

TITLE: Management of Chronic Rhinosinusitis
SOURCE: Grand Rounds Presentation, UTMB, Dept. of Otolaryngology
DATE: May 9, 2006
RESIDENT PHYSICIAN: Jean Paul Font, MD
FACULTY PHYSICIAN: Matthew Ryan, MD
SERIES EDITORS: Francis B. Quinn, Jr., MD and Matthew W. Ryan, MD

"This material was prepared by resident physicians in partial fulfillment of educational requirements established for the Postgraduate Training Program of the UTMB Department of Otolaryngology/Head and Neck Surgery and was not intended for clinical use in its present form. It was prepared for the purpose of stimulating group discussion in a conference setting. No warranties, either express or implied, are made with respect to its accuracy, completeness, or timeliness. The material does not necessarily reflect the current or past opinions of members of the UTMB faculty and should not be used for purposes of diagnosis or treatment without consulting appropriate literature sources and informed professional opinion."

Introduction

Sinusitis is one of the most common health care challenges in the United States. The incidence of sinusitis in the United States, as per national census data, has been estimated at 14.1% of the adult population. According to the American Academy of Otolaryngology, this condition leads to direct health care costs of \$3.4 billion per year and chronic sinusitis alone results in 18 to 22 million US physician office visits annually.

The word Rhinosinusitis is replacing the term sinusitis because sinusitis is often preceded by rhinitis and rarely occurs without concurrent nasal airway inflammation. Rhinosinusitis has been defined by the American Academy of Otolaryngology as an inflammation of the nose and sinuses. It is believed that this condition comprises a spectrum of inflammatory and infectious diseases.

The site of sinus and nasal obstruction is important. The ostiomeatal complex is a region of key importance for the development of rhinitis-induced sinusitis. The area comprises the hiatus semilunaris, a curvilinear groove between the uncinate process and the bulla, and through which the frontal, anterior ethmoid and maxillary sinuses drain into the nasal cavity. Inflammation or anatomic obstruction by a mass on this area blocks drainage from these three sinuses, leading to stagnation of secretion and creation of a culture medium for infection to develop.

Unfortunately, the accuracy of reported rhinosinusitis cases is difficult to ascertain. The diagnosis on the basis of symptoms is common but can be unreliable. This concern is especially true for the accurate diagnosis of chronic rhinosinusitis (CRS). A rhinosinusitis task force in 1997 outlined "major" and "minor" criteria for diagnosing sinusitis. The major criteria include facial pain, nasal obstruction, hyposmia, purulence on examination, and fever. While, minor criteria include headache, fatigue, dental pain, and cough. Studies have found the criteria to be sensitive but not specific. Currently the gold standard for the diagnosis of chronic rhinosinusitis is computed tomography.

The classification of Rhinosinusitis is based on duration of sign and symptoms into acute, subacute and chronic. Acute is defined as lasting up to four weeks, with total resolution of symptoms. The term recurrent acute has also been adopted and is defined as four or more episodes per year, with resolution of symptoms between attacks. Subacute is persistence of signs and symptoms for more than four weeks, but less than twelve weeks with total resolution of symptoms. Finally, Chronic is 12 weeks or more of signs and symptoms.

Successful management of rhinosinusitis via medical or surgical treatment is achieved in the majority of patients. In some cases symptoms resolve spontaneously. Treatment of chronic rhinosinusitis is intended to reduce symptoms and signs, improve quality of life, and prevent disease progression or recurrence.

Medical treatment is the initial treatment choice before opting for surgery in patients who do not improve. Many medical treatments have been recommended or employed. Evidence for their efficacy is rarely strong, partly because of the poor-quality trials in unselected groups of patients². Chronic rhinosinusitis involves multifactorial etiology. The condition does not respond by simply making an empiric antibiotic selection. There are several predisposing factors in chronic rhinosinusitis which include host factors like allergic rhinitis, viral illness (children in daycare), gastroesophageal reflux, anatomic obstruction, immunodeficiency, genetics, congenital. There are also environmental factors such as irritants (cigarette smoke), microbial (viral, fungal and bacterial) and even medication inducing rhinitis medicamentosa. The quest and identification of factors predisposing to chronic rhinosinusitis is key to guide appropriate management.

The most common indication for sinus surgery is failing medical therapy of chronic sinusitis. Approximately 200,000 U.S. adults undergo sinus surgery per year. Relative indications include persisting obstruction to sinus aeration (e.g., polyp, concha, septum), specific area of recurring disease and chronic or recurrent acute rhinosinusitis who have not responded adequately to medical therapy. Absolute indications include complications like brain abscess, meningitis, subperiosteal abscess, sinus mucocele or pyocele, fungal sinusitis (all varieties), massive polyposis (obstructing sinuses) and neoplasm or suspected neoplasm (causing sinus obstruction).

Frequently a combination of measures is employed in an individual patient. Some management are directed at improving sinus ventilation and drainage like oral hydration, saline irrigation, mucolytics and decongestants. There are others designed to reduce inflammation corticosteroids, antihistamines, macrolides and anti-leukotriens. Finally, there are those designed to treat infection such as anti-biotics and antifungals, treat an anatomic abnormality and those directed at avoidance of allergens. The key to breaking a cycle of recurrent or chronic sinusitis is the aggressive combination of antibiotics with therapies directed at predisposing conditions for a length of time adequate to allow for healing of upper respiratory tract mucosa with recovery of local immune defense¹⁴.

Allergens and Irritants

Up to 30% of the adult population is allergic by skin testing to at least one common aeroallergen, and the percentage is probably much greater among patients presenting with a

history of chronic sinusitis. Allergic rhinitis is probably the second most common predisposing condition to chronic sinusitis in children (after viral upper respiratory infection) and perhaps the most common predisposing factor in adults¹⁴. A combination of allergic history and positive skin prick testing is key in the management of chronic sinusitis in a patient with allergic rhinitis. This condition causes mucosal inflammation and hypertrophy predisposing to blockage of the ostiomeatal complex. This is the reasoning behind innovating research directed at treating the antiinflammatory response as a route of medical management in chronic rhinosinusitis.

Sign and symptoms of chronic rhinosinusitis occur in response to irritant exposure. There is increasing evidence to support the theory that exposure to air pollution can impair mucociliary protection and potentiate sensitivities to common aeroallergens by stagnation of these agents. Avoidance and protection against smoke, pollution, and occupational irritants usually is advised to counteract these predisposing factors.

Saline Irrigation

Use of intranasal saline has been shown to decrease nasal symptoms and improve quality of life in allergic rhinitis and chronic rhinosinusitis. Saline spray increases mucociliary flow rates counteracting the effects of irritants and other numerous factors that affect mucociliary clearance. It also has a brief vasoconstrictive effect that leads to some short term symptomatic relief. Also, nasal saline irrigation mechanically rinses away predisposing agents such as aeroallergens like pollen, mold, dust, and particulate of air pollution. Although it has some symptomatic relief, patients with chronic rhinosinusitis are told to use saline at least twice daily as a preventative measure rather than starting when clinical symptoms manifest.

An acidic milieu is thought to cause the “gel” state (more viscous) of mucus to predominate, whereas an alkaline milieu is thought to cause the “sol” state to predominate. This is the rationale for adding baking soda to saline irrigation solutions.

Mucolytics

Guaifenesin is the most commonly used mucolytic agent. High doses of this medication are required to obtain an effect on mucous. At these amounts, patients often experience emesis and abdominal pain. Wawrose in 1992 showed significant improvement of nasal congestion and symptomatic relief in patients with AIDS and low CD4 counts.

Corticosteroid

It is sometimes contradictory to use an anti-inflammatory agent that can lead to immunosuppression like corticosteroids in the treatment of sinusitis which is considered having a significant association with microbial infection. Nonetheless, a short course of steroids can induce a significant anti-inflammatory and beneficial effect in the management of severe nasal mucosal congestion in allergic rhinitis patients. This brief period induces symptomatic relief and reduction of nasal and sinus mucosal inflammation promoting a better scenario for the management with topical agents, improving compliance and rate of benefit. Corticosteroids have multiple immunomodulator mechanisms including stabilization of mast cells against mediator release, block formation of inflammatory mediators, and inhibit chemotaxis of inflammatory

cells. It is important to keep in mind the adverse effect of systemic steroid use and the contraindications that include diabetes, peptic ulcer disease, glaucoma, severe hypertension, and advanced osteoporosis. Even a short course of steroids can significantly increase the blood pressure and glucose levels in patients with predisposition to hypertension and diabetes. Close monitoring and immediate withdrawal for side effects is warranted.

Topical nasal corticosteroids are a very effective form of treatment for allergic rhinitis and chronic rhinosinusitis. Their anti-inflammatory effect is localized and their systemic absorption has been shown to be negligible. The local reduction of inflammation prevents blockage and improve patency of the ostiomeatal complex. After use by at least 7 days, nasal corticosteroids have been shown to inhibit both immediate and late-phase reactions to antigenic stimulation in patients with allergic rhinitis¹⁴. An estimated 90% of patients with allergic rhinitis will experience improvement in nasal allergy symptoms including chronic nasal congestion with topical nasal steroid preparations accounting for a marked increase in popularity of these medications over the last decade¹⁴.

Some common adverse effects of topical nasal steroid use include nasal irritation, mucosal bleeding, and crusting. Septal perforation is a rare complication and the risk can be increased for patients living in very dry climates. The ingredient propylene glycol contained in the preparations is responsible for this complains. This can be alleviated by switching to an aqueous delivery system. The addition of nasal saline wash in conjunction with topical steroids can lessen or eliminate these common adverse effects.

Decongestants

Decongestants are α -adrenergic agonists that induce a sympathetic response leading to vasoconstriction of dilated mucosal blood vessels. Decongestants are best used for short (3–5 days) courses at the beginning of treatment for sinusitis or allergic rhinitis.

The most common oral decongestants are pseudoephedrine and phenylpropanolamine. This systemic agents achieve symptomatic relief, but lead to several adverse effects that are related to its sympathetic stimulation including insomnia, heart palpitations, and elevated blood pressure. Oral decongestants are indicated principally for symptomatic relief of nasal congestion and have not been shown to have therapeutic efficacy for the treatment of sinusitis¹⁴.

Topical agents include phenylephrine and oxymetazoline. This agents lead to a local excitation of alpha adrenergic receptors leading to a localize vasoconstriction and decrease of mucosal edema. All topical agents exhibit rebound vasodilation, which can be demonstrated by rhinometric analysis of nasal resistance as early as 3 days after beginning therapy. Clinical rebound congestion or rhinitis medicamentosa usually requires at least 10 days to 2 weeks of topical decongestant use to become apparent. This is the reasoning of using decongestants for short (3–5 days) courses at the beginning of treatment for sinusitis or allergic rhinitis.

Antibiotics

The use of antibiotics in chronic sinusitis is a topic of high controversy. It's efficacy, duration of therapy and agents to be use have been extensively debated. Some consensus is

apparent on the idea that antibiotic therapy for chronic sinusitis should be based on culture results. This is based on the increase in antibiotic resistance that have been increasing consistently throughout the decades.

The culture can be obtained by direct visualization under endoscopy of purulent secretions from the middle meatus. Although the maxillary tap is the gold standard for culture diagnosis, this method is highly uncomfortable to the awake patient. Although there is not a definite large randomized control trial comparing both techniques, the endoscopic technique correlates well with the maxillary tap and is less traumatic to the alert patient. Nevertheless, the maxillary taps still a very effective tool especially on the ICU setting.

The first-line antibiotics for chronic rhinosinusitis include amoxicillin-clavulanate and second- or third-generation cephalosporins. The respiratory quinolones are helpful second line agents for refractory cases to first line antibiotics.

Bacteria have developed multiple mechanisms of resistance. Alteration of the penicillin binding proteins is the most common reason for penicillin resistance in *Streptococcus pneumoniae* infections. This mechanism of resistance is overcome by increasing the penicillin component to a much higher dose. This is the rationale behind dosing children with 60 to 90 mg/kg per day instead of 40 mg/kg for amoxicillin. *Haemophilus influenzae* also utilize this type of resistance, but to a lesser degree.

According to the American Academy of Otolaryngology approximately 40% of *Haemophilus influenzae* and greater than 90% of *Moraxella catarrhalis* produce beta-lactamase. This enzyme breaks down the beta-lactam antibiotics. Beta-lactamase-mediated resistance to the early second-generation cephalosporins is high among strains of *Haemophilus influenzae* and *Moraxella catarrhalis*. Stabilization of penicillin by adding clavulanate overcomes this enzymatic action.

Newer generation macrolides such as clarithromycin and azithromycin achieve excellent mucosal levels but should be considered backup drugs. Azithromycin appears to be more potent against *Haemophilus influenzae*, whereas clarithromycin may be slightly better against intermediate resistant *Streptococcus pneumoniae*.

Bacteria's have also developed resistance against macrolide and even fluoroquinolones. *Streptococcus pneumoniae* have been shown to develop two different mechanisms of resistance against these two antibiotic families. One of the resistant apparatus is the efflux pump which eliminates the antibiotic from the microorganism interior before it can exert its effect. The other mechanism of resistance is the development of altered target proteins which prevent the connection of the antibiotics to the cell wall or mitochondria stopping its action inside the bacteria.

Authors have noted a doubling of pneumococcal resistance to macrolides over the past 10 years from approximately 10% to 20% leading to recommendations that these drugs (and fluoroquinolones in adults) not be used as first-line therapy for sinusitis¹⁴. Clindamycin is another alternative which should be reserved for culture-documented resistant *Streptococcus pneumoniae*.

Most authors recommend treating chronic sinusitis with a broad-spectrum antibiotic for up to 3 weeks. After 3 to 5 days of treatment there should be symptomatic improvement. After 10 to 15 days of treatment, symptoms should resolve. The logic of continuing therapy for another week is to allow for further diminution of mucosal edema and mucociliary function thus gaining resistance against new infection.

Many clinicians will follow the 3-week treatment course of antibiotics with a 3- to 6-week course of once-daily prophylactic antibiotic therapy for patients with a history of rapid recurrence after previous treatment. The goal is to get the patients through their window of vulnerability to new infection while mucosal recovery.

Prolonged use of low-dose macrolides in patients with chronic rhinosinusitis was found to be effective even when the identified bacterial pathogen was not sensitive to this agent. This management has also been found to decrease the size of nasal polyps.

Antiinflammatory effect of Macrolide

The observation that macrolide antibiotics were steroid-sparing in patients who had steroid-dependent asthma has been present for decades. This was thought to be due to inhibition of steroid metabolism. The concept of using long-term, low-dose macrolides for treatment of Chronic rhinosinusitis evolved further, primarily in Japan⁴.

An interesting aspect of the pharmacokinetics of macrolide antibiotics is their extensive tissue uptake and intracellular accumulation. Macrolides accumulate in inflammatory cells at concentrations up to several hundred-fold higher than concentrations in extracellular fluid. The macrolide antibiotics decrease cytokine production (IL-5, IL-8, GM-CSF, TGF- β , IL-6, IL-8, TNF- α), altered structure and function of biofilm, reduced expression of cell surface leukocyte adhesion molecules, accelerate neutrophil apoptosis, impaired neutrophil oxidative burst, decrease secretion and improve mucociliary clearance, and Inhibited release of elastase, protease, phospholipase C, and eotaxin A by *P aeruginosa*⁴.

Meta-analysis of anti-inflammatory effect of macrolides in Chronic rhinosinusitis

Type of study	Dosage 24h (mg)	Duration (months)	Macrolide	Results	Reference
Prospective, randomized, controlled trial, n = 90	1000 (2 wk)	3	Clarithromycin	As effective as surgery in chronic sinusitis	Ragab, 2004
Prospective, open, n = 17	500	12	Erythromycin	12 responders, mucocillary transport, headache, postnasal drip, all improved, $P < .05$	Cervin, 2002
Prospective, open, n = 20	1000	0.5	Clarithromycin	Improvement in CD68, IL-6, IL-8, TNF- α and clinical parameters	Macleod, 2001
Prospective, open, n = 20	400	3	Clarithromycin	Reduction of IL-8 in nasal lavage, decreased nasal polyp size	Yamada, 2000

Cervin et al. 2005

The above table shows several of the prospective studies done in the use of macrolides in long term management of chronic rhinosinusitis (CRS). Clarithromycin is the macrolide most studied in CRS. While Azithromycin lack studies in CRS. The table shows the marked success of this management in the symptomatology, reduction of cytokines in the tissue, decrease in nasal polyp size and effectiveness in comparison to surgery. The long term use in the above table varies, but an average of 3-12 month is seen.

Gastroesophageal Reflux (GERD)

There is a new trend of research in the involvement of GERD in upper airway pathologies. Reflux is said to be associated to chronic rhinosinusitis. The mechanism is not cleared and studies are necessary to further enlighten this discussion. However, it is thought that the reflux of acid content reach the nasopharynx and nasal cavities leading to chronic mucosal irritation and sinusitis.

Adult patients with chronic sinusitis and a history of heartburn could benefit from antireflux regimen including precautions and medication. In young children the relation is more evident presumably due to the closer proximity between the esophageal inlet and larynx to the soft palate and nasopharynx. Suspicion should rise in children with chronic congestion, rhinorrhea, excessive spitting up in infancy, low weight percentile, failure to thrive, chronic stridor and reactive airway disease.

Viral infections

Viral infections are the most common predisposing factors for sinusitis in children. Day care is an important risk factor for the development of viral infections due to the proximity and relation characteristics of children in this environment. The current management for viral infections is prevention by frequent hand washing and decrease exposure. Children with chronic rhinosinusitis may benefit from changing to a day care with fewer numbers of children to reduce viral exposure. Also an alternative are vacation periods from the daycare to allow for resolution of symptoms and decrease mucosal inflammation and improve mucociliary clearance as a measure for improving natural resistance to the condition.

Interferon alpha-2 (IFN α 2) can potentially block the penetration of viruses through respiratory mucosa. Intranasal IFN α 2, when used as a once-a-day nasal aerosol, has been shown to potentially prevent colds in people exposed to family members with upper respiratory infections. Although medications like Interferon alpha2 has shown some improvement its usage is limited by its cost.

References

1. Algorithms for management of chronic rhinosinusitis. Nagi MM - *Otolaryngol Clin North Am* - 01-DEC-2005; 38(6): 1137-41, vii
2. Medical management of chronic rhinosinusitis. Scadding GK - *Immunol Allergy Clin North Am* - 01-FEB-2004; 24(1): 103-18
3. Rhinosinusitis. Winstead W - *Prim Care* - 01-MAR-2003; 30(1): 137-54
4. Anti-inflammatory effects of macrolide antibiotics in the treatment of chronic rhinosinusitis. Cervin A - *Otolaryngol Clin North Am* - 01-DEC-2005; 38(6): 1339-50
5. Chronic Rhinosinusitis. Ferguson BJ - *Otolaryngol Clin North Am* - 2005 Dec; 38(6); xiii-xv
6. Chronic rhinosinusitis. Denburg J - *Immunol Allergy Clin North Am* - February 2004; 24(1); IX
7. Allergy and chronic rhinosinusitis. Krouse JH - *Otolaryngol Clin North Am* - 01-DEC-2005; 38(6): 1257-66, ix-x
8. Classification and management of rhinosinusitis and its complications. Jackson LL - *Otolaryngol Clin North Am* - 01-DEC-2005; 38(6): 1143-53
9. Chronic upper airway cough syndrome secondary to rhinosinus diseases (previously referred to as postnasal drip syndrome): ACCP evidence-based clinical practice guidelines. Pratter MR - *Chest* - 01-JAN-2006; 129(1 Suppl): 63S-71S
10. The role of bacteria in chronic rhinosinusitis. Brook I - *Otolaryngol Clin North Am* - 01-DEC-2005; 38(6): 1171-92
11. Chronic rhinosinusitis and superantigens. Seiberling KA - *Otolaryngol Clin North Am* - 01-DEC-2005; 38(6): 1215-36, ix
12. Chronic rhinosinusitis (CRS). Cummings - *Otolaryngology: Head & Neck Surgery*, 4th ed., 2005. p 1169–1170
13. Rhinosinusitis. Osguthorpe JD.- *American Academy of Otolaryngology-Head and Neck Surgery* Fifth Edition
14. Rhinosinusitis: Current Concepts. Rosen F & Ryan M - Grand Rounds Presentation, UTMB, Dept. of Otolaryngology. May 1, 2002.