

Chronic Rhinosinusitis and Aspirin-Exacerbated Respiratory Disease



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KEYWORDS

- Aspirin-exacerbated respiratory disease • Asthma • Chronic rhinosinusitis
- Chronic sinusitis • Nasal polyps

KEY POINTS

- Patients with concomitant chronic rhinosinusitis and asthma often have more severe disease that is difficult to control with standard pharmacotherapy.
- Treatment must focus on treating both the upper and lower airway inflammation because an insult in one area often leads to subsequent inflammation in the other.
- A subset of patients have aspirin-exacerbated respiratory disease (AERD) characterized by asthma, chronic rhinosinusitis with nasal polyposis, and intolerance of COX-1 inhibitors.
- In addition to standard anti-inflammatory therapy, patients with AERD often require an aspirin desensitization followed by long-term aspirin therapy to manage their disease.
- Recognizing the presence of chronic rhinosinusitis in patients with severe asthma allows for management of the upper and lower respiratory tracts and improved disease control.

INTRODUCTION

A large percentage of patients with severe asthma have concomitant chronic rhinosinusitis (CRS), which represents a distinct group of patients with severe, often refractory upper and lower airway inflammation.^{1,2} Such patients frequently have similar inflammatory mediators throughout the upper and lower airways as described by the unified airway concept. CRS is a broad clinical syndrome defined by persistent mucosal inflammation of the nasal and paranasal cavities and can impact asthma control.³ This article discusses definitions, phenotypes, evaluation, and treatment of CRS.

DEFINITIONS

The terminology for rhinosinusitis is variable and often classified by duration (**Table 1**).^{4,5} CRS is a heterogeneous disease with complex pathophysiology and is

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Table 1 Rhinosinusitis classifications	
Classification	Duration
Acute rhinosinusitis	Rhinosinusitis symptoms lasting <4 wk
Subacute rhinosinusitis	Rhinosinusitis symptoms lasting 4–12 wk
Chronic rhinosinusitis	Rhinosinusitis symptoms lasting >12 wk
Acute bacterial rhinosinusitis	Acute sinusitis with bacterial etiology
Viral rhinosinusitis	Acute sinusitis with viral etiology
Recurrent acute rhinosinusitis	4 or more annual episodes of rhinosinusitis without persistent inflammation in between

often simplified into patients with or without nasal polyps (CRSwNP; CRSsNP). CRSwNP is further subdivided into those who do not tolerate aspirin or other cyclooxygenase (COX)-1 inhibitors, termed aspirin-exacerbated respiratory disease (AERD). AERD was previously termed Samter triad and is often referred to as aspirin-sensitive rather than aspirin-tolerant asthma.

UNIFIED AIRWAY HYPOTHESIS

The unified airway hypothesis is a concept that closely links the upper airways, including the middle ear, nose, paranasal sinuses, and the entire lower airway as one functional, interconnected group with shared inflammatory features.^{6,7} Prior studies have shown that 78% of patients with asthma have nasal symptoms⁸ and up to greater than 84% of sinus computed tomography (CT) scans were abnormal in patients with severe asthma.² The prevalence of asthma in CRS ranges from 45% to 65% in patients with CRSwNP and 18% in CRSsNP. One study found that 94% of patients with CRS had asthma with 88% having severe persistent disease.^{9–11}

Patients with CRS and asthma often have severe respiratory disease requiring more aggressive management.¹² Such patients have been found to have lower quality of life measures, higher rhinosinusitis severity scores, and poor outcomes after functional endoscopic sinus surgery compared with the nonasthmatic group.^{13,14} Moreover, when CRS is treated (medically or surgically), asthma symptoms improve and the need for asthma-related medications decreases.^{12,15,16}

CRS had been found to have similar airway remodeling as the bronchial mucosa in patients with asthma with nearly indistinguishable microscopic findings including mucosal edema, submucosal gland and bronchial smooth muscle hypertrophy, collagen deposition, basement membrane thickening, and subepithelial fibrosis in the lamina reticularis.¹⁷ However, Chanez and colleagues¹⁸ showed that the extent of eosinophilic inflammation, reticular basement membrane thickness, and percent of the epithelium shedding is greater in bronchial than nasal mucosa of patients with asthma with perennial rhinitis. Several studies have shown that antigens placed in the nose up-regulate inflammatory cells, primarily eosinophils, and their mediators in the distal bronchi. Similarly, antigen placement into the bronchi with a bronchoscope results in upregulation of inflammatory mediators in the nose, suggesting that stimulation can occur anywhere within the unified airway.^{19,20} Corren and colleagues²¹ found that nasal provocation with allergen delivery to the nose led to a significant increase in bronchial hyperresponsiveness compared with placebo, but there were no changes in forced expiratory volume in 1 second (FEV₁). Generally, it seems that either

challenging or treating the upper airway effects bronchial hyperactivity but does not truly impact lung function as measured by FEV₁.

PATHOPHYSIOLOGY

CRS is no longer considered primarily an infectious disease but rather a disease of endogenously driven inflammation.²² CSwNP is a distinct phenotype with a Th2 cytokine signature similar to eosinophilic/allergic asthma with robust expression of interleukin (IL)-4, IL-5, and IL-13. White patients with nasal polyps usually have high levels of tissue eosinophils, neutrophils, mast cells, and B cells. Epithelial cytokines TSLP²³ and IL-33²⁴ have been implicated in driving Th2 inflammation by directly activating innate lymphocyte cells-2, which release substantial amounts of IL-5 and IL-13. Conversely, Asian patients with nasal polyps have a more variable pattern of tissue infiltration and cytokine expression with more neutrophils, fewer eosinophils, and a Th1/Th17 pattern with elevated interferon (IFN)- γ , IL-6, IL-1 β , and IL-17.^{25,26} The pathophysiology of CRSsNP is thought to be driven by a breakdown of innate immunity leading to frequent recurrent episodes of acute sinusitis, bacterial colonization, and biofilm formation.²⁷

ALLERGIC FUNGAL RHINOSINUSITIS

It was previously believed that nearly all cases of CRS were driven by response to common airborne fungal elements.²⁸ Fungal elements, specifically *Alternaria*, were thought to stimulate peripheral blood mononuclear cells and lead to the release of Th1 and Th2 cytokines, including IFN- γ , IL-4, IL-5, and IL-13. It was thought that these sensitized T cells activated eosinophils and led to degranulation with subsequent tissue damage causing the symptoms of CRS.²⁹ Since then, this hypothesis has become more controversial. First, eosinophils are not generally important cells types in host defense against fungi. Second, attempts at replicating the sensitization of peripheral blood mononuclear cells to fungal antigens have failed.^{30,31} Most importantly, although smaller studies have shown some improvement in nasal polyps with topical antifungals,³² double-blind placebo-controlled trials have failed to show efficacy of antifungal therapy modifying the disease process.^{33,34} Now, fungi are no longer viewed as the primary cause of the development of all CRS, but some investigators suspect fungi play a role in a subgroup of patients with CRS.

BACTERIA IN CHRONIC RHINOSINUSITIS

Although the microbiome of the sinonasal tract remains poorly characterized, there are several theories regarding the proposed role of bacteria in CRS.³ The superantigen hypothesis suggests exotoxins from *Staphylococcus* bacteria behave as superantigens amplifying local inflammatory responses fostering polyp formation.^{35,36} Patients with CRSwNP have been shown to carry *Staphylococcus aureus* in a high percent of patients.³⁷ It is not clear whether superantigens from these bacteria are causative but they may accentuate the pre-existing inflammatory response in these tissues.³ The biofilm hypothesis describes bacterial biofilms that have been found in 42% to 75% of patients with CRS with or without nasal polyps.^{38,39} Biofilms form a highly organized protective extracellular matrix that allows bacteria to evade host defenses and conventional antibiotics. However, there is no direct evidence to suggest that biofilms play a role in the initial establishment of CRS.⁴⁰ Although Tatar and colleagues⁴¹ found regression of biofilms in patients treatment with oral macrolides for 2 weeks, Videler and colleagues⁴² found a lack of efficacy of low-dose azithromycin in patients with

CRS treated for 3 months with regards to symptom scores, nasal endoscopic findings, peak nasal inspiratory flow, and microbiology.

ATOPY

Allergic rhinitis often precedes the development of asthma and has been shown to worsen asthma control.^{8,43,44} However, severity of CRS by clinical and radiographic parameters has not been found to demonstrate significant correlations with atopic status.⁴⁵ AR is thought to be a superimposed factor rather than a causative factor in CRS that contributes to the overall inflammatory burden seen in CRS.⁴⁶ There are limited data with poor evidence to support that allergen avoidance or immunotherapy improves CRS, but rather treatment of AR along with aggressive therapy for the underlying eosinophilic inflammation is necessary.^{46–48} Allergy testing via skin prick testing or allergen-specific immunoassays to detect IgE-specific antibody may be helpful in patients with seasonal exacerbations of rhinitis or asthma, but is not routinely necessary in all patients with CRS.

ASPIRIN-EXACERBATED RESPIRATORY DISEASE

Patients with AERD (**Box 1**) have greater morbidity than patients with aspirin-tolerant asthma with more emergency department visits, hospitalizations, and corticosteroid bursts.⁵⁴ Patients often suffer hyposmia or anosmia, which correlates strongly with the diagnosis.⁵⁵ The authors have previously reported that CRSwNP patients with AERD had more severe sinus CT scores, more sinus surgeries, and prednisone use than aspirin-tolerant individuals.¹⁰ Berges-Gimeno and colleagues⁵¹ studied 300 patients with AERD and showed that nearly all (94%) had either complete sinus opacification or mucoperiosteal thickening on radiography. Patients with asthma often have an increased dependency on systemic corticosteroids and a higher frequency of severe exacerbations and reduced lung function.⁵⁴

The exact mechanism of AERD is uncertain but is characterized by eosinophilic infiltration with abnormal arachidonic acid metabolism.⁵⁶ Most patients with AERD are not atopic suggesting that the pathogenesis is independent of atopy.⁵⁰ Both the respiratory tract and polypoid tissue from patients with AERD have shown eosinophilic infiltration and activation with the presence of eosinophilic granule contents, cysteinyl leukotrienes (cysLTs), IL-5, eotaxin, RANTES, and IFN- γ .^{56,57} In addition to these

Box 1 AERD Facts

- AERD is manifested by adult-onset asthma, CRSwNP, and intolerance of COX-1 inhibitors.
- Patients usually present in the third or fourth decade of life.
- Estimate of AERD prevalence from 2014 meta-analysis: 7% of patients with asthma have AERD and twice as many patients with severe asthma have it.
- COX-inhibitor sensitivity can develop in any stage of the disease as AERD evolves over time. Commonly begins with rhinitis initially. One study showed asthma appeared 2 years after onset of rhinitis on average, with intolerance to COX-1 inhibitors and nasal polyposis 4 years after.
- Ingestion of COX-1 inhibitors is usually dose-dependent and leads to an exacerbation of underlying rhinosinusitis and asthma with nasal congestion, conjunctivitis, rhinorrhea, laryngospasm, and/or bronchoconstriction within 30 minutes to 3 hours.

Data from Refs.^{49–53}

cytokines the authors have shown that aspirin desensitization in this cohort decreases sputum IL-4 levels, which in part regulates the cysteinyl leukotriene expression.⁵⁷ Therefore, the increase in proinflammatory cysLTs, such as LTC₄, LTD₄, and LTE₄ and their receptors, may be a consequence of the rich TH2 environment consisting of IL-4, IL-5, and IL-13. Additionally, there is a decrease in regulatory prostaglandins, such as prostaglandin E₂ and its receptors, in sinonasal passages of patients with AERD.^{58,59}

In patients with AERD, CRS and asthma are severe and relatively refractory to pharmacotherapy.⁶⁰ Nasal polyps in patients with AERD tend to require surgical treatment and have high rates of recurrence after surgery compared with patients with CRSwNP who tolerate aspirin.^{60,61} Inflammation progresses despite avoidance of COX-1 inhibitors and often aspirin desensitization is warranted for added therapeutic benefit. Patients with AERD should be managed with topical therapies, such as nasal saline rinses and off-label use of topical steroids. For patients who fail medical therapy, surgical intervention may be indicated. Unfortunately, patients with AERD respond less well to surgery than aspirin-tolerant patients and often require multiple procedures.⁶² McMains and Kountakis⁶³ reported that up to 80% of patients with AERD who had not undergone aspirin desensitization required an additional sinus surgery within 24 months of their last surgery. Despite surgical intervention, medical treatment with topical nasal steroids is necessary following surgery. Moreover, aspirin desensitization followed by continuous aspirin therapy has been shown to improve quality of life, nasal, and asthma symptoms scores. It also reduces the frequency of polyp formation, sinus infections, and need for systemic corticosteroids 6 and 12 months after therapy.^{64–66}

EVALUATION AND TREATMENT

Accurate diagnosis of CRS not only requires a thorough history, but also confirmation of sinonasal mucosal inflammation, such as polyps, mucosal edema, or purulent mucus.^{67,68} Symptoms of CRS most commonly include nasal obstruction (81%–95%), facial congestion, pressure or fullness (70%–85%), discolored nasal discharge (51%–83%), and hyposmia (61%–69%). Two or more of these symptoms is highly sensitive for diagnosing CRS but symptoms alone are fairly nonspecific.^{67,69,70} Several studies have shown that greater olfactory dysfunction indicates greater sinonasal disease, correlates with the degree of inflammation in patients with polyps, and is predictive of radiographic sinus scores.^{67,71} Loss of smell was found to be the sole predictor of persistent mucosal inflammation after sinus surgery.⁷²

Imaging

CT and MRI can be used to confirm the diagnosis of CRS, but based on the increased cost and possible overdiagnosis, CT scan without contrast is preferred.⁵ CT scanning allows for the ability to quantify the extent of disease based on opacification of paranasal sinuses,⁷³ monitor disease progression, and provide anatomic detail necessary to guide potential surgery,⁷⁴ but it does not necessarily correlate with symptom severity.⁷⁵ Ten Brinke and colleagues² found that patients with more extensive sinus disease on CT scans were more likely to have evidence of airway inflammation based on peripheral and sputum eosinophilia and elevated exhaled nitric oxide. Patients had more severe CT sinus scores were more likely to have aspirin sensitivity but CT scores did not correlate with nasal symptoms, asthma control, or FEV₁. CT scanning is also helpful in excluding aggressive infection or neoplastic disease that could mimic CRS. If such findings are noted, follow-up MRI should be performed.⁷⁴

Corticosteroids

Topical corticosteroids are widely recommended in the treatment of CRS,⁷⁶ and their efficacy at reducing nasal symptoms has been supported by multiple systematic reviews but some subgroup analyses have shown more benefit in patients with polyps rather than those without.^{77–80} Ragab and colleagues¹² found that treating with an oral macrolide, nasal irrigation, and topical steroids resulted in significant improvement in asthma symptom scores, increased FEV₁, reduced need for bronchodilators, and systemic steroids with decreased hospitalizations. However, when evaluating nasal steroids alone, a meta-analysis by Lohia and colleagues⁸¹ showed nasal steroids improved FEV₁, asthma symptom scores, and rescue medication use compared with placebo, but in patients already on orally inhaled corticosteroids, the addition of intranasal steroids did not lead to any specific changes in clinical asthma outcomes.

A short course of oral corticosteroids has been shown to shrink polyp size and improve nasal symptoms and nasal flow.^{82,83} Oral corticosteroids can be used as a bridge to surgery or in severe cases of CRSwNP that are refractory to topical therapy. However, the latter is preferred because of less adverse systemic effects. Aukema and colleagues⁸⁴ found that fluticasone nasal drops reduced the need for surgery in patients with CRS compared with placebo and hypothesized that nasal drops allow for better delivery into the middle meatus than nasal sprays. Long-term treatment with budesonide saline irrigation for at least 12 weeks has been reported to maintain improvement in nasal symptoms, polyp size, and nasal flow in those first treated with oral corticosteroids.⁸⁵ Jang and colleagues⁸⁶ evaluated postoperative patients who used budesonide saline irrigation versus those who did not and found lower CRS symptom scores and improved endoscopy findings in the treatment group.

Antibiotics

There is no clear evidence that oral antibiotics are beneficial in CRS. Unnecessary prescription of antibiotics can lead to unwanted side effects, increased health care costs, and induce antimicrobial resistance. Patients with CRS may have occasional episodes of acute bacterial sinusitis, which may require oral antibiotics. Acute bacterial rhinosinusitis must be recognized and treated because it can lead to serious complications including meningitis, brain abscess, orbital cellulitis, and orbital abscess.^{87,88} For CRSwNP, chronic topical or intravenous antibiotics are not recommended but select oral antibiotics, especially macrolides, have shown some benefit based on their anti-inflammatory effects.^{46,89}

Leukotriene Modifiers

Elevated cysLT concentrations in patients with CRSwNP suggest that leukotriene modifiers would have clinical benefit.⁹⁰ Leukotriene modifiers have shown benefit in upper airway disease with improvement in nasal congestion and hyposmia.⁹¹ Furthermore, in a systematic review, Rix and colleagues¹¹ found that montelukast significantly improved nasal symptoms, nasal endoscopy and CT imaging, pulmonary symptoms, and asthma medication intake, whereas no effect was seen on pulmonary function tests.

Surgery

Various authors have studied the effect of surgical treatment of CRS on asthma outcomes with variable findings. Ragab and colleagues¹² found surgical intervention led to a decrease in asthma medication use, hospitalization, exhaled nitric oxide and improved FEV₁ but no significant change in asthma symptom scores. The overall

conclusion was that medical therapy was superior to surgical therapy. In another systematic review, Vashishta and colleagues⁹² found that endoscopic sinus surgery improves asthma control with decreased exacerbations, hospitalizations, and use of systemic and inhaled corticosteroids. However, pulmonary function was unchanged. Chen and colleagues⁹³ found functional endoscopic sinus surgery improved asthma control as measured by symptom scores but asthma medication use and pulmonary function testing remained stable. In a systematic review, Rix and colleagues¹¹ reported that two studies found significant improvement in FEV₁, whereas one did not. These variable results emphasize the need for high-quality research to answer such questions.

BIOLOGIC THERAPY

There is a large unmet need for newer therapies for CRS, because of the poor therapeutic response to current treatments with a high rate of recurrence or persistence of disease. Recent studies with biologic agents have shown promising results. A small study of CRSwNP and asthma patients treated with omalizumab, a human monoclonal antibody against IgE, resulted in improved rhinitis and asthma symptom scores and improved sinus CT scores but no improvement in FEV₁.⁹⁴ A larger study showed that omalizumab reduced nasal endoscopic polyp scores, improved CT scans, decreased nasal and asthma symptoms, and improved quality of life scores in patients with nasal polyps and asthma regardless of atopic status.⁹⁵ Mepolizumab, a humanized IgG1 monoclonal antibody against IL-5, was used to treat 20 subjects with nasal polyps with prominent eosinophilia. Twelve subjects showed improvement in symptom scores and sinus CT score.⁹⁶ A recent phase II multinational, randomized, double-blind, placebo-controlled study evaluated dupilumab, a human monoclonal antibody against IL-4R α , which inhibits IL-4 and IL-13 activity, in patients with bilateral nasal polyposis but the results have not yet been released.⁹⁷

SUMMARY

CRS and concomitant asthma often lead to a severe, persistent clinical course that is often difficult to treat and refractory to therapy. Patients with CRSwNP are often more difficult to treat than those without nasal polyps and have a Th2 cytokine pattern. A subset of patients have AERD with CRSwNP, asthma, and intolerance to COX-1 inhibitors. Such patients often have an even more severe clinical course with recurrent nasal polyps often requiring multiple surgeries and asthma that does not respond to traditional therapies. Diagnostic measures include a thorough history, direct visualization, imaging with CT, and an aspirin challenge when indicated. Successful treatment requires addressing inflammation in the upper and lower airways and focuses on the use of topical anti-inflammatory therapies, nasal irrigation, and leukotriene modifiers. In select cases, the use of aspirin desensitization, endoscopic sinus surgery, and occasionally oral corticosteroids or antibiotics are indicated. Novel monoclonal antibody therapies have shown some promising results, but more studies need to be performed.

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