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Diagnosis and Management of Rhinosinusitis: Highlights from the 2015 Practice Parameter

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Abstract Rhinosinusitis is a commonly diagnosed disease in the USA. Rhinosinusitis is classified as acute, recurrent, or chronic (with or without nasal polyps). While acute rhinosinusitis is diagnosed by history and physical examination, chronic rhinosinusitis and recurrent acute rhinosinusitis are diagnosed based on symptoms and the presence of disease on either a sinus CT scan and/or endoscopy. Management of uncomplicated acute rhinosinusitis includes analgesics, saline irrigation, and/or intranasal steroids. Antibiotics and intranasal steroids are recommended for acute bacterial rhinosinusitis. Intranasal and oral steroids with antibiotics are recommended to treat chronic rhinosinusitis although the evidence for antibiotics is weak. Biologics such as omalizumab and mepolizumab are being investigated for the treatment of chronic rhinosinusitis with nasal polyps. Surgery may be indicated in management of refractory chronic rhinosinusitis and rarely for acute bacterial rhinosinusitis. This review discusses highlights of the updated 2014 practice parameter and up-to-date evidence from other literature sources.

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Introduction

Rhinosinusitis is one of the most commonly diagnosed diseases in the USA with a prevalence of 13 % in adults based on a US National Health Interview Survey in 2012 [1]. The research and data surrounding rhinosinusitis is ever evolving and expanding. In 2014, an updated practice parameter was published regarding the diagnosis and management of rhinosinusitis. This review focuses on highlights of the updated practice parameter, as well as up-to-date evidence from other literature sources.

Definition

Rhinosinusitis is defined as inflammation of the nasal cavity and paranasal sinuses. Signs and symptoms of rhinosinusitis may include purulent rhinorrhea, postnasal drainage, anosmia, nasal congestion, facial pain or pressure, or headache. Cough and fever may also be present in patients with rhinosinusitis [2••, 3–5]. Acute rhinosinusitis (ARS) is defined as signs and symptoms occurring less than 12 weeks, whereas chronic rhinosinusitis (CRS) consists of signs and symptoms lasting for 12 weeks or longer in association with objective evidence of inflammation observed on nasal endoscopy and/or sinus CT scan (detailed in Table 1). ARS includes both viral rhinosinusitis and acute bacterial rhinosinusitis (ABRS). CRS is further classified as CRS with nasal polyps (CRSwNP) or CRS without nasal polyps (CRSsNP) based on the presence or absence of nasal polyps. The disease is further classified as recurrent acute rhinosinusitis (RARS) if

Table 1 Classification of rhinosinusitis

Acute rhinosinusitis (ARS)	Up to 4–12 weeks of purulent nasal drainage accompanied by nasal obstruction, facial pain/pressure/fullness
Viral rhinosinusitis	Symptoms or signs are present for less than 10 days and symptoms are not worsening
Acute bacterial rhinosinusitis (ABRS) (0.5–2 % of all acute viral infections)	a. Symptoms or signs fail to improve within 10 days or more beyond the onset of URI or
	b. Symptoms or signs worsen within 10 days after an initial improvement (double worsening)
Chronic rhinosinusitis (CRS)	Symptoms lasting greater than 12 weeks with objective evidence of inflammation on endoscopy and/or sinus CT scan
Chronic rhinosinusitis without nasal polyps (CRSsNP)	Nasal polyps are not present
Chronic rhinosinusitis with nasal polyps (CRSwNP)	Nasal polyps are present

With permission from Peters AT et al. Diagnosis and management of rhinosinusitis: a practice parameter update. Ann Allergy Asthma Immunol. 2014 Oct;113(4):347–85. Up-to-date practice parameter highlighting new evidence and information regarding the pathogenesis, diagnosis, and management of acute and chronic rhinosinusitis

patients have at least three episodes of acute bacterial rhinosinusitis in 1 year. These patients are asymptomatic between infectious episodes.

Pathogenesis

Most acute rhinosinusitis is viral in origin. Only about 1.5 % of sinus infections are believed to be bacterial with *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* being the most commonly cultured bacteria [6]. The exact pathogenesis of CRS is not known though obstruction of the osteomeatal complex, impaired mucociliary clearance, biofilm formation, and impaired immune barrier leading to a local innate or acquired immunodeficiency are some of the theories proposed for the inflammation associated with CRS [7]. CRSsNP was previously believed to be predominantly Th1 mediated inflammation with elevated IFN gamma and elevated TGF-β [8]. In a recent study published by Stevens et al. [9••], the researchers failed to find evidence of Th1 bias or elevated IFN- in CRSsNP. CRSwNP is characterized by type 2 inflammation which is predominantly eosinophilic with lower TGF-β and decreased Treg function [8]. In CRSwNP, it is hypothesized that polyclonal IgE against staphylococcal enterotoxins induces type 2 eosinophilic inflammation which is believed to promote nasal polyp formation [10].

Clinical Evaluation

Acute Rhinosinusitis

The diagnosis of ARS can be made based on history and physical examination. Most ARS is caused by viruses and is diagnosed when symptoms of an upper respiratory infection (URI) last less than 10 days. ABRS is diagnosed in patients with URIs continuing longer than 10 to 14 days with the sinonasal symptoms noted earlier [2••]. On physical examination, patients may have sinus tenderness on palpation, mucosal erythema, and discolored nasal and oropharyngeal secretions. Acute rhinosinusitis is a clinical diagnosis, and consider a sinus CT scan in patients with ABRS only if there is concern for acute complications such as orbital cellulitis or CNS spread [2••].

Chronic Rhinosinusitis and Recurrent Acute Rhinosinusitis

CRS presents with similar symptoms as acute rhinosinusitis; however, fever and pain are not as prominent. Decrease in sense of smell especially suggests CRSwNP. When evaluating patients for CRS or RARS, clinicians should consider imaging or endoscopy after history and physical examination given the overlapping symptoms with perennial rhinitis and atypical facial pain [11] or vascular headache. Sinus CT scan is the preferred imaging modality and the gold standard to clarify the extent of disease and specific location or locations of obstruction in acute or chronic sinus disease [12]. The sinus CT scan should be performed 4 to 6 weeks after initiating medical therapy and is required before surgical intervention or if rhinosinusitis complications are suspected [2••]. If a patient has unilateral CRS type symptoms, radiographic imaging should be performed to exclude a tumor, anatomic defect, or foreign body. MRI is the imaging modality of choice if soft tissue evaluation is required, such as with suspected tumors.

Comorbidities Associated with Rhinosinusitis

Due to the high prevalence of allergic rhinitis in patients with rhinosinusitis, patients with RARS or CRS should be evaluated for environmental allergens while recognizing that non-allergic rhinitis can also accompany CRS [2••]. Further, allergic fungal rhinosinusitis (AFRS), which is a distinct form of

CRS, requires allergic sensitization to fungi such as aspergillus. Many studies in all age groups backed the association between AR and rhinosinusitis, ranging from 36–60 % in children [13], 25–31 % in young adults [14, 15], and 40–84 % in adults [16–18]. DeYoung et al. [19•] have published a systematic review of immunotherapy for CRS patients in which seven uncontrolled and non-randomized studies were. With immunotherapy, there was improvement in symptoms, endoscopic examination, radiographic assessment, decrease in need for revision surgery, and decrease in need for oral and intranasal corticosteroids. Due to the limited amount of data currently, there is weak evidence to support the use of immunotherapy as an adjunctive treatment in CRS.

Gastroesophageal reflux disease (GERD), asthma, and otitis are often comorbid conditions associated with CRS. Previously, GERD was suggested as a cause of rhinosinusitis, and patients with refractory rhinosinusitis were advised to treat GERD prior to consideration of surgical intervention [20]. A recent meta-analysis performed by Flook and Kumar [21] concluded that the evidence linking CRS and GERD is weak with no randomized controlled trials available. The current practice parameter recommends evaluating patients for GERD if the patient has appropriate symptoms with the understanding that GERD co-exists rather than explains the etiology of rhinosinusitis [2••].

Other conditions that may be associated with difficult to treat RARS and CRS include immunodeficiencies such as common variable immunodeficiency, IgA deficiency, or specific antibody deficiency. Cystic fibrosis should be considered in individuals who develop CRS at a younger age or in any child with nasal polyps.

Treatment

Acute Rhinosinusitis

Initial management of uncomplicated ARS is supportive therapy with analgesics, topical intranasal steroids, and/or saline irrigation. Although the evidence is limited, these ancillary treatments may provide symptomatic relief.

Treatment with antibiotics is recommended for uncomplicated ABRS only if symptoms last longer than 10 days or if symptoms worsen after initial improvement [2••]. The antibiotics currently approved by the FDA for ABRS are azithromycin, clarithromycin, amoxicillin-clavulanate, cefprozil, cefuroxime, loracarbef, levofloxacin, trimethoprim-sulfamethoxazole, and moxifloxacin. No studies have shown superiority of one antibiotic over the other [22••]. Due to increasing resistance, the Infectious Disease Society of America recommends amoxicillin-clavulanate as first-line therapy and doxycycline, levofloxacin, and moxifloxacin in patients allergic to penicillin [23••]. For this reason, the current practice parameter recommends evaluation of beta-lactam allergy by penicillin skin testing and/or graded oral challenge if the beta-lactam antibiotic is most appropriate for treatment [2••].

Intranasal steroids (INS) may be used as monotherapy or adjunctive therapy with antibiotics in patients with ABRS [2••]. Three studies indicated improved symptoms with INS as monotherapy compared with placebo or antibiotic [24, 25•, 26]. A Cochrane Database review of the literature indicated modest beneficial effect with INS in resolution or improvement of symptoms when used as an adjunct to antibiotics in patients with ABRS [27]. In contrast, systemic corticosteroids have not been well studied, and the data is limited. Venekamp et al. [28•] published a randomized, double-blinded, placebo-controlled trial comparing 30 mg per day of prednisolone monotherapy to placebo for 7 days with no superiority found. The most recent Cochrane Database review found that systemic corticosteroids are effective as an adjunct to oral antibiotics though the data was limited and there was significant risk of bias [29]. There is currently insufficient evidence that supplements such as zinc and vitamin C, herbal supplements, antihistamines, and decongestants are of benefit in ABRS [30–32]. While the evidence is also limited, saline irrigation may provide symptomatic relief by enabling mucus clearance [33].

Chronic Rhinosinusitis

Pharmacotherapy for CRS includes INS, oral corticosteroids, nasal irrigation, and antibiotics. Antibiotic treatment for CRS is controversial due to limited evidence though the current recommendation is that clinicians should use systemic antibiotics for acute exacerbations of CRS [2••]. The most appropriate use of antibiotics should be in patients with persistent purulent drainage [34]. If the purulence persists despite antibiotic use, sinus culture is strongly recommended [34].

Clinical studies showing beneficial effect of long-term use of macrolide antibiotics are limited and do not differentiate between CRSsNP and CRSwNP [2••]. Observational studies examining 3- to 6-week courses of antibiotics delivered by nasal irrigation or nebulization have indicated improvement in symptoms [35], endoscopic improvement [36], and an increase in infection-free intervals [37]. Examples of antibiotics studied include mupirocin [37] and topical aminoglycosides [38] for refractory CRS with culture proven *Staphylococcus aureus* infection. Topical aminoglycosides should be used with caution and only for a defined treatment period, as there is measureable but low systemic absorption [2••, 39]. In one study, 23 % of cystic fibrosis patients developed sensorineural hearing loss after frequent irrigations with topical aminoglycosides [40].

Nasal saline irrigation is also recommended as an adjunctive treatment for CRS patients, as this has shown to improve quality of life, decrease medications, and diminish the number of infections [41–43]. Distilled or boiled tap water should be used, and patient should be advised to clean the device to prevent bacterial contamination [44]. A Cochrane Database

review evaluating the efficacy and safety of nasal saline irrigation provided evidence that hypertonic saline may be better than isotonic saline [42]. If patients have underlying allergic rhinitis, anti-histamines can be considered for treatment of symptoms [2••, 23••]. However, neither oral nor topical decongestants are advantageous in maintenance treatment for CRS [2••].

There is limited data regarding prolonged antibiotic treatment in refractory cases though historically this has been recommended for patients with CRSsNP [2••] One small study on patients with CRSsNP treated with roxithromycin supported the use of systemic antibiotics for the treatment of adult patients though further trials with larger patient populations are needed [45]. Based on the study published by Dubin et al. [46], adult patients with CRSsNP refractory to previous antibiotic treatment were treated with 150 mg of clindamycin three times a day (13 patients), amoxicillin-clavulanate (2 patients), or doxycycline (1 patient) for 6 weeks. CT sinus scan was performed at baseline, week 3, and week 6 of treatment. Lund-MacKay scores improved in 6 patients between weeks 3 and 6, and only 1 of these 6 patients was recommended to have sinus surgery after 6 weeks of treatment. Thus, some patients with CRSsNP may benefit from prolonged antibiotic treatment. However, a recent study did not show a difference in clinical outcomes between 3- and 6-weeks of antibiotic therapy in CRS patients [47•].

In patients with CRSwNP, doxycycline has been found to cause a statistically significant decrease in polyp size, significant decrease in nasal secretion of eosinophil cationic protein, and significant effect on post nasal discharge [48]. Of note, doxycycline did not cause statistically significant improvement in nasal peak inspiratory flow rate [49].

Oral steroids have shown benefit in the treatment of CRS. Amoxicillin-clavulanate alone was compared to amoxicillin clavulanate in combination with oral steroids for the treatment of CRS in a prospective randomized study [50]. The study arm with amoxicillin-clavulanate plus steroid demonstrated improved symptoms and radiographic scores compared to antibiotic alone. This study included patients with both CRSsNP and CRSwNP. A short course of oral steroids in patients with CRSwNP has shown to decrease polyp size and improve symptoms, including transient improvement in smell [2••, 51, 52]. INS (sprays and aerosols) are recommended for treatment in CRSsNP and CRSwNP. Published studies have consistently shown INS to be superior to placebo in improving nasal patency, decreasing nasal symptoms, diminishing polyp size, and improving quality of life though studies have not compared one INS to another [2••, 23••, 53]. In the Cochrane Database published in 2011, 10 randomized controlled trials ($n = 590$) were included comparing INS to placebo or other medications [54]. Six of the studies had low risk of bias, and four included had a medium risk of bias. INS was found to be beneficial in the treatment for CRSsNP and the adverse effects were minor.

CRSwNP and Biologic Therapy

New medical therapies are being studied in patients with CRS, especially in CRSwNP. Although not approved for commercial use, anti-IgE monoclonal antibody (omalizumab) and IL-5 monoclonal antibodies (mepolizumab and reslizumab) have shown benefit in patients with CRSwNP. While a prior randomized controlled study by Pinto et al. in 2010 [55] found no statistically significant improvement when patients with CRS were treated with omalizumab, Gevaert et al. [56••] in 2013 noted significantly decreased total nasal endoscopic polyp scores after 16 weeks of treatment with omalizumab compared with placebo. The authors also noted improvement in upper and lower airway symptoms and quality of life scores. The patients included in this study were allergic and non-allergic patients with CRSwNP and asthma. Anti-IL-5 monoclonal antibody (mepolizumab) has also shown benefit in the treatment of CRSwNP. In a study published by Gevaert et al. [2••, 57], a randomized double blinded placebo controlled trial of mepolizumab was studied in patients with CRSwNP who failed "standard care for CRSwNP." Mepolizumab treatment was associated with a significant decrease in nasal polyp size 1 month after dosing in 12 of the 20 patients ($P = .028$ vs. placebo) with no relation between mepolizumab response and nasal IL-5 levels [59••]. The FDA recently approved Mepolizumab for severe eosinophilic asthma. Reslizumab, another anti-IL-5 antibody antagonist, has been studied in patients with CRSwNP and demonstrated improved nasal polyp scores in patients with increased IL-5 concentrations in nasal secretions [58]. Lastly, neither topical antifungals (sprays or irrigations) [2••, 59] nor systemic terbinafine [2••, 60] were found to be advantageous in the treatment of CRS, as the published clinical trials of antifungal treatment did not show benefit.

CRS and Surgical Management

Surgical intervention may be required in ABRS to provide drainage when there is significant risk of intracranial complication or periorbital/orbital abscess. Surgery may also be considered in the management of CRS when medical treatment has been exhausted. Surgical therapy is directed toward removing mucosal disease and improving drainage. Surgery may also provide access for topical therapy. Surgical management of rhinosinusitis has expanded since the previous practice parameter was published. Balloon dilatation of sinus ostia may be considered in a small sub-segment of patients with early or localized disease but its efficacy is not believed to be comparable to traditional functional endoscopic sinus surgery (FESS) [61, 62•, 63•]. In 2006, a Cochrane Database review for CRSsNP and CRSwNP concluded that FESS could not be considered superior to medical therapy [2••, 64]. A Cochrane Database review published in 2014 focusing on

CRSwNP patients could not conclude FESS conferred benefit over medical therapy [65]. In addition, steroid eluting stents have been evaluated after FESS. It is believed that the local concentration of steroids in the sinus mucosa will decrease inflammation and promote healing after surgery. Steroid eluting stents have demonstrated decreased need for lysis of adhesions, decrease in post-op oral steroid requirements, and reduction in polyp size compared to controls in prospective randomized placebo-controlled multi-center trials [66•, 67•, 68]. Finally, although surgical therapy can result in significant improvement in the majority of patients with CRS in terms of symptoms and quality of life measures, continued medical treatment is usually required in the long-term management of patients with CRS.

Conclusion

There is a gap in current understanding of rhinosinusitis in terms of classification, diagnosis, treatment, and prevention of co-morbidities. Despite the advancements in the field, patients with rhinosinusitis often remain symptomatic and have poor quality of life despite treatment. For advancements to continue, essential evidence needs to be furthered. At this time, the underlying trigger that leads to the development of CRS remains unknown and the knowledge on cytokines and underlying pathology must be expanded upon. Furthermore, many studies examining therapies do not have control groups. Therapeutic trials must be completed using placebo controlled, randomized, double-blinded methods.

Compliance with Ethical Standards

Conflict of Interest Dr. Dass declares no conflicts of interest. Dr. Peters is a consultant for Greer Laboratories.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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