Medical management of chronic rhinosinusitis

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Citation

Abstract
Sinusitis is a common health problem that leads to frequent visits to primary care physicians and to ear, nose and throat specialists in all over the world. It contributes to a significant amount of health care expenditure due to direct costs arising from physician visits and antibiotics, as well as indirect costs related to missed days at work and a general loss of productivity due to a decrease in life-quality of those affected.

Patients with chronic rhinosinusitis also suffer from a poor quality of life and the disease is often associated with other co-morbid conditions such as asthma, eczema and otitis media. A better understanding of the pathogenesis and etiology of chronic rhinosinusitis is essential in order to develop effective therapies. Recently, there has been an evolving concept of an “one airway disease” as the lower and upper airways, paranasal sinuses and middle ear are related anatomically and functionally. Hence, disease in one portion of the airway is prone to spill over into other parts of the airway. This is extremely important to realize as therapy of the patient with sinusitis may lead to improvements in lung function. If gastroesophageal reflux is included, then interactions of the upper and lower airways and the gastrointestinal tract become clinically relevant. Since the majority of patients with sinusitis also suffer from rhinitis, the term rhinosinusitis may be more appropriate. One fifth of patients with chronic sinusitis also have nasal polyposis and a subset of these patients suffer from the aspirin-sensitivity syndrome often associated with asthma and rhinitis.

There is conflict in the criteria for diagnosis of acute or chronic sinusitis. Patients who have been symptomatic for 3 weeks or less are considered to have acute disease while those having prolonged symptoms lasting longer than 6 weeks or more are referred to as having chronic disease.

INTRODUCTION
Sinusitis is one of the most common health care challenges in the world. 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 believe that this condition comprise a spectrum of inflammatory and infectious diseases. The site of sinus and nasal obstruction is important. The ostiomeatal complex is the regions of key importance for the development of rhinosinusitis. 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 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). The diagnosis of chronic rhinosinusitis has been facilitated by an algorithim that has been widely adopted. This is published in a number of formats, including the Bulletin of American Academy of Otolaryngology and Head and Neck Surgery (table 1).
Medical management of chronic rhinosinusitis

Figure 1
Table 1: Diagnosis of chronic rhinosinusitis*.

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Minor criteria</th>
</tr>
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<tbody>
<tr>
<td>Facial pain/pressure</td>
<td>Headache</td>
</tr>
<tr>
<td>Facial congestion/fullness</td>
<td>Fever</td>
</tr>
<tr>
<td>Nasal obstruction/blockage</td>
<td>Halitosis</td>
</tr>
<tr>
<td>Nasal discharge/purulence/discoloration</td>
<td>Fatigue</td>
</tr>
<tr>
<td>Post nasal discharge</td>
<td>Dental pain</td>
</tr>
<tr>
<td>Hyposmia/anosmia</td>
<td>Cough</td>
</tr>
<tr>
<td>Purulence in the nasal cavity on examination</td>
<td>Ear pain, pressure/fullness</td>
</tr>
</tbody>
</table>

*Chronic rhinosinusitis is defined as a condition of greater than 12 weeks’ duration that includes two or more major symptoms or at least one major symptom and two or more minor symptoms.

The major criteria include facial pain, nasal obstruction, hyposmia, and purulence on examination. 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 sign 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.

The bacteriologic characteristics of chronic sinusitis are markedly different of acute sinusitis. The technique used to harvest the cultures, as well as the local patterns of disease, will significantly affect the prevalence of different organisms. Table-2 shows findings that are typical of a reported case series, with exception that most series report a higher incidence of staphylococcus.

Table 2: Bacteriology of chronic sinusitis.

<table>
<thead>
<tr>
<th>Organism</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus viridans</td>
<td>26</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>12</td>
</tr>
<tr>
<td>Hemophilus parainfluenza</td>
<td>16</td>
</tr>
<tr>
<td>Hemophilus influenzae</td>
<td>10</td>
</tr>
<tr>
<td>Anaerobes</td>
<td>10</td>
</tr>
<tr>
<td>Miscellaneous gram negative aerobes</td>
<td>19</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>2</td>
</tr>
</tbody>
</table>

The relative incidence of anaerobic bacteria in chronic sinusitis continues to be debated. The incidence ranges from 0 to nearly 100%. It also common for no growth from the cultures of patients with chronic sinusitis. The reasons for this unknown, although possible explanations include noninfectious inflammation, anaerobic infection and viral infection.

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 patients. 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, and 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.
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 other 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 defense.

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 adults. 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 anti-inflammatory 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 potenitates sensitivities to common aeroallergens by stagnation of this 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 counter acting 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. Nasal saline irrigation also 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, where as 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

Characteristically, chronic sinusitis forms thick viscid secretions. Any assistance in reducing viscosity of the secretion is helpful aiding sinus drainage and patient comfort.

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. Other agents used previously are saturated solution of potassium iodide, acetyl cysteine and carbocysteine.

CORTICOSTEROID

Systemic 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 consider 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 induce 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.
monitoring and immediate withdrawal for side effects is warranted.

Topical corticosteroid: 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 rhinitis. 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 decade.

Currently, there are many products available, with no evidence to indicate that one is better than others. Initially, the spray is usually administered at the highest dose recommended and continued for at least 1 month. Often, a prolong treatment course of 3 to 6 months will be prescribed to help prevent recurrence. In patient with hyperplastic sinusitis or severe accompanying allergies, an indefinite course of nasal steroid therapy is prescribed.

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 complaints. 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.

A recent report has suggested that topical steroids may lead to open angle glaucoma. However, this was convincingly demonstrated only with prolonged use of pulmonary aerosols, which generally result in greatly increased blood level of active drug. A second study of nasal topical steroids only failed to show any increased in risk for ocular complications.

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.

Systemic decongestant: 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 sinusitis.

Topical decongestant: 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. Its 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 has 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 randomize 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.

For initial empiric therapy, the antibiotic must cover the bacteria known to occur in this condition, specifically, staphylococcus, anaerobes, and gram negative bacilli. For this reason, amoxicillin/clavulanic acid is the preferred choice. Alternatives include clindamycin, cefuroxime and clarithromycin. Second line therapy would include
ciprofloxacin, cefprozil or levofloxacin.

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 rational behind dosing children with 60 to 90 mg/kg per day instead of 40 mg/kg for amoxicillin. Haemophilus influenzae also utilizes 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.

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 Japan.

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. Clarithromycin is the macrolide most studied in CRS. While Azithromycin lack studies in CRS.

**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 daycare 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 α2) can potentially block the penetration of viruses through respiratory mucosa. Intranasal IFN α2, 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. 

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References

Medical management of chronic rhinosinusitis

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