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Clinical Commentary Review

Infectious Chronic Rhinosinusitis

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Chronic rhinosinusitis (CRS) is a persistent inflammatory disease that affects a multitude of people worldwide. The pathogenesis of CRS involves many factors including genetics, status of the sinonasal microbiome, infections, and environmental influences. Comorbidities associated with CRS include asthma, allergic rhinitis, bronchiectasis, and certain kinds of immunodeficiency. CRS can be divided into different subtypes based on endotypes and phenotypes. Infectious CRS is one such category. The etiology of infectious CRS is usually secondary to chronic bacterial infection that commonly begins with a viral upper respiratory tract infection. Humoral antibody deficiencies can underlie difficult-to-treat or recurrent CRS. Infectious CRS can be treated with antimicrobials, topical or oral corticosteroids, and nasal saline irrigations. Patients with CRS and humoral immunodeficiency may require an aggressive treatment approach including immunoglobulin replacement therapy. Despite advancements in the field of CRS, targeted therapies and reliable biomarkers are still lacking. © **2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;4:584-9)**

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Chronic rhinosinusitis (CRS) is a complex disease characterized by inflammation of the paranasal sinuses and sinonasal mucosa.[1] Persistent sinonasal symptoms lasting at least 12 weeks and objective findings of sinonasal inflammation via nasal endoscopy[2] or computed tomography[3] of paranasal sinuses are recommended for the diagnosis of CRS for clinical and research purposes as diagnosis based only on symptoms may not be accurate.[4,5] The pathogenesis of CRS is multifactorial with infectious, genetic, and environmental factors all playing a role in the disease process. Yet, the exact contribution of each of these factors is unclear. Infections associated with CRS are typically viral or bacterial, but in some cases may be fungal. CRS exacerbations triggered by these infectious pathogens will be referred to as infectious CRS in this review, but this term is not well defined in the literature. The role of bacterial infections in CRS is unknown and viral infections in CRS are not well studied, but viruses may be associated with acute rhinosinusitis. This review will elaborate on infectious CRS, specifically focusing on bacterial infections, underlying reasons for the infections and the associated comorbidities. All other forms of CRS will be discussed elsewhere in this journal.

DEMOGRAPHICS

CRS affects up to 31 million people (12.5% of the population) in the United States alone. CRS without nasal polyps (CRSsNP) and CRS with nasal polyps (CRSwNP) account for approximately 60%-65% and 33% of all CRS cases, respectively.[1] This chronic disease results in reduced quality of life by causing poor sleep, fatigue, and bodily pain.[6] CRS is associated with significant health care costs and based on a systematic review can lead to an annual expenditure of 2014 US dollar equivalent of $9.9 billion in direct costs and $13.1 billion in indirect costs.[6-8] A survey-based study identified that over a 5-year period, close to 48 million outpatient visits in the United States were for CRS and antibiotics were prescribed 69% of the time.[9] We suspect that a great majority of these clinic visits were because of infectious CRS exacerbations, suggesting significant utilization of health care resources. Difficult-to-treat CRS and recurrent acute rhinosinusitis (RARS) may be associated with humoral immunodeficiency[5] as discussed later. A small percentage of patients with refractory sinusitis have genetic disorders such as cystic fibrosis (CF) and primary ciliary dyskinesia (PCD) that increase the risk to develop this disease.[10]

CLINICAL CHARACTERISTICS

Patients with CRSsNP generally present with symptoms of facial pain and purulent drainage, whereas those with CRSwNP may have similar symptoms but predominantly complain of nasal obstruction with or without hyposmia or anosmia.[11] Patients with CRS have some degree of persistent sinonasal symptoms, whereas patients with RARS are symptom free between episodes of acute exacerbations. Patients who complain of constant nasal congestion and have thick "peanut butter-like" secretions in their nasal or sinus cavities should be evaluated for allergic fungal rhinosinusitis.[5]

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Abbreviations used
CF- Cystic fibrosis
CFTR- Cystic fibrosis transmembrane conductance regulator
CRS- Chronic rhinosinusitis
CRSsNP- Chronic rhinosinusitis without nasal polyps
CRSwNP- Chronic rhinosinusitis with nasal polyps
CVID- Common variable immunodeficiency
NTHI- Nontypeable Haemophilus influenzae
PCD- Primary ciliary dyskinesia
RARS- Recurrent acute rhinosinusitis
SAD- Specific antibody deficiency
SNP- Single nucleotide polymorphism
STAT3- Signal transducer and activator of transcription 3
URTI- Upper respiratory tract infection

COMORBIDITIES

Allergic rhinitis, asthma, bronchiectasis, immunodeficiencies, CF, PCD, and autoimmune diseases such as eosinophilic granulomatosis with polyangiitis are associated with CRS, but their causality in the development of CRS has not been proven.[1,5,11,12] Some of these comorbid and coexisting medical conditions can either predispose patients with CRS to develop infectious exacerbations or are a consequential outcome of this chronic sinonasal condition. Asthma and CRS often coexist; asthma exacerbations are associated with CRS exacerbations and treatment of CRS results in improved asthma control.[13,14] A large percentage of patients with bronchiectasis have CRS, and the presence of CRS is associated with more severe bronchiectasis.[15] Disorders of the mucociliary transport system may contribute to the development of CRS as well. CF is caused by a defect in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene,[16] and specific mutations in *DNAH5* and *DNAH11* are found in patients with PCD. CF and PCD are discussed further in other sections of this journal issue.

PATHOPHYSIOLOGY

The exact pathogenesis of CRS remains unknown.[17] Pathophysiology of CRS is complex and is based on the fundamental principle of dysfunctional interaction between the host and environmental factors at the interface of the sinonasal mucosa. As a result, multiple different mechanisms have been proposed.[18] *Staphylococcus aureus (S. aureus)* is implicated in the pathogenesis of nasal polyps.[18] Both local and systemic IgE to *S. aureus* enterotoxins have been demonstrated in patients with CRSwNP, and the levels of specific IgE directly correlated with type 2 eosinophilic inflammation characteristic of CRSwNP.[19,20] This concept will be further discussed in other parts of this journal series.

The role of bacteria in CRS is unclear. The sinus cavity is not a sterile zone and is colonized by various species of bacteria. Polymicrobial bacterial species have been identified in healthy and diseased sinus mucosa by conventional culture and molecular techniques.[21-23] It is proposed that colonizing bacteria can contribute to the pathogenesis of CRS via formation of biofilms. Biofilms are composed of layers of live bacteria within a matrix of protein and nucleic acid. These bacterial plaques on mucosal surfaces allow infectious pathogens to develop antimicrobial resistance and evade host defenses[24] because these bacteria are metabolically inactive, potentially leading to infectious CRS exacerbations. Studies suggest that bacterial biofilms are a cause of recalcitrant CRS.[25] Alteration in the sinonasal microbiome may also contribute to the pathogenesis of CRS. Patients with CRS have microbiome dysbiosis,[26] which is characterized by reduced bacterial diversity and an increase in relative abundance of specific bacterial species compared with healthy individuals.[27] This altered microbial flora contributes to the phenotypic differences between patients with CRS and those without CRS.

An "immune barrier hypothesis" as a cause of CRS has also been proposed.[18] Epithelial cells secrete host defense molecules, which include small peptides and enzymes. Small peptides such as defensins and cathelicidins and large enzymatic proteins such as lysozyme and lactoferrin kill bacteria.[28] Abnormalities in the epithelial cell barrier function result in an impaired immune system and allow colonization by infectious pathogens such as bacteria and fungi. The S100 family of proteins produced by epithelial cells plays an important role in cell differentiation, barrier function, and antimicrobial activity. Studies in patients with CRS have shown reduced levels of S100 proteins, psoriasin, and calprotectin, which may potentially increase susceptibility to infections.[28,29] Another family of epithelium-secreted proteins called PLUNC (palate, lung, and nasal epithelium clone), which is involved in innate immunity, was profoundly reduced in polyp tissue of patients with CRSwNP.[30,31] Additional abnormalities in the innate immune system that may contribute to infectious CRS include reduced expression of *SPINK5*, a gene responsible for expression of epithelial protein, LEKT1, which is decreased in CRS but is important for epithelial barrier function.[32] Epithelial cell host defense molecule release is regulated by signal transducer and activator of transcription 3 (STAT3),[12] and blunting of STAT3 signaling has been demonstrated in CRS and may be responsible for decreased antimicrobial protein release from epithelial cells in nasal polyps.[33]

A noteworthy innate immunity receptor that may play a role in CRS pathogenesis is the bitter taste receptor, T2R38, which is activated by bacterial products.[34] T2R38 stimulates epithelial cells to produce nitrous oxide and helps kill bacteria and assists in mucociliary clearance of pathogens and prevention of upper respiratory tract infections (URTIs).[35] T2R38 gene polymorphism (TAS2R38 genotype) makes the bitter taste receptor inactive and predisposes patients to gram-negative URTIs and is a risk factor for the development of CRS.[34] All these defects in the epithelial cell barrier function create an impaired innate immune system and may make the sinonasal mucosa vulnerable to pathogens and microbial colonization. Overall, there is no single cause but multiple factors that make a host susceptible to CRS.

PATHOGENS IN INFECTIOUS CRS

Although patients with CRS have ongoing sinonasal symptoms, some of them may develop episodic worsening of symptoms that may be characterized by purulent nasal discharge. Both aerobic and anaerobic bacterial species can be obtained from diseased and nondiseased sinus mucosa of those suffering with CRS.[36] Overall, *S. aureus* is the most common organism isolated in patients with CRS.[21] Based on molecular diagnostics, *S. aureus, Staphylococcus epidermidis*, and *Propionibacterium acnes* are the abundant organisms in patients with CRS.[21,22] In general, fewer bacterial pathogens are identified from the sinus mucosa via conventional culture compared with molecular-based techniques.[21] Aside from *S. aureus*, pathogens that are cultured

TABLE I. Common bacterial organisms sampled from patients with CRS

Organisms identified via culture[23]	Organisms identified via molecular diagnostics[22]
Gram-positive bacteria	Gram-positive bacteria
Coagulase negative *Staphylococcus*	*Staphylococcus* species
Staphylococcus aureus	*Propionibacterium* species
Peptostreptococcus species	*Peptoniphilus* species
Gram-negative bacteria	Gram-negative bacteria
Haemophilus influenzae	*Prevotella* species
Pseudomonas aeruginosa	*Pseudomonas* species
Bacterioides species	*Porphyromonas* species

CRS, Chronic rhinosinusitis.

from patients with CRS include coagulase negative *Staphylococcus, Haemophilus influenzae (H. influenzae)*, and *Streptococcus pneumoniae*.[22,23] Additionally, patients with CRS with purulent secretions have increased abundance of *Prevotella, Streptococcus*, and *Veillonella* species as identified via quantitative DNA PCR.[22] In contrast with usual community-acquired rhinosinusitis exacerbations, nosocomial rhinosinusitis exacerbations are predominantly caused by gram-negative bacteria such as *Pseudomonas aeruginosa (P. aeruginosa), Proteus mirabilis*, and *Klebsiella pneumoniae*.[37,38] Commonly isolated organisms from patients with CRS are summarized in Table I. Microorganisms that are not detected either via conventional culture or with molecular diagnostics are likely part of the resident microbiome and probably help maintain a healthy sinus mucosa. Additionally, it may be that some nonpathogenic bacteria within the sinus mucosa are indeed responsible in the CRS disease process, but their exact role is unclear. Viral URTIs can contribute to CRS exacerbations too. In one study, coronavirus was identified via molecular sequencing as the most common virus in patients with CRS.[39] Although the exact role of viruses in CRS exacerbation is not certain, they likely contribute to the disturbance of the symbiotic microbiome and lead to clinical disease.

IMMUNODEFICIENCY AND INFECTIOUS CRS

Patients with difficult-to-treat CRS should be evaluated for an underlying immunodeficiency.[5] Antibody deficiencies are the most common primary immunodeficiency associated with CRS. A recent meta-analysis of antibody deficiency in patients with CRS reported a combined prevalence of IgG, IgA, and IgM deficiencies in 13% of patients with recurrent CRS and 23% of patients with difficult-to-treat CRS.[40] Antibody deficiencies can occur because of defect in antibody production (common variable immunodeficiency, IgA or IgM deficiency) or because of poor antibody function (specific antibody deficiency). Common variable immunodeficiency (CVID) is the most common symptomatic antibody deficiency and is characterized by the reduction in IgG levels by more than 2 standard deviations in association with low IgA and/or IgM levels. In addition, there is impaired response to polysaccharide and protein antigens in CVID. More than 50% of patients with CVID have CRS.[41] The prevalence of selective IgA deficiency (IgA level <7 mg/dL)[42] is estimated at 1 in 300 to700 people.[43] Most IgA deficient patients are asymptomatic; however, approximately 7% of patients with CRS may have IgA deficiency.[40]

TABLE II. Humoral immunodeficiency disorders associated with recurrent infectious CRS[42]

Diagnosis	Laboratory findings
Common variable immunodeficiency (CVID)	Low IgG and low IgA or IgM levels with lack of functional response to polysaccharide vaccines (poor T-cell-independent antibody response), normal or low B-cell numbers
Specific antibody deficiency (SAD)	Poor functional response to polysaccharide vaccines (poor T-cell-independent antibody response) with normal immunoglobulin levels, normal B-cell numbers
Selective IgA deficiency	Low IgA (<7 mg/dL) with normal IgG and IgM levels, normal B-cell numbers
IgG subclass deficiency	One or more low IgG subclasses with normal total IgG level, normal B-cell numbers

CRS, Chronic rhinosinusitis.

Specific antibody deficiency (SAD) is defined as an impaired response to immunization with polysaccharide antigens such as Pneumovax in the setting of normal quantitative immunoglobulin levels (IgG, IgA, and IgM) and a history of recurrent or prolonged sinopulmonary infections.[1,44] An adequate response to a polysaccharide vaccine is not well defined; however, 50%-70% of pneumococcal serotypes should be above 1.3 mcg/mL after vaccination.[43] In a retrospective review of patients with difficult-to-treat CRS, up to 23% of the patients were noted to have SAD.[44] Humoral immunodeficiencies that are typically associated with infectious CRS are summarized in Table II. Patients with CRS and immune dysfunction may require a more aggressive treatment strategy, which includes prophylactic antibiotics to prevent recurrent infectious CRS exacerbations, early culture-based antibiotic therapy, immunoglobulin (Ig) replacement therapy,[1] or early surgical management.[45]

ODONTOGENIC RHINOSINUSITIS

Odontogenic rhinosinusitis should be suspected in patients with dental pain and in those patients who have had a recent dental or oral surgical procedure. Dental infections can cause odontogenic rhinosinusitis, specifically involving the maxillary sinuses, and are typically unilateral.[5,46] Up to 10% to 12% of maxillary sinusitis cases are believed to be due to odontogenic infections. Odontogenic rhinosinusitis occurs when the schneiderian membrane, the membrane lining the maxillary sinus mucosa, is breached because of a dental infection or after a dental procedure.[46] Bacterial organisms that are commonly found in the oral flora typically cause odontogenic rhinosinusitis and include both aerobic and anaerobic species. Treatment of odontogenic rhinosinusitis is important because untreated infections can extend to the orbital and cranial structures and cause serious complications. Furthermore, the underlying odontogenic infection should be addressed either via endodontic therapy (root canal) or removal of the infected source to prevent recurrence of odontogenic rhinosinusits.[46]

TREATMENT

Treatment options for CRS include topical intranasal steroid, oral antibiotics, topical antibiotics, nasal saline irrigation, oral

steroids, or combination of oral antibiotics and steroids.[5] Difficult-to-treat CRS may require surgery and CRS in the setting of an underlying immunodeficiency may necessitate prophylactic antibiotics or Ig replacement therapy. Topical intranasal steroids help decrease sinonasal inflammation and can be extremely effective in managing some patients with CRS.[5] Nasal saline irrigation removes mucus and assists in clearing bacterial biofilms.[4] The combination of both topical intranasal steroid and nasal saline irrigation may be helpful in CRS, but among these 2 treatment options, topical intranasal steroid is superior as single therapy alone.[47] Although treatment with oral antibiotics is usually the first therapeutic option utilized in CRS, strong evidence for using oral antibiotics in CRS is lacking in the literature. There are only 3 placebocontrolled studies evaluating treatment with oral antibiotics in CRS.[48-50] A Cochrane review on systemic antibiotics for CRS, which included only 1 randomized study, showed limited effectiveness of macrolide therapy.[51] Since then, one study showed that long-term use of azithromycin for the treatment of CRS did not show benefit compared with placebo.[49] Another study evaluating the use of oral antibiotics was in patients with CRSwNP and will be discussed in other sections of this journal.[50] Oral antibiotics may be most useful in infectious CRS exacerbations and especially in those patients with purulent drainage. Topical antibiotics may be effective in CRS, but they are more likely to benefit post—sinus surgery patients or those patients who receive culture-directed antibiotics.[52] Finally, oral steroids can provide symptomatic relief from nasal congestion and improve sense of smell in patients with CRSwNP.[5] Retrospective studies looking at oral antibiotics and steroids together in patients with CRS have demonstrated improvement in symptoms, decrease in radiographic severity of sinus disease,[53] and decreased likelihood of sinus surgery.[54] Although there are some available therapies for CRS, better, reliable, and more targeted treatment options are necessary.

GENETICS

The high prevalence of CRS in inherited syndromes such as CF, PCD, ataxia telangiectasia, and Young's syndrome suggests that genetics likely plays a role in the development of CRS.[55] Genetic association studies have helped identify numerous single nucleotide polymorphisms (SNPs) in genes involved in innate (ie, toll-like receptor pathway)[17] and adaptive immunity, arachidonic acid metabolism, and sinonasal tissue remodeling.[16] However, many of these genetic study findings have been limited by lack of reproducibility of results and conflicting data.[16] Large-scale genome-wide association studies that can replicate discovered genetic data are needed to validate the association of gene-specific SNPs identified in patients with CRS. To date, the association of CRS and *CFTR* gene mutations is the most promising finding due to replication of data in various studies.[16] The high prevalence of CRS in patients with CF suggests that the *CFTR* gene may be involved in the pathogenesis of CRS.

BIOMARKERS

Biomarkers for the diagnosis of infectious CRS exacerbations are currently lacking. There is no biomarker that is consistently used to identify an acute CRS exacerbation. Although direct sinus cavity culture results are used in clinical practice for management of CRS, these are not always reliable due to the high rate of bacterial colonization of the sinus mucosa. In a study of chinchillas infected with nontypeable *H. influenzae* (NTHI) strains, 2 NTHI proteins were discovered in sinonasal secretions and show promise as potential biomarkers for active disease.[56] Large-scale human studies are required for validation of these types of biomarkers.

RECOMMENDATION FOR INFORMATION TO BE OBTAINED TO DETERMINE THE PHENOTYPE

An approach should be established to identify patients with infectious CRS. Patients with recurrent infectious CRS exacerbations or difficult-to-treat CRS, who fail empiric treatment with combination of topical or oral antibiotics with or without steroids, should undergo nasal endoscopy and get culture-directed antibiotic therapy if indicated. This is the best diagnostic approach that is available currently, but it is important to note that culture-based diagnosis may not be as accurate as molecular diagnostics. Concomitant immunodeficiency should also be suspected in this subset of patients, and laboratory workup including complete blood count with differential, quantitative immunoglobulins (IgG, IgA, and IgM), specific antibody response to polysaccharide antigens (IgG antibody response 4 weeks postvaccination after pneumococcal polysaccharide vaccine), complement function, and if necessary, measurement of B- and T-cell numbers by flow cytometry should be performed.[5] Patients with high-risk sexual behavior should undergo HIV screening to exclude an acquired immunodeficiency.[5] Prophylactic antibiotics or Ig replacement therapy should be considered in patients with recurrent exacerbations of infectious CRS and proven defect in humoral immunity.[5] Any patient with CRS with concern for immunodeficiency or with the presence of atypical or opportunistic pathogens in the sinonasal mucosa should be referred for evaluation to a clinic specializing in allergy, sinus disease, and immunodeficiency. If anatomic abnormalities such as deviated nasal septum are believed to be the cause of recurrent infectious CRS exacerbations, the patient should be referred to an otolaryngologist for surgical evaluation.[5] Additionally, any patient diagnosed with nasal polyps or CRS at an early age and with *P. aeruginosa* cultured from the sinonasal cavity should be evaluated for CF.[5]

RESEARCH QUESTIONS AND FUTURE DIRECTIONS

More focused research is needed in identifying defects in innate immunity and mucociliary clearance, impact of sinonasal microbiome, allergy, and genetics to develop new preventative and therapeutic options for the management of CRS. For example:

- Antibiofilm-directed interventions could help minimize CRS exacerbations by targeting the colonizing microbiome.[5]
- Specific genotyping directed toward bitter taste receptor (T2R38) may help identify a specific endotype of CRS.[34]
- More efforts are needed to identify the true impact of oral antibiotics and the optimal duration of antibiotic use in infectious CRS.

Although biomarkers for CRS are being developed, larger scale studies need to be conducted in humans to confirm the validity of these diagnostic tests before they can be marketed for clinical use. Overall, given the complexity of CRS, microbiome

fingerprinting may be the next step in developing the precise diagnostic approach for this disease.

CONCLUSION

Infectious CRS is a subtype under the umbrella of CRS. Infectious CRS exacerbations can be triggered by viruses that cause URTIs or because of an imbalance among the bacterial species making up the sinonasal microbiome. There have been significant discoveries in understanding the complex pathogenesis of CRS, with an ongoing focus on the microbiota within the sinus cavities. Nevertheless, unique biomarkers to identify an infectious CRS exacerbation and evidence-based treatment options for CRS are still lacking and are gaps that need to be investigated further.

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