

Rostrum

Medical Management Strategies in Acute and Chronic Rhinosinusitis

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Chronic rhinosinusitis, historically, has been considered to be caused by upper airway anatomical abnormalities. However, today that concept has changed, for it is now recognized as an inflammatory disorder of the nasal and sinus mucosa. Acute rhinosinusitis is usually caused by a viral infection, whereas chronic rhinosinusitis is a persistent and heterogeneous inflammatory disorder with increased expression of type 1, 2, or 17 cytokines in the nasal and sinus mucosa, similar to that which occurs in asthma. Exacerbations are caused by aeroallergens in the allergic individual and irritants, pollutants, and viral/bacterial infections in all subjects. It may be categorized by phenotypes, examples of which include chronic rhinosinusitis with nasal polyps or chronic rhinosinusitis without nasal polyps. Defined endotypes are based on underlying pathophysiological mechanisms. Knowledge of chronic rhinosinusitis endotypes will optimize management by employing targeted medical therapies. Understanding that rhinosinusitis is a heterogeneous inflammatory disease has led to the identification of a variety of different predisposing conditions, new medical treatment options, and the concept that rhinosinusitis is primarily a medical problem. © 2020 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;■:■-■)

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A transition in the surgical treatment of chronic rhinosinusitis (CRS) occurred over the last decade of the 20th century, a change from radical sinus surgery, for example, Caldwell-Luc or antral window operations, to functional endoscopic sinus surgery (FESS). This modification of the preferred surgical procedure occurred during the otolaryngology residency of one of the authors (SHC). Some attendings were still conducting radical surgery at that time, whereas younger attendings, familiar with endoscopic surgery techniques, were performing FESS. FESS involves enlarging the natural ostiomeatal complex (OMC) using an endoscope. The natural ciliary function within the sinuses moves mucous secretions toward the OMC.¹ FESS was viewed as

a physiologic correction of the cause of CRS, at the time presumed to be primarily anatomical obstruction. CRS was considered a primarily surgical condition with the thought that FESS would result in long-term resolution.

Now, almost 30 years later, there is another change in the concept of the management of CRS, that is, importance of medical management with new medical treatment options. These options are coupled with a greater understanding of chronic inflammation. Treatment of intraorbital or intracranial complications of rhinosinusitis (RS) still requires surgery. However, these complications are less common due to *Streptococcus pneumoniae* and *Haemophilus influenzae* vaccinations, identification and treatment of underlying predisposing illnesses, methods by which predisposing problems can be avoided and treated, newer and unique medication delivery systems, and introduction of biologic agents. These nonsurgical treatments provide a rationale that RS is primarily a medical disease requiring surgical intervention when medical therapy fails.

DEFINITION OF RHINOSINUSITIS (ACUTE RHINOSINUSITIS, RECURRENT ACUTE RHINOSINUSITIS, AND CHRONIC RHINOSINUSITIS)

Rhinitis and sinusitis occur together in most individuals. Thus, guidelines and expert panel documents use the term RS instead of sinusitis.² RS will be a general term used collectively in this paper to refer to all types of sinusitis, including acute, chronic RS with or without nasal polyps (NP), fungal, and others. However, the general public and most physicians and other health care professionals continue to use the term sinusitis. The European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS 2012)³ defines RS as an inflammatory disease of the nasal and the paranasal sinus mucosa characterized by 2 or more symptoms, one of which is nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip). Other potential symptoms include facial pain/pressure and reduction or loss of smell.³ In addition to 2 or more symptoms, at least one of the 2 objective findings is required. These include: (1) endoscopic evidence of NP or mucopurulent discharge or

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Abbreviations used

ABRS- Acute bacterial rhinosinusitis
AERD- Aspirin-exacerbated respiratory disease
ARS- Acute rhinosinusitis
CRS- Chronic rhinosinusitis
CRSsNP- CRS without NP
CRSwNP- CRS with NP
CT- Computed tomography
ECP- Eosinophilic cationic protein
FDA- Food and Drug Administration
FESS- Functional endoscopic sinus surgery
INCS- Intranasal corticosteroid
NERD- NSAID-exacerbated respiratory disease
NP- Nasal polyps
NSAID- Nonsteroidal anti-inflammatory drug
OMC- Ostiomeatal complex
RARS- Recurrent acute rhinosinusitis
RS- Rhinosinusitis
URI- Upper respiratory infection

edema/mucosal obstruction primarily in the middle meatus; (2) computed tomographic (CT) radiographic imaging demonstration of mucosal changes (ie, edema) in the OMC or sinuses. The diagnosis of CRS is established if these symptoms and objective findings persist longer than 12 consecutive weeks without a symptom-free period.

CRS is a heterogeneous disease with different underlying pathophysiologic mechanisms. The primary mechanism is inflammation rather than infection, although exacerbations are often associated with infection. Acute rhinosinusitis (ARS) is caused by microorganisms, primarily viruses, with 0.5% to 2.0% of subjects developing acute bacterial rhinosinusitis (ABRS) after such an infection.⁴⁻⁶ Thus, the initial therapy of ARS should not be an antibiotic. Recurrent, acute rhinosinusitis (RARS) can be confused with CRS. However, it has symptom-free periods with exacerbations more than 4 to 6 times a year, rather than persistent symptoms over 12 weeks' characteristic of CRS. Predisposing factors, such as allergic and nonallergic rhinitis, anatomical abnormalities, primary and secondary immunodeficiency diseases, and mucosal abnormalities, should be considered for RARS. Predisposing conditions for infections may be less likely with CRS, in contrast to RARS, as CRS is a chronic, inflammatory condition rather than a recurrent or chronic infection.

ARS is the symptomatic inflammation of the paranasal sinuses and nasal cavity lasting less than 4 weeks. Some experts suggest that the term subacute RS be used if symptoms continue longer than 4 weeks but less than 12 weeks.² Although viruses, bacteria, and fungi can cause this disease, the majority are due to viral upper respiratory infections (URIs) of the nasal cavity and paranasal sinuses. A viral ARS presents clinically and radiographically similar to ABRS but is time limited. Sinus CT scans of more than 75% of subjects with viral URIs show opacification of the infundibulum or OMC.⁷ Approximately 80% of individuals with these radiographic findings normalize within 2 weeks without treatment. These data demonstrate that only a limited number of ARS cases will benefit from antibiotic treatment and that sinus imaging is not useful unless serious complications, such as the intraorbital or intracranial extension of the infection, are suspected. The 2012 Infectious Diseases Society of America guidelines for ARS

recommend empiric antibiotic therapy⁸ if: (1) unremitting symptoms or signs compatible with ARS persist for more than 10 days; (2) severe symptoms, high fever (39°C [102°F]), purulent nasal discharge, or facial pain, occur for at least 3 to 4 consecutive days at the beginning of the illness; or (3) fever, headache, or nasal discharge develop after improvement of a typical viral URI ("double-sickening"). The guidelines recommend amoxicillin-clavulanate versus amoxicillin for penicillin-tolerant individuals with weak evidence in adults and strong evidence in children, the latter based on the greater prevalence of beta-lactamase producing organisms. The guidelines also recommend high-dose oral amoxicillin-clavulanate (2 g twice daily in adults) for subjects in an area with high endemic rates (10% or greater) of invasive, penicillin-non-susceptible *S. pneumoniae* and with severe infection, defined as fever (39°C [102°F]), suspected intracranial complications, age above 65 years, recent hospitalization, prior antibiotic use within 1 month, or primary/secondary immunodeficiency. Doxycycline or fluoroquinolones (levofloxacin or moxifloxacin) are recommended for adults with a history of penicillin/beta-lactam allergy, whereas third-generation cephalosporins or clindamycin is recommended for children with beta-lactam allergy. If there is no significant response to appropriate antibiotic treatment, sinus culture via rhinoscopy is indicated to possibly isolate the offending organism and identify optimal antibiotic sensitivity. Intranasal corticosteroid (INCS) treatment is recommended for ARS and ABRS to improve sinus drainage and prevent secondary or complicated bacterial infection.³ An oral corticosteroid, as adjunctive therapy, can be effective for short-term relief of ABRS symptoms. Saline irrigation can also be helpful to treat ARS and ABRS.³

As previously stated, surgical intervention is indicated for intraorbital or intracranial complications. These serious complications have decreased significantly because of the introduction of *S. pneumoniae* and *H. influenzae* vaccinations, better recognition and treatment of predisposing factors, and more effective antibiotics.

UNDERSTANDING PHENOTYPES AND ENDOTYPES TO IMPROVE TREATMENT OF CHRONIC RHINOSINUSITIS

CRS can be divided into phenotypes based on clinical characteristics or traits, for example, CRS without NP (CRSsNP) and CRS with NP (CRSwNP). Endotypes, in contrast to phenotypes, are biologic subtypes that are defined by pathophysiologic mechanisms. Biological markers, such as tissue eosinophils, IL-5, IL-13, eosinophilic cationic protein (ECP), periostin, and IgE, are helpful to identify endotypes. Likewise, gene variances, such as in the bitter taste receptor, cystic fibrosis transmembrane conductance regulator, or IL-4 promoter, indicate that CRS is a complex, heterogeneous group of diseases with different underlying pathophysiologic mechanisms. Identifying CRS endotypes will enhance the efficacy of targeted biological treatments. Therefore, because of its heterogeneity, optimal CRS medical management ultimately will not rely solely on phenotypes. For example, geographical and racial differences in cytokine profiles occur in subjects with CRS from different regions of the world and various ethnicities.⁹ Europeans show a high proportion of IL-5-positive NPs. However, Chinese subjects with NPs are much less likely to be IL-5 positive. Even within China, there are significant differences in CRS cytokine profiles.

It was previously thought that CRSwNP is eosinophilic and CRSsNP neutrophilic. However, more than 50% of CRSsNP subjects may have eosinophilic inflammation as indicated by the presence of Charcot-Leyden crystals and eosinophil cationic protein.¹⁰ These observations suggest that biologic agents that target eosinophilic inflammation and the T2 pathway may be effective for some CRSsNP. Biomarkers to endotype CRS are necessary for optimal use of specific biologic therapy. Peripheral blood eosinophils are a reasonably reliable, although not ideal, biomarker for asthma endotypes. However, blood eosinophils and other blood biomarkers fail to reflect T2 inflammation in CRS. For example, there are no significant differences in treatment outcomes between high and low blood eosinophil groups in a phase II clinical trial of mepolizumab (anti-IL-5) for CRSwNP.¹¹ IL-5 levels in nasal secretions did predict treatment response in a smaller reslizumab trial that needs confirmation.¹²

PROPER USE OF RHINOSCOPY AND IMAGING

A fiberoptic rhinoscopic examination is essential to diagnose the CRS phenotype before initiating medical treatment. Anterior rhinoscopy only visualizes the anterior one-third of the nasal cavity and is inadequate to visualize the posterior nasal cavity and nasopharynx. Rhinoscopy is a simple, low-risk, cost-effective procedure that should be performed routinely in subjects with persistent upper airway problems. Just as office spirometry is a routine procedure to assist in the diagnosis of airflow obstruction, so too should rhinoscopy be used regularly for RS. The primary objective outcome of phase III clinical trials of dupilumab and phase II clinical trials of other biologic agents is based on the NP scores as determined by rhinoscopy.^{13,14} Rhinoscopy is also important to identify other abnormalities of the nasal cavity, pharynx, and larynx. These abnormalities may include enlarged adenoids, often associated with sleep apnea in children, clinically relevant nasal septal deviation, laryngopharyngeal acid reflux, and upper airway malignancy. Rhinoscopy may also be useful to isolate offending organisms in RS by endoscopy-guided culture.

A CT scan of the paranasal sinuses may also be obtained to assess potential reasons for lack of symptomatic improvement, anatomical abnormalities, the likelihood of fungal sinusitis, and potential complications. Although a sinus CT can detect unusual structural alterations, such as a concha bullosa, Haller cell, or a paradoxical middle turbinate (lateral convexity), these structural alterations are usually not the cause of RS. There is a concern for the overuse of CT scans as a source of radiation exposure and increased cancer risk in all age groups.¹² Two or three conventional CT scans result in radiation doses in the range of 30 to 90 mSv, and such imaging is sometimes ordered for pre- and postsurgical evaluation, even in children.¹⁵ Many institutions now use cone beam CT scanners with lower radiation exposure. An additional concern is that CT scans are commonly misinterpreted. For example, a CT scan report may state, "Mucosal thickening in the maxillary sinuses and OMC opacification consistent with CRS." This may automatically trigger a physician to conclude that the patient has CRS, not understanding that both viral and bacterial ARS, a benign mucous retention cyst, or other reasons can account for these findings.

OPTIMAL USE OF LOCAL AND SYSTEMIC GLUCOCORTICOSTEROIDS

The treatment options for CRS are summarized in Table I. INCS are an effective treatment for RS but are limited in their efficacy by inconsistent nasal distribution, especially in the presence of severe nasomucosal edema or large NPs. Conventional nasal sprays deliver less than 5% of metered INCS into the middle meatus, the critical area of the nose for drainage of the maxillary, anterior ethmoid, and frontal sinuses. Several different delivery strategies, such as nebulization or irrigation, are used to overcome this maldistribution. For example, an appropriately powered randomized clinical trial of topical budesonide saline irrigation versus INCS nasal sprays shows no difference in outcome for the patient-based quality of life score or objective (endoscopy and CT scores) assessments.⁴⁴ However, a 2019 Food and Drug Administration (FDA)-approved device for intranasal fluticasone, which is breath-assisted, is now indicated for the treatment of NP (Xhance; Optinose, Yardley, Pa). It significantly reduces NP size by improving the delivery of the CS into the OMC.^{16,29} Ideally, a study including a conventional INCS spray treatment group to directly compare both treatments would enhance confidence in the results of this study. Xhance is not approved to treat CRSsNP. However, ongoing phase III clinical trials are in progress for this phenotype.

Another new device is the mometasone drug-eluting stent (Sinuva; Intersect ENT, Menlo Park, Calif) that can be inserted in an outpatient setting. This is FDA approved for recurrent NP.³⁰ It slowly releases mometasone over a 3-month period but ultimately has to be removed. Some subjects cannot tolerate the device due to increased nasal crusting, mucus production, and a perceived bad odor. A similar CS eluting stent (Propel; Intersect ENT) is also FDA approved and can be used after surgical polypectomy and ethmoidectomy. Propel is not approved for outpatient use. Studies of increased CS delivery into the upper airway require long-term follow-up to assess whether there are significantly more systemic or local side effects. However, the side effects of enhanced topical nasal versus systemic CS, a treatment commonly used for CRS, should be less.

Long-term topical decongestants combined with INCS for CRS is another treatment modality that requires an additional study. Nasal congestion is usually the most bothersome symptom with any upper airway disease. Two studies indicate that several weeks of continuous topical oxymetazoline does not cause "rebound phenomenon" when concomitantly used with INCS.^{31,32} Topical decongestants may enhance the delivery of INCS in the presence of nasal mucosal edema and improve the quality of life and sleep. Oral CS, used for 3 to 7 days, is another option to reduce severe mucosal edema and large NP and enhance subsequent INCS efficacy.

LONG-TERM ANTIBIOTICS AND ASPIRIN DESENSITIZATION

Appropriate antibiotics are an effective treatment for some subjects with acute exacerbation of CRS. However, there is no evidence for the optimal duration of therapy. Most clinicians use them for 7 days to 4 weeks. It makes sense to continue the antibiotics as long as the patient is improving or until they are asymptomatic, that is, have no mucopurulent discharge. The antibiotic of choice is a beta-lactam, or if beta-lactam allergic,

TABLE I. Treatment options for chronic rhinosinusitis

Treatment options	Key points	References
Evidence-based initial treatments for CRS		
Topical corticosteroids	Educate in use (avoid directing spray toward septum)	Djupestrand ¹⁶
		Mastalerz et al ¹⁷
		Holmberg et al ¹⁸
		Tos et al ¹⁹
		Lund et al ²⁰
Saline irrigation	High volume (>200 mL) irrigation	Harvey et al ²¹
		Friedman et al ²²
		Liang et al ²³
Short-term oral antibiotics	1-4 wk	Gehanno and Cohen ²⁴
		Namyslowski et al ²⁵
Systemic corticosteroids	During acute exacerbation or for severe edema to improve topical corticosteroid delivery	Krofflic et al ²⁶
		Van Zele et al ²⁷
		Hissaria et al ²⁸
Evidence-based treatments for refractory CRS		
Topical corticosteroids with novel delivery systems*	Xhance (Exhalation drug delivery system: fluticasone propionate)	Leopold et al ²⁹
	Sinuva (mometasone eluted stent)	Han and Kern ³⁰
Topical corticosteroids with topical decongestant†	Concomitant use of topical decongestants with topical corticosteroids reduces the risk of rhinitis medicamentosa	Rael et al ³¹
		Thongngarm et al ³²
Aspirin desensitization therapy*	Confirmed AERD or NERD patients	Laidlaw ³³
	Aspirin sensitivity not confirmed by graded challenge will not likely benefit	Berges-Gimeno et al ³⁴
Long-term antibiotics†	Macrolides, doxycycline	Wallwork et al ³⁵
	Longer than 3 mo	Varvyanskaya and Lopatin ³⁶
		Pinto Bezerra Soter et al ³⁷
Biologic agents*	Dupilumab—FDA approved	Bachert et al ¹¹
	Omalizumab, mepolizumab: results of the phase III clinical trials are pending	Gevaert et al ¹²
	Rhinoscopic scoring of nasal polyps important to monitor response	Bachert et al ¹³
		Bachert et al ¹⁴
		Gevaert et al ³⁸
Treatments with limited evidence for CRS		
Topical or oral antihistamines	CRS patients with allergic rhinitis and other types of rhinitis	Sylvester et al ³⁹
Leukotriene modifiers	May be of value in AERD/NERD or in allergic disease	Wentzel et al ⁴⁰
Topical antibiotics	Some ENT surgeons use after functional endoscopic sinus surgery	Videler et al ⁴¹
Mucolytics	Subjects with postnasal drip	Kaszuba and Stewart ⁴²
Allergy immunotherapy	Allergen immunotherapy may benefit for CRS patients with allergy. Possible benefit in AFRS	Gan et al ⁴³

AERD, Aspirin-exacerbated respiratory disease; AFRS, allergic fungal rhinosinusitis; CRS, chronic rhinosinusitis; ENT, ear, nose, and throat; FDA, Food and Drug Administration; NERD, nonsteroidal anti-inflammatory drug–exacerbated respiratory disease; NP, nasal polyps.

*For CRS with NP alone.

†Both for CRS with NP and CRS without NP.

doxycycline or fluoroquinolones. Culturing nasal secretions has a low yield, whereas visual observation via rhinoscopy-guided collection of mucopurulent, sinus discharge may better confirm the diagnosis and identify the causative organism(s) and sensitivities.

Randomized, double-blind controlled trials of long-term antibiotic therapy (up to 12 weeks) with a macrolide or

doxycycline for CRSwNP suggest efficacy.³⁵⁻³⁷ Macrolide therapy is based on the combined antimicrobial and anti-inflammatory properties of macrolides.⁴⁵⁻⁴⁷ A study of macrolide therapy in CRSsNP suggests a better response in subjects with normal versus high IgE. This suggests that CRSsNP with type 1 (Th1) or type 17 (Th17) endotypes (not type 2) may benefit more from prolonged macrolide therapy.

Long-term studies with a larger study population of these 2 phenotypes of CRS are necessary. Antibiotic resistance and hearing loss are potential complications of long-term macrolide therapy. Twenty days of oral doxycycline reduces the size of NPs and nasal secretion concentration of myeloperoxidase, ECP, and matrix metalloproteinase-9.²⁷ The clinical benefit of doxycycline was detected 12 weeks after therapy, suggesting a modulation of the underlying inflammatory disease.

Another important treatment option for refractory CRSwNP with aspirin or nonsteroidal anti-inflammatory drug (NSAID) hypersensitivity is aspirin desensitization followed by high-dose daily ASA. Aspirin-exacerbated respiratory disease (AERD) or NSAID-exacerbated respiratory disease (NERD) is characterized by CRSwNP, asthma, and respiratory signs and symptoms induced by aspirin and other NSAIDs that inhibit the cyclooxygenase-1 enzyme. It has a prevalence of approximately 30% of subjects with both asthma and CRSwNP.³³ The diagnosis is often missed because the respiratory reactions may not occur immediately but be delayed 1 to 3 hours after NSAID ingestion. An accurate AERD/NERD diagnosis is critical to ensure patient safety, that is, to avoid all cyclooxygenase-1-inhibiting NSAIDs and to potentially enable disease-specific treatment, aspirin desensitization therapy. Oral aspirin challenge is the gold standard to diagnose AERD. However, a clear history of adult-onset asthma, NP, and 2 or more NSAID-induced respiratory reactions are sufficient to establish the diagnosis. Aspirin desensitization and therapy are an important treatment option for recurrent/refractory NP in subjects with AERD. High-dose ASA, 325 to 1300 mg per day, after desensitization can reduce the size and recurrence of NP and the need for sinus surgery and systemic CS.^{33,34}

ROLE OF BIOLOGIC AGENTS IN CHRONIC RHINOSINUSITIS

There are various clinical trials using omalizumab (anti-IgE),³⁸ reslizumab (anti-IL-5),¹² mepolizumab (anti-IL-5),¹¹ and dupilumab (anti-IL-4R α)¹⁴ to treat CRSwNP. Dupilumab became the first FDA-approved biologic agent for CRSwNP in 2019. Its approval is based on 2 international phase III randomized, double-blind, placebo-controlled, multicenter clinical trials of subjects ≥ 18 years with CRSwNP.¹³ The addition of subcutaneous dupilumab every 2 or every 4 weeks for 24 or 52 weeks to INCS compared with INCS alone significantly reduced the nasal polyp score, nasal congestion, and the Lund-Mackay CT scores and improved the sense of smell. All clinical parameters improved significantly after 4 weeks of therapy. Lung function in subjects with asthma also improved, as previously demonstrated in dupilumab asthma trials. The most common side effects include injection site reactions, nasopharyngitis, and headache.

The subjects included in these studies had refractory CRSwNP. More than 63% had more than 1 and 15% more than 3 prior sinus surgeries. The sense of smell, an important quality of life issue, significantly improved within 4 weeks of treatment. Studies also suggest that dupilumab may be initiated with FDA-approved every 2 weeks' dosing and then switched to every 4 weeks, depending on symptom improvement and on the decrease in NP size monitored with rhinoscopy. It may even be possible to increase the injection interval to greater than 4 weeks, mitigating additional cost. Surgical therapy versus dupilumab

may be preferred by some patients because of the cost of long-term dupilumab, but the risk benefit of these 2 options must be considered. Dupilumab is a good option for CRS subjects with recurrent NP who are not surgical candidates or do not improve with surgery.

ADDITIONAL THERAPIES

There is little or no evidence to support the use of oral or intranasal antihistamines, sodium cromolyn, mucolytics, leukotriene modifiers, or allergen immunotherapy to treat CRS or prevent it. In addition, there is no good evidence to support the use of topical antibiotics. The absence of evidence does not necessarily prove lack of benefit, but these therapies cannot be recommended based on evidence-based medicine.

CONCLUSIONS

CRS is an inflammatory disease with multiple phenotypes. Type 2 inflammation is frequently involved in CRS, as with asthma and atopic dermatitis. Its diagnosis is primarily made by a detailed history and physical, laboratory studies, fiberoptic rhinoscopy, and imaging. After a detailed history and physical examination, rhinoscopy is an essential procedure to diagnose and manage RS. Therefore, it is an important skill for physicians, including allergists and immunologists, who care for patients with these diseases. Treatment includes diagnosing and optimally treating predisposing conditions and the appropriate use of antibiotics, topical INCS, sinus irrigation, and effective biologic agents. When complications occur or medical management fails, surgery should be considered. Likewise, diseases that predispose to CRS, such as abnormalities in mucociliary function, cystic fibrosis, and immunodeficiency, should be considered. Better identification of endotypes is forthcoming and will result in more specific targeted therapies.

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