is performed. Ironically, the speed with which the microdebrider functions can be considered 1 of its largest shortcomings. The microdebrider does not discriminate between orbital fat or muscle and polypoid mucosa and will remove these tissues with equal efficiency. Bhatti et al.[1367] presented 2 unique cases of microdebrider-associated ocular injury during ESS and reviewed the literature concerning orbital injury during ESS, They concluded that detailed preoperative review of imaging is essential prior to surgery and that great care must be taken when performing an ethmoidectomy. They also recommend prompt intervention in the case of orbital injury. Despite the seriousness of injury related to the microdebrider, it continues to be a safe and effective instrument.[1368]

Balloon catheters are increasingly deployed during ESS. Bolger et al.[1369] reported the initial results of balloon catheter dilation on patients with 24 weeks of follow-up and no significant adverse events were noted. Vaughn[1370] reviewed a number of uncontrolled studies pertaining to the use of transnasal balloon catheters and determined that the number of serious complications was low. Nonetheless, scattered reports[1371,1372] indicate the possibility of

catheter-related complications, including ethmoid CSF leak,[1373] which serves as a reminder that any tool used during ESS may lead to complications. Transantral balloon catheters that dilate the maxillary sinus ostium and infundibulum have shown no significant adverse events after initial use[1374] and after 1 year of follow-up.[1375]

Fortunately, major complications in ESS are rare. These reports nonetheless highlight that significant complications can occur and that attention to details, meticulous dissection, and effective perioperative medical management of the patient are essential to help avoid these complications.

XI. Pediatric Rhinosinusitis

XI.A. Pediatric ARS

XI.A.1. Pediatric ARS: Definition and Incidence

ARS is 1 of the most common problems encountered by medical practitioners throughout the world.[7,178,205,1376] There is a strong relation between viral URIs and ARS and most agree that the clinical diagnosis of pediatric ARS of bacterial etiology can be made clinically in 1 of 3 situations: URI symptoms (nasal discharge, congestion and cough) persisting for more than 10 days; an abrupt increase in severity of symptoms after initial improvement (also known as double sickening); or a URI that seems more severe than usual (high fever, copious purulent nasal discharge, cough, and severe local pain).[7,1376]

EPOS defined pediatric ARS as the sudden onset of 2 or more of the following symptoms: nasal blockage/obstruction/congestion or discolored nasal discharge or cough (daytime and nighttime) for <12 weeks.[7] The 2012 EPOS further subdivides pediatric ARS into 3 categories: acute viral RS; acute postviral RS; and ABRS. Acute postviral RS is defined as the increase of symptoms after 5 days or persistent symptoms after 10 days with less than 12 weeks' duration. ABRS is differentiated from the above conditions by the presence of at least 3 symptoms/signs including: discolored discharge (with unilateral predominance) and purulent secretions; severe local pain (with unilateral predominance); fever (>38°C); elevated ESR/CRP; and double sickening. In contrast, the AAP 2013 "Clinical Practice Guidelines for the Diagnosis and Management of Acute Bacterial Sinusitis in Children Aged 1 to 18 Years"[1376] defines ABRS as persistent illness, ie, nasal discharge (of any quality) or daytime cough or both lasting more than 10 days without improvement or worsening course, ie, worsening or new onset of nasal discharge, daytime cough; or fever after initial improvement; or severe onset, ie, concurrent fever (temperature ≥39°C/102.2°F) and purulent nasal discharge for at least 3 consecutive days.[1376] EPOS defines pediatric ARS by symptoms lasting <12 weeks with complete resolution whereas symptoms lasting >12 weeks without complete resolution are consistent with CRS.[7] Subacute rhinosinusitis is not included, as has been done for adult RS in other consensus documents and guidelines, because it is not clear that this is a distinct clinical entity.[4]

Most estimates of the incidence of pediatric ARS are based on the above criteria. In a longitudinal study of 112 children age 6 to 35 months, 623 URIs were observed over a 3-year period and episodes of RS as defined in the previous paragraph were documented by the investigators in 8% of the cases. [1377] In an older study, 159 full-term infants were followed prospectively for a 3-year period and the frequency of URIs and complicating RS were evaluated.[1378] The authors calculated the percentage of children experiencing symptoms beyond 2 standard deviations from the mean duration of respiratory symptoms (range, 16 to 22 days) and took that as an indicator of ARS. The incidence based on these assumptions ranged between 4% and 7.3% and was highest for children in their first year of life and in daycare. Another study evaluating 2135 children with respiratory complaints found that 139 fulfilled the criteria for ARS (6.5%).[1379] In 2 studies that queried children presenting to pediatric practices for any reason and identified those who had symptoms consistent with ARS, the incidence was 9.3% (121/1307)[1380] and 8.3% (249/3001),[1381] respectively. In a study of 2013 children, the addition of a positive Water's view to clinical symptoms decreased the incidence estimate negligibly (7.2% to 6.7%).[1382]

XI.A.2. Pediatric ARS: Pathophysiology

Pediatric ARS, like adult ARS, is a disorder that involves inflammation of the nasal and paranasal sinus mucosa. Through various mechanisms—such as epithelial damage and cytokine upregulation—viruses activate inflammatory pathways and the parasympathetic nervous system to generate the symptoms of ARS.[1383] The inflammatory process leads to edema, engorgement, fluid extravasation, mucus production, and obstruction of the sinus ostium. Similar to adults, the OMC is believed to be the critical anatomic structure in ARS and is entirely present, though not at full size, in newborns. The normal movement of mucus by mucociliary transport toward the natural ostia of the sinuses and eventually to the nasopharynx can be disrupted by any ciliary dysfunction or edema related to mucosal inflammation. Ostial obstruction impedes normal ventilation and drainage of the sinuses, which can lead to bacterial infection and ARS.

Nearly 30 years ago, cultures were obtained from children with maxillary sinus opacification documented by Water's X-ray by means of maxillary sinus taps and the most frequently isolated organisms were *Streptococcus pneumonia* (in approximately 30%), nontypeable *H. influenzae*, and *M. catarrhalis* (in approximately 20% each).[1384,1385] In these studies 25% to 30% of the aspirates were sterile. Because of the difficulty in performing maxillary sinus aspirates in healthy children, no recent data on the bacteriology of ARS is available. Although in adults it has been shown that middle meatal cultures mirror maxillary contents, this has not been confirmed in the context of pediatric ARS. Further, 1 study shows that the middle meatus is colonized with *S. pneumoniae*, *H. influenzae*,

and *M. catarrhalis* in healthy children.[1386] Because of these constraints, recent estimates of the microbiology of ARS are extrapolated from those of acute otitis media, a condition with traditionally similar microbiology.[1376] The routine use of pneumococcal conjugate vaccine has been associated with a decrease in recovery of *S. pneumoniae* from the middle ear fluid of children with acute otitis media (AOM) and a relative increase in the incidence of recovery of *H. influenzae*.[1387] Assuming that approximately 25% of the maxillary sinus aspirates would still be sterile, as documented in earlier studies, one would extrapolate the current bacteriology of ARS to consist of *H. influenzae* and *S. pneumoniae* (30% each) and *M. catarrhalis* (10%).[1376] There is 1 limitation to extrapolating ARS conditions from those of AOM. Although the AOM visit rate for children younger than 18 years dropped after the introduction of the heptavalent pneumococcal conjugate vaccine in the United States, the visit rate for ARS remained stable at 11 to 14 visits per 1000 children between 1998 and 2007.[14]

XI.A.2.a. Pediatric ARS: Contributing Factors. Conditions that can contribute to ARS include rhinitis (allergic and nonallergic), coexisting medical conditions (CF, immune deficiency, ciliary dyskinesia), and environmental factors (smoking, daycare).[1388] Chronic conditions such as CF, immune deficiency, and ciliary dyskinesia are more likely to be associated with CRS.

There are scant data on the correlation of AR and ARS in children. In a retrospective study of 92 patients with RARS, children with allergies sustained 1.09 more sinus infections than nonallergic patients, a significant difference.[1389] 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%).[1390] The percentage of positive skin-prick test results was similar in both groups (96.4% in ARS and 96.9% in CRS). Most of the available studies suffer from referral bias because they are conducted in allergy practices.

Adenoiditis can have a very similar clinical presentation including anterior and posterior purulent drainage and cough and is relevant in the differential diagnosis in the pediatric age group. In a study of adenoid size evaluated by MRI in a patient cohort with no symptoms related to the adenoids or adenoid disease, adenoid size was larger in the pediatric age group and declined with advancing age.[1391,1392] Peak size was between 7 and 10 years of age and largest dimensions were in the group 4 to 15 years old. In an attempt to differentiate between adenoiditis and ARS based on endoscopic findings, Marseglia et al.[1393] performed a cross sectional study of 287 consecutive children in whom ARS was suspected based on symptoms lasting for more than 10 days. Nasal endoscopy was performed and the diagnosis of ARS was made if purulent discharge was identified in the OMC or sphenoethmoidal recess, 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 and 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 (age 2 to 5 years) whereas isolated ARS was more frequent in older children. Although this study has limitations, such as the manner in which the diagnosis was made, one would expect drainage from the sinuses to involve the adenoids as it moves posteriorly within the nasal cavity. This, combined with the lack of a more objective measure to diagnose ARS, would suggest the available data support the coexistence of infection of the adenoids and the paranasal sinuses. It is also evident that based on clinical presentation alone, the differentiation between adenoiditis and ARS in children is difficult.

XI.A.3. Pediatric ARS: Diagnosis

The clinical diagnosis of ARS in children is challenging because symptoms are often subtle and the history is limited to observation of the child and subjective evaluation by the child's parent. When evaluating a child with suspected ARS there is a wide differential diagnosis including: acute viral RS, acute postviral RS, ABRS, intranasal foreign body, adenoiditis, CF, PCD, and unilateral choanal atresia/stenosis. The initial diagnostic workup for such patients should include a thorough history and physical examination and nasal endoscopy, when appropriate.[7] Because some younger children might not tolerate nasal endoscopy, clinicians are sometimes hindered in their physical examination and have to rely on history and/or imaging studies for appropriate diagnosis. Symptom profiles of ARS in children include fever (50-60%), rhinorrhea (71-80%), cough (50-80%), and pain (29-33%).[20] In a 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 Water's projection. In these children, the most troublesome symptoms were PND, nasal obstruction, and cough.[1394] 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.[1395]

The physical exam in children 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.

As far as factors that could predict the presence of ARS in the context of URIs, prospective studies using the above

definitions (see Section XI.A.1) to identify ARS after URI (prolonged duration or double-sickening) supplemented the clinical diagnosis by obtaining plain X-rays of the sinuses. In 1 of these studies, 54 of 258 (21%) children with presumed ARS had normal sinus radiographs, suggesting that they just had URI and not ARS.[1396] The absence of green nasal discharge and disturbed sleep, as well as milder symptoms, was associated with the diagnosis of URI and not ARS. No physical findings were particularly helpful in distinguishing between children with normal vs abnormal radiographs.

Obtaining a culture is usually not necessary in the context of uncomplicated ARS. It might be useful in patients who have not responded to conventional medical treatment within 48 to 72 hours, in immunocompromised patients, in the presence of complications, and if the child presents with severe illness and appears toxic.[20,1397] Although the gold standard is a maxillary sinus tap, this is a relatively invasive procedure and is difficult to perform in a child in the office.

The diagnosis of pediatric ARS is generally made on clinical grounds and imaging is not routinely necessary. Several studies have reported the presence of incidental abnormalities of the sinuses on CT scan in asymptomatic children[1398,1399] and the occurrence of abnormal CT or MRI sinus findings in a large proportion of children with viral URIs.[1400–1402] This reinforces the notion that, like in adults, every URI is essentially an episode of RS with common involvement of the paranasal sinuses by the viral process. As a result, the AAP's clinical practice guidelines[1376] state that imaging does not have a role in distinguishing acute viral from acute bacterial RS and does not have a role in uncomplicated ARS.

XI.A.4. Pediatric ARS: Management

Current guidelines recommend only symptomatic treatment for children with uncomplicated ARS.[7,1376] The 2012 EPOS further recommends antibiotic therapy for children with complications or concomitant disease that could be exacerbated by ARS. The initial antibiotic of choice remains amoxicillin; additional first-line agents include amoxicillin-clavulanate and cephalosporins.[7] 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. The AAP cautions practitioners to monitor patients for symptom improvement/resolution within 72 hours of the initial treatment decision and to consider initiation of antibiotic therapy for patients observed or adjustment of antibiotic therapy for patients treated with amoxicillin with or without clavulanate if there is not clinical improvement.[1376] For patients allergic to amoxicillin, the AAP guideline recommends a second-generation or third-generation cephalosporin as monotherapy for ABRS because the vast majority of patients with such sensitivity tolerate cephalosporin therapy.[1376] For patients under 2 years of age with a documented type-1 hypersensitivity to penicillins and moderate to severe ABRS a combination of clindamycin and cefixime is suggested.[1376] A fluoroquinolone, such a levofloxacin, can also be used to treat ABRS in patients with a severe penicillin allergy.[1376] It should be noted that levofloxacin does not have an FDA-approved indication for ABRS in children and has potentially serious side effects, including tendonitis and tendon rupture, that should be considered prior to the initiation of therapy.

In contrast, the 2012 Infectious Disease Society of America (ISDA) clinical guideline for the management of ABRS recommends amoxicillin-clavulanate for empiric therapy for ABRS in children.[178] 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, 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.[178] Macrolides, trimethoprim-sulfamethoxazole, as well as second-generation 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.[1376] 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*.[178] 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.[178] The ISDA recommends antibiotic treatment for a duration of 10 to 14 days.[178]

Regarding adjunctive treatments, the 2012 EPOS indicates a role for INCS in the management of pediatric ARS.[7] A recent Cochrane review failed to detect any evidence supporting the efficacy of nasal decongestants, antihistamines, or nasal irrigations in the management of pediatric ARS.[205] There is no role for ESS in children with uncomplicated ARS (Table XI-1).

- Aggregate Grade of Evidence: A (Level 1a: 4 studies).
- Benefit: Reduction in duration and severity of symptoms.
- Harm: Antibiotic resistance, gastrointestinal complications, risk of allergic reaction
- 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

TABLE XI-1. Evidence for management of pediatric ARS

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusions
Shaikh[205]	2014	1a	Systematic review	Multiple	N/A	No evidence supporting the use of nasal decongestants, antihistamines, or nasal irrigations
Wald[1376]	2013	1a	Systematic review	Multiple	N/A	Definition, evaluation, and management recommendations
Chow[178]	2012	1a	Systematic review	Multiple	N/A	Treatment recommendations
Fokkens[7]	2012	1a	Systematic review	Multiple	N/A	Definition, evaluation, and management recommendations

N/A = not applicable.

- Policy Level: Recommendation.
- Intervention: Antibiotics should be given to pediatric patients with ARS although the specific antibiotic and exactly when to intervene differ among clinical practice guidelines.

XI.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%).[7,1376] Orbital complications are the most common complications of pediatric ARS and range from preseptal cellulitis to orbital abscess, as described by Chandler.[232] Additional orbital complications can include blindness, optic neuritis, corneal ulceration, and panophthalmitis. Intracranial complications can include epidural abscess, subdural abscesses, brain abscess, meningitis, and 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. The 2013 AAP guidelines on ABRS recommend obtaining a contrast-enhanced CT scan of the paranasal sinuses and/or an MRI with contrast whenever a child is suspected of having orbital or central nervous system complications of ABRS. The 2012 EPOS guidelines recommend imaging for every complication other than preseptal cellulitis.[7,1376] Early orbital complications can sometimes be managed with IV antibiotics alone, whereas the more severe complications of pediatric ARS may require a combination of IV antibiotics and surgical treatment.

XI.B. Pediatric CRS

XI.B.1. Pediatric CRS: Incidence/Prevalence

The incidence and prevalence of pediatric CRS (PCRS) are unknown. Patients with chronic rhinorrhea, nasal congestion, and cough may be commonly seen in primary care and otolaryngology. In an attempt to understand how many of these children actually have PCRS, 196 children 3 to 14 years of age presenting with these symptoms were examined with CT scans. Maxillary sinus involvement was noted in 63%, ethmoid in 58%, and sphenoid in 29% of these children.[1403] In a separate study, the incidence of anatomical variations as a possible cause of PCRS has been reported, with agger nasi cells present in 15.9%; concha bullosa in 10% to 19%; NSD in 13%; and infraorbital ethmoid cells in 5.3% to 7.5%. However, there was no control group to determine whether those anatomical variations were seen in a higher incidence in PCRS group compared to children with no RS.[1404]

XI.B.2. Pediatric CRS: Pathophysiology

The pathophysiology of PCRS is not very well understood and is thought to be multifactorial, possibly involving bacteria, biofilms, adenoiditis, and/or inflammatory cellular changes.

Bacteriology has not changed over the last 2 to 3 decades, except for a rise in *S. aureus* and anaerobic bacteria. In a study by Muntz and Lusk in 1991,[1405] the most common species were alpha hemolytic *Streptococcus* and *S. aureus*, followed by *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*. Anaerobes were seen in 6% of children. All those were specimens obtained at time of sinus surgery.[1405] In a more recent study, the most common species were alpha hemolytic *Streptococcus* followed by *H. influenzae*, *S. pneumoniae*, *S. aureus*, and anaerobes in 8% of surgical specimens.[1406] Several other studies between 1991 and 2010 were performed without much change from 2 decades ago. When examining the susceptibility of organisms over time, there was an increase rate of resistance for *H. influenzae* as well as *S. pneumoniae* species. Resistance to ampicillin among *H. influenzae* rose from a little over 50% in 2001 to more than 70% in 2006.[1407]

Adenoids are what distinguish PCRS from adult CRS. The adenoids are thought to act as a reservoir of bacteria. Bernstein et al.[1408] in 2001 found that bacteria from adenoids correlated with lateral nasal wall cultures in 89% of cases with PCRS. Shin et al.[1409] cultured the adenoids

in patients with various degrees of abnormalities of their maxillary sinuses on Waters views and found a significant increase in bacterial isolation rate with increasing severity of RS. Coticchia et al.[1410] examined 16 adenoid samples for biofilm. Seven were children with CRS and 9 were children with OSA. All adenoid samples of children with CRS had biofilm on their surface, covering an average of 95% of the surface area compared to only 2% coverage of the surface area of the adenoids in children with OSA.[1410] It is also believed that some children may have chronic adenoiditis with no CRS because symptoms of the 2 entities cannot be distinguished without CT scan of the sinuses.[1411] There is controversy whether the size of the adenoids matter in children with PCRS. Children with symptoms of RS who had a CT scan of the sinuses and underwent an adenoidectomy were investigated and results showed no correlation between the size of the adenoids and the severity of disease on CT scan.[1412] This suggests that symptoms can be due to adenoiditis and that the bacterial reservoir of the adenoids, more than their size, was the cause of symptoms in these children.[1412] There is also some evidence to suggest that the adenoids act as an immunological organ. In 1 study comparing the Ig expression of adenoid tissues of patients with adenoid hypertrophy to those with CRS, there was a significantly lower expression of IgA in the adenoids of children with CRS. This suggests that the adenoids in CRS children cannot mount a strong local immune response. Whether this is a primary deficiency or a secondary response to chronic nasal discharge cannot be determined from this study.[1413]

In order to examine inflammatory cellular changes, Chan et al.[1413] compared maxillary sinus biopsies of children with CRS to adult archival maxillary sinus tissue. They noticed more neutrophils and more lymphocytes in the pediatric mucosa compared to adult mucosa. The adult mucosa had more eosinophils and major basic protein–positive cells. They also found less epithelial disruption and thickening of the basement membrane in children compared to adults.[1413] In a similar study, sinus specimens were obtained from children with CRS and compared to samples that were obtained from adults. Even though the children were older in this study compared to the other study (mean 11.6 vs 3.9 years), the children's samples had less eosinophils and less epithelial damage than the adult samples.[1414]

XI.B.2.a. Pediatric CRS: Contributing Factors. Asthma has been shown to be a factor in children with CRS. At times asthma not responding to medical therapy can be the only presenting symptom of PCRS. The relationship between asthma exacerbations and PCRS has been shown in several studies. In a series of 48 children with moderate to severe asthma refractory to medical treatment with daily wheezing for 7 months, 80% of children were able to discontinue their asthma medications after their CRS was treated medically or surgically. Eighty percent of these children had normal findings on sinus X-rays after treatment. Asthma symptoms returned when RS recurred.[1415] In another study of 18 children with poorly controlled asthma, RS was treated with oral antibiotics and intranasal and systemic corticosteroids. They were evaluated at baseline and 1 month later. Their sinonasal symptoms resolved with 8 of 18 children having intermittent asthma and 10 of 18 children having mild asthma based on their symptoms and spirometry compared to baseline. These and other studies support the concept that controlling the CRS in these children will contribute to controlling their asthma.[1416]

The association between AR and the development of PCRS is controversial. Some studies have shown a possible association, whereas others suggest that allergy is not a significant factor. In a 2007 study of 2200 children who were referred for chronic respiratory symptoms, 351 were diagnosed with CRS. They underwent skin-prick testing: 29.9% were found positive, an incidence similar to that noted in the general population (31.8%).[1417] Similarly, in a study of 4044 children with PCRS, AR was found to be present in 26.9% of patients. Sedaghat et al.[1418] in 2013 reviewed a cohort of children with AR and found that patients who developed PCRS did not have any evidence of more severe AR. The association between AR and PCRS is thought to be multifactorial.[1418]

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.[592,1419,1420] Management with IVIG for those children resulted in decrease in antibiotic intake and reduced episodes of CRS. Children with CRS may benefit from an Ig evaluation and also titers for tetanus, diphtheria, and *Pneumococcus*.

CF is an autosomal recessive genetic disease associated with a high incidence of PCRS and nasal polyposis. Any child with NPs should be evaluated for the presence of CF with a sweat test and, potentially, DNA testing.[1421] Children who present with NPs as a component of PCRS represent a distinct subgroup and should be dealt with accordingly.[1422]

PCD is a rare cause of PCRS. Any disruption to the mucociliary function can result in PCRS. PCD is the most common cause of ciliary dysfunction and should be suspected in PCRS patients who are not responding to medical and even surgical treatment. PCD 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; with the association of CRS, PCD is known as Kartagener's syndrome.[1423] Screening tests include nasal NO and in vivo tests such as the saccharin transit test, which shows slower mucociliary transit time. Those screening tests can be falsely negative in a good percent of the children. A more definitive test is to obtain a mucosal sample preferably from the carina (another option is posterior tip of inferior turbinate) and examine the specimen for cilia with light and electron microscopy. The most common abnormality is lack of outer dynein arms or a lack of both inner and outer dynein arms.[1424,1425]

TABLE XI-2. Summary of selected evidence for PCRS management

Study	Year	Study design	Conclusion
Brietzke[1426]	2014	Systematic review	Evidence-based expert panel consensus in the diagnosis and management of PCRS
Makary[1433]	2013	Systematic review	ESS offers a surgical alternative in the treatment of CRS in children with an excellent safety profile. Higher LOE is necessary
Fokkens[7]	2012	Systematic review	Treatment evidence and recommended management algorithm provided
Setzen[1434]	2012	Systematic review	CT imaging in PCRS is recommended in the setting of treatment failures and complications, either of the pathological process itself or as a result of iatrogenic complications
Ozturk[1429]	2011	RCT	The addition of oral corticosteroids to oral antibiotics reduced clinical PCRS symptoms and CT findings
Wei[787]	2011	RCT	High tolerance, compliance, and effectiveness of saline irrigation support its use as a first-line treatment for PCRS
Brietzke[1430]	2008	Systematic review	Adenoidectomy should be considered first line therapy for medically refractory, uncomplicated pediatric RS, given its simplicity, low risk profile, and effectiveness
Ramadan[1432]	2008	Retrospective series	For pediatric patients with LM scores greater than 6, the addition of maxillary sinus irrigation at the time of adenoidectomy was found to improve clinical symptoms of PCRS 1 year postprocedure
Ramadan[1431]	1999	Cohort study	Prospective, nonrandomized cohort evaluation revealing higher success in PCRS patients failing medical therapy undergoing ESS in comparison to adenoidectomy

Controversy and uncertainty exists about the role of GERD in PCRS. An association has been suggested; however, there is lack of evidence to support this association. In a recent consensus statement on PCRS, there was agreement that empiric treatment for GERD in the context of PCRS is not indicated. Similarly, consensus was not reached regarding the contribution of GERD in the pathogenesis of PCRS.[1426]

XI.B.3. Pediatric CRS: Diagnosis

PCRS is defined as signs and symptoms of nasal congestion, colored nasal discharge, facial pressure or pain, or cough that has been present for 12 or more weeks.[1427] Two or more symptoms are needed to diagnose PCRS. These symptoms should be accompanied by findings of purulent discharge, and mucosal edema/changes on anterior rhinoscopy/nasal endoscopy. Nasal endoscopy when feasible will provide information that will aid in the diagnosis. Also, this will allow examination of the adenoids and nasopharynx, as well as determine the presence of polyps.[1426]

Plain X-rays have no role in the diagnosis of PCRS. Findings on plain radiographs have been shown not to correlate well with those from CT scans in patients with PCRS. In a prospective study, children with CRS symptoms were imaged using plain radiographs and CT. The findings on plain radiographs did not correlate with those on CT scan in 75% of the 70 patients studied. About 45% of the patients had normal findings on plain radiographs but at least 1 sinus with an abnormality of that sinus shown on CT scan, and in 35% of the patients with an abnormality of at least 1 sinus on plain radiographs that sinus was normal on CT scan.[1428] Once PCRS is suspected in young children these symptoms can be a manifestation of chronic adenoiditis with or without RS. At this point the only mechanism to distinguish whether CRS is associated with chronic adenoiditis is by the use of CT scan of the sinuses. In a study comparing 66 children with CRS symptoms to 192 control children having CT imaging for nonsinus indications, it was noted that children with a LM score of 5 or more had a sensitivity and specificity of 86% and 85%, respectively, of having CRS, whereas a CT score of 2 had an excellent negative predictive value of CRS, making the diagnosis of chronic adenoiditis more likely.[1411] It should be noted that use of CT should be reserved for when surgery is being considered and not utilized routinely to make the diagnosis of PCRS.

XI.B.4. Pediatric CRS: Management

Management of PCRS can pose a challenge to the otolaryngologist and result in a difficult course for patients and families. Certain treatment principles should assist in guiding optimization of outcomes. Recent position papers have summarized the current state of the literature and clinical consensus on PCRS[7,1426] (Table XI-2).

PCRS management should focus on long-term behaviors and nasal hygiene to limit disease burden. The goal of restoring sinonasal homeostasis may be achieved by

quelling mucosal inflammation and initiating targeted antibiotics.[7]

PCRS management therefore begins with medical therapies. Consensus exists that nasal saline irrigations are beneficial in the pediatric population with 1a LOE.[7,1426] Adherence of the pediatric population with nasal saline irrigations may be considered with skepticism, though with parental assistance, compliance is greater than 90%.[787]

Reports on the efficacy of INCS such as fluticasone and mometasone are conflicting.[7] However, given the low systemic absorption and low risk profile, use of INCS is recommended as first-line therapy as a component of conservative medical management and postoperative treatment regimens, particularly in patients suspected to have IgE-mediated pathophysiologic processes.[7] Double-blinded, randomized prospective data supports the use of systemic corticosteroids in addition to antibiotics for symptomatic and radiographic improvements in children with CRS.[1429] 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. Randomized prospective studies supporting nasal antihistamines or decongestants are lacking.

Both EPOS and clinical consensus support empiric broad-spectrum treatment with transition to culture-directed antibiotics for 3 to 12 weeks, though there is need for high LOE studies.[7,1426] Initial empiric treatment should cover *S. pneumoniae*, *M. catarrhalis*, nontypeable *H. influenzae S. aureus*, and possibly anaerobic bacteria. Amoxicillin/clavulanate or second-generation (cefuroxime) and third-generation (cefdinir and cefixime) cephalosporins are first-line antibiotics. Patients with penicillin allergy may be prescribed cephalosporins, and if allergies are demonstrated to both, may alternatively be prescribed a macrolide or clindamycin. Randomized prospective double-blinded data did not find statistical differences in topical gentamicin irrigations over saline alone in the pediatric population.[787]

Contributing comorbid conditions may increase the complexity of management and addressing underlying factors that are worsening CRS should be attempted. Examples include consideration of GERD, immunodeficiencies, PCD, and CF. Randomized prospective data and clinical consensus supporting the role of anti-reflux medication in PCRS treatment are lacking.[1426]

Consideration for surgical intervention is made after failed conservative nasal hygiene and medical management. An official definition for appropriate medical therapy and failure of such therapy is lacking. It is suggested that medical management prior to surgery should, however, include a course of antibiotic therapy, topical nasal and/or systemic corticosteroids, and nasal saline irrigation.[7]

Surgical options are age-dependent and anatomy-dependent. In younger children, adenoid hypertrophy may play a larger role in treatment than ESS of the relatively underdeveloped sinuses. Clinical consensus that adenoidectomy alone is an effective treatment for PCRS is strong in children up to 6 years old and supported through 12 years of age, though evidence is lacking beyond this age group.[1426] The role of adenoid tissue in CRS may be obstructive and/or serve as a reservoir for bacterial growth. A 2008 meta-analysis of 9 studies found clinical improvement, as judged by caregivers, in 70% of children with CRS after adenoidectomy. The quality of the constituent studies was judged as moderate, with five level 2b evidence studies and four level 4 reports.[1430] A 1999 prospective, nonrandomized cohort analysis analyzed success of adenoidectomy and ESS, where failure was defined as persistence of symptoms and need for additional procedure at 6 months postoperatively. Adenoidectomy had a 47% success rate, whereas ESS had a 77% success rate.[1431] For pediatric patients with LM scores greater than 6, the addition of maxillary sinus irrigation at the time of adenoidectomy was found to improve clinical symptoms 1 year after the procedure. [1432]

There are several potential roles of ESS in PCRS. One use for pediatric ESS in CRS is opening anatomic corridors for irrigation and topical therapy delivery. Most data supporting ESS is retrospective, though a 2013 review cites success rates over 82% with a complication rate of 1.4%.[1433] Newer technologies such as balloon sinus dilation do not yet have robust data supporting their efficacy in children. Finally, consensus exists that CT imaging is recommended prior to ESS, and IGS has a role in revision ESS or if distorting polyposis is present.[1426,1434] Though a potential for therapeutic improvement is acknowledged, consensus was lacking regarding turbinoplasty or excision of obstructive concha bullosa because of the lack of pediatric-specific evidence in the literature. Unlike the adult population, postoperative debridement is not felt to be essential.[1426]

XI.B.5. Pediatric CRS: Complications

The etiologic role of PCRS in nasal and paranasal complications is likely an anatomic, bacteriologic, and inflammatory vulnerability to an ARS exacerbation. Literature associates orbital complications (91% of RS complications), osteomyelitis of the frontal bone (Pott's puffy tumor), meningitis, subdural empyema, epidural abscess, and brain abscess with ARS or AECRS.[1435] As such, incidence of these complications specifically secondary to PCRS is lacking. Limited retrospective evidence suggests a potential contribution of CRS on the development of paranasal sinus frontal osteomyelitis. One of 5 cases in a series of pediatric osteomyelitis of the frontal bone was felt to be secondary to PCRS.[1436] Postsurgical intracranial complications have been reported in the CF population, prompting the recommendation of systematic follow-up.[1437]

Orbital, periorbital, or neurologic symptoms should prompt rapid multidisciplinary evaluation, imaging, IV antibiotics, and potentially surgical intervention. Central nervous system complications should be treated with

IV cefotaxime or ceftriaxone and vancomycin pending cultures and susceptibilities.[7]

Complications associated with surgical intervention for PCRS include the spectrum of potential complications for ESS. The rate of major and minor complications is cited at 0.5% to 1% and 5%, respectively.[1438] Major complications include orbital hematoma and CSF leak. More frequent minor complications are bleeding and synechiae. A recent review of ESS extensively details these complications.[1438]

XII. Special Considerations in Rhinosinusitis

XII.A. RS Special Considerations: Chronic Granulomatous Diseases

Chronic granulomatous diseases (CGD) include granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis), Churg-Strauss syndrome, and sarcoidosis. All CGD conditions produce hallmark perivascular or perilymphatic noncaseating granulomas. GPA and Churg-Strauss syndrome cause systemic, necrotizing, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, whereas sarcoidosis produces a chronic inflammatory disease of uncertain etiology.

GPA can affect any organ system with classic manifestations of systemic illness, otitis media, nodular infiltrates on chest radiograph, renal disease, and subglottic stenosis. From the rhinologic perspective, progressive ischemic necrosis of the nasal epithelium and internal structures can occur, resulting in epistaxis, nasal stenosis, septal perforation, and saddle nose deformity.[1439] 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.[1440] For these reasons, Churg-Strauss syndrome is also termed eosinophilic granulomatosis with polyangiitis (EGPA). Sarcoid is typified by nodular, infiltrative lesions in the nasal mucosa, but 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. In GPA the nose and sinuses are managed for the most part with nonsurgical treatment, including INCS and saline irrigation therapy. Some series suggest that surgery for CRS, mucocele formation, and nasolacrimal stenosis may be beneficial to control sequelae of GPA for appropriately selected patients.[1441] Systemic manifestations of both sarcoidosis and Churg-Strauss syndrome are managed with chemotherapeutic agents, oral corticosteroids ± immune modulators, but like GPA, the literature supports use of medical management while reserving surgical intervention for persistent rhinologic symptoms in select patients.[1442–1446] Given the epithelial abnormalities present in CGD patients, patients should be counseled regarding suboptimal and/or delayed healing that can follow intranasal procedures.

XII.B. RS Special Considerations: PCD

PCD is a heterogeneous genetic disorder causing defects in cilia structure or function, resulting in compromised MCC from respiratory epithelial surfaces and recurrent airway infections. The term Kartagener syndrome is reserved for PCD cases presenting with the triad of CRS, solid organ transposition (situs inversus), and bronchiectasis. The estimated incidence of PCD is 1 in 15,000 to 30,000 births[1447] and radiographic changes of PCD-associated maxillary sinusitis may be observed as early as 6 months of age.[1448] The constellation of otolaryngology and pulmonary findings associated with PCD include rhinitis, congestion, RS, otitis media, chronic cough, bronchiectasis, and recurrent pneumonia, all to varying degrees of incidence and severity. Nasal polyposis in PCD patients has a reported occurrence rate of 18% to 33% with onset in adolescence.[1447,1449,1450] Diagnosis relies on a combined approach using ultrastructural analysis of respiratory mucosal biopsies via electron microscopy and functional assessment of CBF and pattern.[1451–1453] Low NO production is another measurement useful in the diagnosis of PCD.[1454,1455] PCD is most commonly an autosomal recessive disease, yet testing for mutations in over 30 cilia structural genes linked to PCD is not always feasible.[1456]

In both pediatric and adult PCD patients, aggressive management of upper airway inflammation and infection appears to be critical to maintenance of sinopulmonary health and QoL. Medical management may include regular nasal lavage, INCS, antibiotics, seasonal vaccinations, IV gamma globulin, and prolonged macrolide therapy.[1450] Although the literature regarding the role of ESS in PCD is limited to case reports/series, the literature collectively suggests that moderate improvements in rhinologic symptoms following ESS procedures can be attained for PCD patients. Following ESS, reduced rhinitis, purulent discharge, and nasal congestion are documented, with notable improvements in lower respiratory sequelae.[1450]

XII.C. RS Special Considerations: CF

CF occurs primarily in white populations in 1 in 2000 to 6000 births.[1457] CF is caused by autosomal recessive inheritance of mutations in the CFTR chloride transport gene, and exocrine gland dysfunction. Secretions in general, and the air-surface liquid in particular, become viscous and stagnant in CF patients, impairing MCC, and contributing to frequent bouts of CRS in the upper airway and bronchopulmonary disease in the lower airway. CF patients have an incidence of RS approaching 100%[1458] and 44% to 58% have NPs.[1459,1460]

Medical management in adult and pediatric CF includes nasal saline, INCS, topical antibiotics, dornase alfa, and oral macrolides. Topical saline irrigations are extrapolated for use in CF patients from literature noting improvement in

symptoms and QoL scores in non-CF patients.[696] In a similar extrapolation, hypertonic solutions in nasal lavages are often recommended by extension from positive pulmonary outcomes with nebulized hypertonic solution.[1461] Nasal polyposis in CF is typically less responsive to corticosteroids, possibly due to an increased neutrophilic component, but polyp volume reduction with symptom improvement is reported.[1462,1463] Topical antibiotic use has shown reduced postoperative CF sinus exacerbations, endoscopic score improvement, and reduced symptoms.[782,785,1464] Dornase alfa reduces mucus viscosity and improves objective CRS outcome measures.[1465,1466] Oral macrolides possess antibacterial and anti-inflammatory effects with support for use in CF pulmonary manifestations and may be utilized to treat CF-related CRS.[1467,1468]

ESS for CF-associated CRS improves both QoL and endoscopic scores.[1469] However, ESS in the CF population often has high rates of revision surgery and persistent radiographic abnormalities. In addition, despite radiographic evidence of RS by CT imaging, only a small proportion (10-20%) will have self-reported CRS symptoms/complaints.[1470] There is evidence to support ESS for asymptomatic patients given decreased hospitalization rates for CF lung transplant patients undergoing ESS.[1471] Outside of the transplant literature, pulmonary outcomes for CF patients are mixed despite improved QoL.[1469,1472] Because of the pooling of maxillary sinus secretions seen in CF patients and the frequent need for revision ESS procedures, emerging literature suggests that a widened/inferiorly-extended maxillary sinus antrostomy surgery may permit improved drainage and larger volume irrigant delivery.[1473]

XII.D. RS Special Considerations: Invasive Fungal Rhinosinusitis

Fungal sinus disease is broadly divided as invasive or noninvasive, with invasive fungal sinus (IFS) disease having subcategories that differ based on the histology, clinical presentation, and prognosis. These include acute invasive fungal rhinosinusitis (AIFS), chronic invasive fungal rhinosinusitis (CIFS), and granulomatous invasive fungal rhinosinusitis (GIFS). Therapy for IFS should include appropriate antifungal therapy, surgical debridement, and reversal of the source of immunosuppression when present. There is a paucity of high-level evidence in the literature regarding treatment and survival of AIFS, CIFS, and GIFS. In 2012 a systematic review of survival outcomes in AIFS was performed on 52 studies that met entry criteria.[1474] All of these were case studies or expert reviews (Level 4 and 5 evidence). A literature review of CIFS and GIFS showed even fewer studies available and was restricted to case reports and case series.

XII.D.1. Invasive Fungal Rhinosinusitis: AIFS

Based on a systematic review of AIFS, the disease is limited to patients with impaired host defenses.[1474] Almost any fungus can cause AIFS, if the immunocompromise and inoculation are great enough, but the most common species in North America are *Aspergillus fumigatus*, *Rhizopus*, or *Mucor*, and less commonly *Fusarium*, *Scedosporium*, *Pseudoallescherii boydi*, and dematiaceous fungi. Usually the fungal species cannot be differentiated histologically, but require culture with sporulation to determine species (this may take as long as 3 months). As with all fungi, prior treatment with antifungal therapy may lead to no growth on subsequent culture, so it is important that if AIFS is suspected that fungal cultures be obtained prior to treatment. Knowledge of the fungal species can direct appropriate antifungal therapy. *Aspergillus* has been shown to be more common in neutropenic patients (80% *Aspergillus*, 20% *Mucor*) whereas *Mucor* is more common in diabetic ketoacidosis (80% *Mucor* and 20% *Aspergillus*).[1475]

In addition to antifungal agents, AIFS is treated with attempts at reversing the cause of immunocompromise and conservative surgical debridement. More than 90% of AIFS originates in the nasal cavity with over 60% originating on the MT. If this area is localized and can be surgically excised, survival is improved.[1476] In a systematic review of all AIFS, survival for all patients was approximately 50%; however, certain subsets of patients were found to have significantly improved prognosis, including diabetic patients, those receiving liposomal amphotericin B, or surgery. Mortality rate directly attributable to AIFS has been reported as low as 11% in neutropenic patients, with the vast majority of patients that reverse their neutropenia resolving the AIFS.[1475] Early detection of disease in at risk populations can significantly reduce morbidity and number of surgeries.[1477] Symptoms common to patients with AIFS include facial swelling (>60%), fever (>60%), and nasal congestion (>50%). Negative prognostic factors include advanced age and intracranial extension. Orbital and intracranial symptoms occur in advanced disease and are more common with mucormycosis than aspergillosis.[1478] Sinus CT scans in early stages of AIFS are similar to viral or bacterial RS, with the important difference of AIFS patients having significant intranasal mucosal thickening primarily involving the septum, nasal floor, and lateral wall, and being commonly unilateral. Bony erosion is a late and ominous finding.[1479,1480]

Aspergillus fumigatus is the most commonly cultured fungus in AIFS in North America, afflicting patients who are universally immunosuppressed (usually from antirejection drugs, leukemia, or chemotherapy). Histologically it appears as a septated fungus with 45-degree branching hyphae. Mucormycosis is less common than other fungal causes of AIFS in North America, but is the main cause of AIFS in diabetics (especially in ketoacidosis) and patients with excessive levels of serum iron (ie, from deferoxamine therapy). With the increase in obesity in India and associated untreated diabetes, mucormycosis has become the most common cause of AIFS in India, with an estimated 65,000 deaths/year and over one-half attributed to the rhinocerebral form.[1481] The term mucormycosis

is used to designate invasive fungal infection from any of the 6 fungal species in the order Mucorales, with *Rhizopus oryzea* being the most commonly pathogenic. Histologically, it is a broad, ribbon-like, rarely septate hyphae that has a great affinity for vascular invasion and is notable for rapid growth on media and rapidly progressive disease. Common physical findings include facial and nasal anesthesia, which may precede other findings by several hours. The enhanced survival in diabetics reflects the ability to reverse the diabetic ketoacidosis more readily than other predisposing conditions.

The successful treatment of AIFS is dependent on recovery of immune competence, whether this be recovery of the neutrophil count in hematologic causes, reduction of immune suppression in transplant patients, or resolution of diabetic ketoacidosis and functional neutropenia. The role of surgery is to remove the grossly involved tissue and to reduce the fungal load until immune competence is achieved and adequate antifungal therapy administered. Regardless of the therapeutic measures employed, the ultimate outcome is most dependent on recovery of the immune system. With this in mind, decisions on the extent of surgical resection should take into account the patient's prognosis for immune recovery.[1475]

XII.D.2. Invasive Fungal Rhinosinusitis: CIFS

CIFS is rare and usually occurs in immunocompetent patients or those with very mild immunologic impairment. Duration of symptoms prior to diagnosis can be months to even years and requires long-term systemic antifungals and multiple surgical debridements. The most common fungus in this uncommon condition in North America is *Aspergillus fumigatus*, although a wide variety of fungi have been reported as causal. Orbital apex syndrome commonly develops in association with the invasion of predominately the ethmoid and sphenoid sinuses. The treatment is systemic culture-directed antifungal therapy, usually via an oral route and repeated surgical debridements.[1482,1483]

XII.D.3. Invasive Fungal Rhinosinusitis: GIFS

GIFS is uncommon in the United States, but is more commonly seen in areas such as the Sudan, Pakistan, Egypt, and India. The initial largest series was reported from the Sudan in the 1960s as an "aspergilloma of the paranasal sinuses and orbit," caused by *Aspergillus flavus*.[1484] This would now be classified as GIFS, and unlike CIFS these patients have no detectible cause of immunocompromise and histologically show a granulomatous reaction to the fungal presence. Common clinical findings are a slow development of unilateral proptosis, anesthesia over the affected area, usually in a V2 distribution, unilateral facial pressure, and nasal congestion.The prognosis and treatment recommendations of CIFS and GIFS are the same: systemic antifungals and conservative surgery. Prognosis is dependent on accessibility to systemic appropriate antifungals and conservative surgical debridement.[1485,1486]

XIII. Knowledge Gaps and Research Opportunities

We have witnessed an explosion of research into RS over the last decade. Although this has led to an improved understanding of the pathophysiology of the disease and the impact of medical and surgical therapies, many knowledge gaps remain. This ICAR:RS document outlines the evidence surrounding RS and demonstrates numerous gaps in our current understanding. Although practitioners are generally successful treating ARS and RARS, treating CRSsNP and CRSwNP remain a struggle. CRS is an inflammatory condition and work in other inflammatory diseases may overlap and be relevant. Consequently, multidisciplinary research and collaboration between disciplines, even if not apparently related, should be encouraged to bring in new perspectives to an old problem. Additionally, there are likely differences between adult and prediatric CRS with regard to all of the knowledge gaps identified in the sections below.

XIII.A. Knowledge Gaps and Research Opportunities: Etiology of CRS

Nearly all of our current research into CRS relies upon patients who present with the disease or upon animal models with genetic knockouts or experimental exposures to mimic the inflammatory patterns present in CRS. In adults, CRS occurs primarily in middle-aged patients. We lack an understanding of what factors—genetic, environmental, or both—lead to the development of CRS in a previously healthy patient. Once CRS develops, there are several disease modifying factors that have been discussed in this ICAR:RS. Research opportunities include:

- Understanding development of CRS in previously healthy patients;
- Impact of host vs environmental factors, causative vs modifying factors; and
- Improved animal models.

XIII.B. Knowledge Gaps and Research Opportunities: Clinical Assessment

Our current diagnosis of CRS requires cardinal nasal symptoms and 1 objective sign of nasal inflammation. These rudimentary diagnostic criteria result in a heterogeneous group of "CRS" patients, making it difficult to investigate etiologies and outcomes. Further refinement has been based upon polyp status and eosinophilia. Although the CRSwNP phenotype can be readily determined using endoscopy, it is impacted by surgical state and medical therapies and has limited correlation to symptom severity. Additionally, there is likely a spectrum of disease from CRSsNP with mucosal edema to development of true nasal polyposis that is not accounted for using crude phenotypic classifications. Further refinements in clinical classification would include biomarkers that correlate with symptoms and better predict treatment response.

Additional improvements in understanding how specific symptoms are affected in various CRS patients are sorely needed. Although nasal-specific symptoms are required for the diagnosis of CRS, there is wide variability in the severity of these symptoms. Similarly, CRS has a significant impact upon cognitive function, depression, sleep, and lower airway function, yet we do not understand how certain host or environmental factors result in specific constellations of rhinologic and nonrhinologic symptoms.

Optimal outcome instruments remain elusive. Many studies use patient reported outcome measures. Although these QoL instruments are valuable, they fail to take into account important variables, such as overall disease control, medication usage, and the economic costs of CRS. A complete understanding of the impact of CRS will require a compilation of these metrics. Areas for further research include:

- Clinical classification that correlates with symptom severity;
- Understanding the cause of specific CRS symptoms;
- Endotyping and biomarkers that correlate with clinical presentation and outcomes; and
- Outcome instruments that account for symptom severity, overall disease control, and economic impact.

XIII.C. Knowledge Gaps and Research Opportunities: Medical Treatment of CRS

Current medical treatment of CRS revolves around anti-inflammatory agents. Systemic steroids are effective, yet side effects limit their prolonged use. This has prompted widespread investigation into topical therapies. An improved understanding of the need for delivery to the paranasal sinuses, rather than simple nasal cavity treatments, has resulted in the use of large-volume delivery and steroid-eluting stents. Although these approaches have achieved success, there are still many limitations, such as the need for daily use of rinses or the cost and possible need for periodic replacement of biodegradable stents. Improved delivery methods that permit targeted, sinus-specific delivery of anti-inflammatory agents with minimal side effects and prolonged duration of efficacy are greatly needed. As with other chronic diseases, compliance with CRS therapy may be an issue and needs to be addressed in future research.

In addition to steroids, a number of novel anti-inflammatory agents show promise, such as monoclonal antibodies against IL-5, IL-4R, or IgE.[1487–1490] Currently most of these are administered systemically with significant cost and potential side effects. However, they might have a place in patients with severe disease not controlled by conventional drug therapy and/or surgical intervention, or comorbid asthma.

Regardless of the anti-inflammatory agent or route of administration, none of our currently available strategies including surgery result in a cure for most patients, especially those with CRSwNP. Long term correction of immune dysfunction would offer the chance of a "cure". Research opportunities include:

- Improved delivery of topical therapies;
- Identifying predictors of response for various medical therapies;
- Therapies that are an alternative or complementary to surgery in recurrent disease; and
- Therapies that "normalize" the immune system, ie, a "cure."

XIII.D. Knowledge Gaps and Research Opportunities: Surgical Treatment of CRS

With the exception of balloon dilation, there have been few changes in sinus surgery instrumentation in the last decade. Balloon dilation has stimulated discussion around instrumentation; however, a more logical debate should revolve around the final desired postoperative cavity, ie, which sinuses to operate upon and how large surgical ostia should be for each particular patient and underlying disease process. Research opportunities include:

- Appropriate medical therapy prior to surgery;
- Predictors of response to surgery; and
- Individualized determination of optimal surgical cavity including Draf/Lothrop procedures.

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APPENDIX

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