

The role of medical management in rhinosinusitis

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Acute bacterial rhinosinusitis is one of the most common upper respiratory tract infections leading to patient office visits in the United States. Although most cases of these infections are mild, they are a leading cause of acute morbidity and school and work absenteeism. These infections are one of the leading causes for antibiotic prescriptions, and in 1998, 20% of adult antibiotic prescriptions were written for a diagnosis of acute sinusitis. Even though the majority of the infections are relatively mild, they result in such morbidity that patients demand treatment. The costs of management for the disorder are significant in terms of both medications and work time lost, and research is needed to identify the patients at risk for potential complications. Injudicious usage and indiscriminate overprescription of antibiotics have fostered the rapid development of penicillin-resistant organisms over the past two decades. Drug-resistant *Streptococcus pneumoniae* and β -lactamase-producing *Haemophilus influenzae* and *Moraxella catarrhalis* are becoming the norm, forcing the need to consider alternatives in antibacterial management. Appropriate medical management of this common problem requires a systematic approach with consideration of adjunctive therapy.

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Abbreviation

ABRS acute bacterial rhinosinusitis

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Acute bacterial rhinosinusitis (ABRS) is a common disorder that leads patients to seek medical care for relief of symptoms of facial pain, purulent postnasal discharge, fatigue, and other symptoms related to the infectious and inflammatory process. The diagnosis of the majority of uncomplicated cases relies on an adequate history and physical examination. Therapies to relieve symptoms are recommended early and involve relief of congested nasal membranes to improve drainage of the blocked sinus pathways. Multiple factors contribute to the etiology of the disorder, and until only recently there have not been clear guidelines for the diagnosis and management of this problem. Antibiotics are utilized to hasten the resolution of symptoms and prevent complications, but their use is questioned in the early stages of the disorder.

Definitions and pathophysiology

In 1996, the American Academy of Otolaryngology, Head & Neck Surgery Task Force for Rhinosinusitis developed a working definition of the disorder in order for health care providers to communicate appropriately regarding this disease [1••]. The definitions included criteria for signs and symptoms of this disorder with an understanding of the relationship of the ostiomeatal complex and upper respiratory viral events for allergic disorders that may predispose patients to obstruction of this narrow drainage pathway. Rhinosinusitis is manifested by an inflammatory response involving the mucous membranes of the nasal cavity and the paranasal sinuses. Inflammatory mediators contribute to the edema and hypersecretion following a common viral upper respiratory tract infection. Factors contributing to the inflammatory process include allergy, immune deficiencies, cystic fibrosis, other mucociliary dyskinesias, and structural abnormalities, but usually there is no single cause. Environmental factors may also lead to mucosal hyperreactivity and may predispose to infection.

Acute bacterial rhinosinusitis is usually preceded by a viral upper respiratory tract infection. In children, upper respiratory infections are responsible for about 80% of ABRS cases and allergies cause the majority of the remainder. The majority of these infections resolve without treatment within 5 to 7 days. Due to the presence of common debilitating symptoms, patients seek medical management at an early stage and usually request an antibiotic, but the natural history of a viral illness should preclude antibiotic usage until after the 7th to 10th day of continued symptoms when secondary

bacterial infection is prone to occur. Gwaltney *et al.* [2] showed the relationship of viral illness to rhinosinusitis and abnormal findings on CT scans. The average adult contracts one to two viral infections per year and children average more: three to six viral infections per year. Approximately 0.5% of all upper respiratory viral infections lead to ABRS secondarily. Thus, in the United States, there are up to 20 million cases per year.

Experimental obstruction of the ostiomeatal complex has led to the development of dependent bacterial sinusitis. Viral illnesses tend to promote ostial obstruction as evidenced by CT scan and magnetic resonance imaging studies [2]. Medical clearance of the obstruction should theoretically prevent primary infection or may improve and relieve secondary bacterial infection.

Diagnostic methodology

Most clinicians base their diagnosis of ABRS on symptoms characteristic of the disorder. These symptoms include nasal congestion, facial pain in the maxillary and frontal areas, dental pain, thick discolored postnasal discharge and hyposmia, as well as associated symptoms of fever and cough (especially in children). Physical signs of ABRS are tenderness of the sinus cavities to palpation and observation of thickened postnasal secretions on anterior rhinoscopy and oral examination with mild periorbital edema [3]. Nasal rhinoscopy using endoscopes may also document purulence at the ostiomeatal complex region, polyp formation, or edema, as well as predisposing anatomic factors such as deviated nasal septum, concha bullosa, or paradoxical turbinates.

Appropriate cultures of the ostiomeatal region should guide otolaryngologists to a proper choice of an antimicrobial regimen, but culture of nasal secretions traditionally has not been correlated with the findings on antral puncture. The gold standard of diagnosis has traditionally been culture of the maxillary sinus via antral puncture. However, recent evidence has linked the association of endoscopic-guided cultures (obtained with fine-wire swabs) to those of antral aspirates; 85.7% of endoscopic cultures corresponded to bacteria present in the maxillary antrum [4]. More recently, Vogan *et al.* [5] noted that endoscopically guided middle meatal cultures were accurate and identified the predominant bacterial pathogen in 90% of cultures. Laboratory evaluation of ABRS may also include nasal cytology (looking for neutrophils), sweat chloride tests, and mucociliary transport studies, which evaluate the timing of the passage of saccharin through the nose to the posterior oropharynx.

Antibiotic therapy

Antibiotics have traditionally been used as effective eradicators of bacterial sinus infections. Gwaltney *et al.* [6] showed that antibiotics improved symptoms and

decreased or eradicated bacteria from the maxillary sinus. When used appropriately, antibiotics are effective in the management of bacterial respiratory tract infections, leading to more rapid resolution of infection and relief of symptoms. They can also help prevent the progression of disease from acute to chronic manifestations. Traditionally, antibiotic regimens are based on empiric knowledge of the most common pathogens responsible for the disorder, predominantly *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*, and penicillin, amoxicillin, and ampicillin have been the standard therapies in nonallergic patients. Other antimicrobials, including the cephalosporins, macrolides, sulfa-based antibiotics, and the fluoroquinolones, have been utilized in comparative studies over the years.

Bacterial resistance and antimicrobial usage

Surveillance studies have documented the prevalence of intermediate and resistant *S. pneumoniae* to penicillin over the past two decades [7,8]. The resistance patterns have been a major concern for health care providers who used to depend on the susceptibility of the most common pathogens to penicillin. Bacteria develop resistance to penicillin by alteration of penicillin-binding proteins or by production of β -lactamases, which degrade the antibiotic. β -lactamase production is the primary method of resistance to penicillin for isolates of both *H. influenzae* and *M. catarrhalis*. During the past 15 years, the prevalence of β -lactamase production has increased and remains at approximately 40% for *H. influenzae* and at 98% for *M. catarrhalis*. Brook [9] notes that β -lactamase-producing bacteria can express their pathogenicity directly through their ability to cause infections and indirectly by production of the enzyme. This protects penicillin-susceptible pathogens from penicillin. Consequently, this phenomenon explains penicillin failure in the management of group A β -hemolytic streptococcal tonsillitis.

The fluoroquinolones (especially the second-generation ones) have proven to be highly potent and are efficacious in the eradication of the pathogens responsible for ABRS. They act by inhibition of the enzymes responsible for supercoiling of the DNA molecule within the bacterial nucleus. Currently, there is little evidence of resistance to this class of antimicrobials, yet there is widespread concern that abuse of this class of antibiotics will lead to rapid rise of resistance as seen with the other classes of antimicrobials.

Contributing to the spread of resistant microorganisms is the extensive use of antibiotics. Factors contributing to this antibiotic overuse include patient expectations (patients consult physicians and expect an antibiotic to be prescribed); clinician time constraints; defensive

medicine; and avoiding the potential sequelae of not prescribing for a patient who has a bacterial infection. Studies in Finland showed that the consumption of erythromycin was related to an increase in the development of erythromycin-resistant group A streptococci. Yet, after 2 years, a significant decline in macrolide-resistant group A *Streptococcus* infection occurred after use of the macrolide antibiotics was reduced. Drug-resistant *S. pneumoniae* appears to be the most prevalent in children under the age of 2 years. The Centers for Disease Control estimate that as many as 50 million antibiotic prescriptions per year could be avoided if clinicians differentiated between viral and bacterial respiratory tract infections. However, symptoms often overlap, and it is believed that bacterial infections may follow viral disease.

Klossek *et al.* [10] evaluated the bacteria of chronic mucopurulent secretions of 394 patients who were referred to the ear, nose, and throat clinic with a diagnosis of chronic rhinosinusitis. Endoscopic-guided cultures were performed. They found that approximately 25% of isolates produced β -lactamase, and there was a decrease in sensitivity to penicillin in 13% of the isolates. Their findings showed that amoxicillin-clavulanate was the most active oral antibiotic *in vitro*. Jiang and Hsu [11] studied 74 patients with chronic rhinosinusitis who took ampicillin (500 mg every 6 hours) 2 weeks preoperatively and obtained specimens at time of surgery. They showed that preoperative antibiotics could eradicate most sensitive bacteria; however, resistant bacteria remained present and active within the sinus cavity following this treatment.

In patients with acute community-acquired bacterial rhinosinusitis, Gwaltney *et al.* [12] showed that ceftibuten as an extended-spectrum cephalosporin was as effective as amoxicillin-clavulanate in establishing a 90% cure rate. Clement and de Gandt [13] evaluated 254 patients for efficacy, tolerability, and safety of azithromycin and amoxicillin-clavulanate in patients with nonsevere acute maxillary and ethmoid sinusitis. They found that the two drugs were well tolerated and equally effective. Dinis *et al.* [14] examined sinus tissue pharmacokinetics with amoxicillin-clavulanate. They administered 875 mg 2 to 4 hours prior to surgery and obtained tissue samples intraoperatively. The samples were then evaluated for tissue concentration levels and showed that amoxicillin penetrated the tissues with excellent levels.

Pharmacokinetics and pharmacodynamic principles

Over the past few years, developments in the evaluation of pharmacokinetics (absorption, distribution, metabolism, and excretion) of antimicrobials has been established [15]. Pharmacodynamics relates to the concentration of the

drug and its pharmacologic effect. There are two distinct relationships of antimicrobials according to the animal models of *in vitro* studies. Antimicrobials may exhibit either time-dependent killing or concentration-dependent killing. Time-dependent antimicrobials include the β -lactams, macrolides, and clindamycin. Once these antibiotics reach a critical concentration, increasing the concentration further will not increase the rate or extend the bacterial killing. Concentration-dependent antibiotics need to achieve a relative value well above the minimal inhibitory concentration of the bacteria. It is necessary for these antimicrobials to obtain a very high peak of concentration and they are not time dependent. The majority of these pharmacokinetic and pharmacodynamic principles can be reviewed at length [1••,7,15].

Guidelines for antibiotic therapy

The most recent data are from the Antimicrobial Treatment Guidelines for ABRS established by the Sinus and Allergy Health Partnership [1••]. This group examined extensive current management methodologies and established a bacterial efficacy rate from a mathematic modeling of ABRS that is based directly on pathogen distribution, resolution rates without treatment, and *in vitro* microbiologic efficacy. Efficacy rates greater than 90% included amoxicillin-clavulanate and the fluoroquinolones gatifloxacin, levofloxacin, and moxifloxacin (and presumably gemifloxacin, a new antibiotic due to be released, will fit into this category). Efficacy rates of 80 to 90% included high-dose amoxicillin, cefpodoxime proxetil, cefuroxime axetil, and cefixime (based on *H. influenzae* and *M. catarrhalis* coverage only) as well as trimethoprim/sulfamethoxazole. Note that the predicted spontaneous resolution rates in patients with confirmed ABRS are approximately 46 to 50%.

Based on the bacterial efficacy rates, the Partnership developed recommendations for antimicrobial therapy. These recommendations were then for patients with mild disease, patients with mild disease who had received antibiotics in the previous 4 to 6 weeks, and patients with moderate disease. It was presumed that patients with fairly severe disease would not be placed into outpatient antibiotic therapy modules and would be treated with intravenous antibiotics. The recommended initial antibiotic therapy for adult patients or children with mild ABRS is amoxicillin-clavulanate, amoxicillin, cefpodoxime, or cefuroxime, based on efficacy data.

Duration of therapy

Treatment regimens suggest 10 to 14 days for adequate duration of therapy in patients who develop ABRS. Some authors recommend an additional 7 days of antibiotic therapy once the patient's symptoms improve. Previous guidelines have suggested up to 21 days of antimicrobial therapy. Duration of therapy still has not been established

adequately as some studies still show that resistant bacteria can remain viable in a closed sinus long after an effective antibiotic regimen has been in place.

Rational antibiotic therapy

Once a diagnosis of acute rhinosinusitis has been established, the health care provider should consider the duration of symptoms. Once the patient's symptoms reach the 7th to 10th day, consideration of a secondary bacterial infection is high and antibiotic therapy should be considered. Management of ABRS should be based on a culture-directed antimicrobial. The most common pathogens previously stated are for the most part responsive to high doses of amoxicillin. If the patient does not respond after an initial 3 days of therapy, adding a β -lactamase inhibitor should be considered. Adjunctive therapy at this time is highly beneficial to help reduce the inflammatory process at the ostiomeatal complex.

Adjunctive therapies

The traditional methodology of warm steam inhalations for inflammatory rhinitis has been modified to include nonprescription nasal saline mists. Methods to promote moisturization of the nasal cavity with removal of thick mucous crusts have been advocated to reduce and minimize symptoms. Nasal saline is readily available and is considered a supportive measure, but no studies prove efficacy. Hypertonic saline has been shown to increase mucociliary clearance and ciliary frequency [16] as well as mucociliary transit times of saccharin [17]. Hypertonic saline was used in children and showed statistical improvement in symptoms as compared with nasal saline alone [18].

Mucolytic therapy should help thin the dehydrated thick mucous secretions and theoretically improve mucociliary function. Guaifenesin, the only current oral mucolytic agent, prescribed at 1200 mg per day, is recommended by many, but no recent studies prove its efficacy.

Decongestants

Decongestant therapy is generally advocated for symptomatic relief of the congestion experienced by patients with ABRS. Topical decongestants (pseudoephedrine hydrochloride, phenylephrine hydrochloride, and oxymetazoline) are usually recommended for a 3- to 5-day course in the acute stage to attempt to open the blocked sinus ostia by α -adrenergic stimulation. The resulting vasoconstriction of the mucosal capillaries promotes shrinkage of the swollen nasal mucosa. Bende *et al.* [19] used oxymetazoline on experimentally induced sinusitis in rabbits. They found that the nose drops actually interfered with the normal defense mechanisms of bacterial rhinosinusitis. In 1997 Yoo *et al.* [20] found that rebound rhinitis medicamentosa was reversed within 48 hours when patients were subjected

to nightly topical decongestants sprays for up to 4 weeks. Side effects of prolonged decongestants may be a significant factor when considering their use. Some studies also show that there may be a reduction of ciliary activity with the use of these medications.

Systemic decongestants may offer patients subjective relief of symptoms of congestion but they have not been shown to have any positive influence on reduction of the severity of the disease nor shortening the duration of disease. Oral decongestants lack the rebound effect of topical medications, and they can be used for a longer period of time.

Antihistamines

Allergic rhinitis is one of the leading ancillary causes for ABRS, and allergic patients may develop an acute episode following a seasonal exacerbation of allergy. Antihistamines may be beneficial in adjunctive therapy for the patient with a history of allergic rhinitis. Controversy surrounds the type of antihistamine to be administered, either first or second generation. The anticholinergic properties of the first-generation antihistamines may tend to reduce the rhinorrhea associated with the inflammation, but the drying effects of these products thicken sinus secretions and possibly slow mucociliary clearance. The newer second-generation antihistamines (acrivastine, cetirizine, fexofenadine, and loratadine) would be favored in patients with an allergic history. Topical antihistamines are currently available (azelastine, levocabastine) and are extremely potent histamine blockers, but no controlled studies of their utilization in rhinosinusitis are available at this time.

Intranasal corticosteroids

Anti-inflammatory therapy has been a consideration for most physicians who treat patients with ABRS. Topical nasal corticosteroid therapy has been both admonished and recommended for adjunctive therapy for this disorder [21]. Widely used in patients with allergic rhinitis and nonallergic rhinitis, they reduce the late-phase reaction, reduce the number of epithelial cells, especially basophils and eosinophils, and reduce the secretory response by inhibiting the cholinergic actions. Yilmaz *et al.* [22] investigated 52 children with ABRS and documented improved recovery rate in the group using intranasal budesonide versus using the group oral pseudoephedrine (Table 1).

Recent studies suggest that the medical management of ABRS can be enhanced with the addition of intranasal steroids. Topical intranasal steroids have marked anti-inflammatory actions to decrease the vascular permeability and to inhibit the release of chemical mediators, especially histamine, leukotrienes, and others. They reduce the cellular influx to the inflammatory site and modify both the early- and late-phase responses in rhinitis. The

Table 1. Intranasal steroids

Generic names	Trade names
Beclomethasone dipropionate	Beclomethasone (GlaxoWellcome, Inc., Research Triangle Pk., NC) Vancenase, Vancenase AQDS (Schering-Plough Corp., Kenilworth, NJ)
Budesonide	Rhinocort Rhinocort Aqua (Astra Zeneca Pharmaceuticals, Wayne, PA)
Flunisolide	Nasarel (Dura Pharmaceuticals, San Diego, CA)
Fluticasone	Flonase (GlaxoWellcome, Inc., Research Triangle Pk., NC)
Mometasone furoate	Nasonex (Schering-Plough Corp., Kenilworth, NJ)
Triamcinolone acetonide	Nasacort, Nasacort AQ (Rhône-Poulenc Rorer Pharmaceuticals, Inc., Collegeville, PA)

same principles hold true in sinusitis; topical intranasal steroids should have marked beneficial effects due to the similarity of the respiratory epithelium in the nose and the paranasal sinuses.

The use of intranasal steroids in children with sinonasal disease brings concerns about the possibility of growth retardation. Intranasal beclomethasone dipropionate was shown to induce a statistically significant slowing of the growth rate in children according to Skoner *et al.* [23]; however, no growth suppression was found in children using mometasone furoate [24]. This debate is ongoing, and caution is recommended in long-term use in children.

The incidence of complications of nasal steroid therapy was investigated by Cervin and Andersson [25], and they found a higher incidence of nasal septal perforations in young women during their first year of therapy. Other complications of prolonged intranasal steroid use include epistaxis and headaches.

Topical nasal steroids are advocated in hyperplastic polypoid rhinosinusitis. Hamilos *et al.* [26] demonstrated gradual response of the nasal polyps to intranasal steroids and showed that they also reduced nasal polyp inflammation but not the expression of proinflammatory cytokines. Damm *et al.* [27] combined the use of oral steroids and intranasal steroids and found markedly reduced polypoid disease, but this medication did not affect the anterior ethmoid area and did not change the need for consideration of surgery.

Systemic corticosteroids

Oral systemic corticosteroids are extremely effective in reducing the inflammation of rhinosinusitis. They dramatically reduce the edema resulting from increased capillary permeability and reduce cellular influx. These

factors promote their use; however, physicians are justifiably reluctant to use them routinely in order to prevent suppression of the hypothalamic-pituitary axis. Generally, they are not recommended for acute infections due to a risk of development of a more fulminant infection. In patients with chronic rhinosinusitis, systemic steroids are indicated. Tapering doses are recommended if they are used for more than 2 weeks. Systemic steroids are useful in treatment of the patient with nasal polyposis, the Samter triad (aspirin sensitivity, polyps, and asthma), and allergic fungal rhinosinusitis.

Allergy immunotherapy

Allergy plays a role in the development of rhinosinusitis, but in the acute stage of bacterial infection, control of the allergic state with medications is deemed important. Nishioka *et al.* [28] showed that allergic patients who received immunotherapy had a better long-term outcome after surgery. Newman *et al.* [29] found an association between extensive sinus disease on CT scan and upper respiratory allergy in 78% of patients. It is the patients who develop recurrent acute rhinosinusitis or who have prolonged symptoms of rhinosinusitis who may be candidates for allergy testing and possible immunotherapy.

Conclusions

Acute bacterial rhinosinusitis is a complicated disorder that is challenging for physicians to diagnose appropriately. Management of the initial stages of the inflammation is based on restoration of the normal mucociliary outflow of the paranasal sinus tract and nose. Humidification techniques and decongestion are efficacious at the early stage, and topical intranasal steroids may have some benefit to reduce the inflammation. After 5 to 7 days of continued symptoms, the provider should consider antibiotic therapy to hasten the relief of symptoms and help to prevent further complications. Initial antibiotic regimens center around therapy for the common pathogens, *S. pneumoniae* and *H. influenzae*, using penicillin or amoxicillin in appropriate dosages. Amoxicillin-clavulanate has the greatest efficacy based on bacterial eradication for both mild and moderate disease. Fluoroquinolones are highly efficacious in eradication of pathogens but should be used sparingly to help prevent the possibility of antimicrobial resistance.

References and recommended reading

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16 Nose and paranasal sinuses

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