Changing diagnostic and treatment strategies for chronic sinusitis

**ABSTRACT:** Treating chronic sinusitis may at times require courses of antibiotics much more prolonged than those used in acute sinusitis, but not all patients with radiographic evidence of sinusitis require antibiotics. Chronic sinusitis and chronic asthma frequently occur together and may share a common pathogenesis. This article explores current knowledge about this common respiratory problem and presents an algorithm for its evaluation and treatment.

Chronic sinusitis is the most frequently reported chronic medical condition in the United States. The National Institutes of Health estimated in 1993 that 32.3 million people in this country have it. In comparison, 24.2 million have allergic rhinitis and 15 million have asthma. Yet, considerable debate continues as to what exactly sinusitis is, what causes it, and how to diagnose and treat it. And anaerobic bacteria and resistance to antibiotics are increasingly complicating its treatment. This paper delves into these issues, and presents my own approach to this problem.

**PATHOPHYSIOLOGY**

Sinusitis, by definition, involves inflammation of the mucosa of the paranasal sinuses (Figure 1). Infection may or may not be involved; if present, it may be viral, bacterial, or fungal.

Acute sinusitis is often presumed to be the result of a bacterial infection, since the inflammation of acute sinusitis is usually thought to be due to bacterial growth in the closed space of an obstructed sinus cavity. However, as will be discussed later, viral colds also often produce abnormalities of the sinus cavities.

Chronic sinusitis, in contrast, implies inflammation but not necessarily infection, lasting 3 months or more. The concept of “chronic hypertrophic sinusitis” is a useful way to consider chronic sinusitis, as it avoids the implication of infection. Hypertrophy or edema of the...
mucosa is usually found, and may be the consequence of allergic or nonallergic attraction and activation of eosinophils in the sinus mucosa in the same way that the chronic eosinophilic inflammation affects the lower airways in asthma.

However, acute bacterial infection may occur on top of chronic hypertrophic sinusitis. Since inflammation can obstruct drainage of the sinus cavities, which consequently become infected, acute episodes of bacterial infection may punctuate the course of chronic sinusitis.

Infections
Most studies of the microbiology of sinusitis were in acute sinusitis.

In a study of children with acute maxillary sinusitis, the most prevalent organisms were Streptococcus pneumoniae, Moraxella catarrhalis, and Haemophilus influenzae. Other studies of acute sinusitis and also of acute otitis media in children found similar results. In contrast, anaerobic bacteria predominated in a study of children with chronic sinusitis. Some of the organisms, such as Propionibacterium acnes, may have been contaminants from the nose or skin.

In adults with acute sinusitis, the most common organisms are also S pneumoniae and H influenzae; however, anaerobes appear more often and M catarrhalis less often in adults than in children.

Fungal sinusitis
In past years, fungal sinusitis was often diagnosed after sinus surgery, when silver-stained specimens revealed fungal hyphae. Mucomycosis of the sinuses of diabetic patients has been recognized for many years. In early reports, Aspergillus species were found in surgical specimens from patients with no known immunosuppression. Histopathologic studies showed chronic fibrosing granulomatous inflammation, and the term “allergic aspergillus sinusitis” was used. The thick pasty material found inside sinuses containing fungal hyphae has been termed “allergic mucin.”

A study by deShazo and Swain reviewed 99 case reports of allergic fungal sinusitis and proposed criteria for diagnosing it (Table 1). On computed tomography (CT), the fungal material was of higher density than the fluid associated with polyps or bacterial exudate. Bony erosion was found on sinus CT in 35.7%. Proptosis due to impingement on the orbit has been reported. Atopy was present in 76.5% and asthma in 56.3%. Nasal polyps were present in 80.2%. IgE was elevated in 74.3%, and fungal precipitins were present in 88.9%. Fungus was cultured in 75.5%, and the following genera were isolated: Bipolaris, Curvularia,
Aspergillus, Drechslera, Exserohilum, Alternaria, Helminthosporium, and Fusarium. These authors suggest that most patients with fungal sinusitis be treated with surgery to aerate the sinus cavities, postoperative oral steroids, and then intranasal steroids. Antifungal antibiotics were not used in most cases, although optimal treatment of fungal sinusitis remains to be determined.

Nasal polyps
Polyps often obstruct paranasal sinus drainage in adults, but are rare in children, except for children with cystic fibrosis. A clinical clue is intermittent nasal obstruction that becomes constant. In a review of 60 patients with maxillary, frontal, or sphenoid sinuses that appeared opaque on CT (a possible sign of polyps), 28% of the medically treated patients had polyps, as did 47% of the surgically treated patients. Nasal polyps can occur in any of the sinuses, and are often responsible for opacification of all of them on CT. Surprisingly, some patients whose sinuses appear opaque on CT seem to avoid infection for long periods. In patients known to have polyps, the appearance of facial pain or headache may signal bacterial infection.

Other causes of obstruction
Nasal septal deviation alone rarely causes sinusitis, but septal deviation, spurs, and ridges reduce the extent of the mucosal swelling necessary to obstruct the nasal passage.

In children, adenoid hypertrophy can completely obstruct the posterior nasal passages. This obstruction may be observed by endoscopy as well as by mirror exam. Angiofibromas are rare causes of constant nasal obstruction in adolescents. Both endoscopy and CT may help detect angiofibromas; treatment is surgical.

In children, foreign objects in the nose must be kept in mind as a cause of sinusitis, especially if unilateral. In adults, cranial tumors rarely invade the nasal passages to produce obstruction.

**Eosinophilia**
Eosinophils invade the epithelium of the airway in nasal polyps, chronic sinusitis, and asthma. Through the years there has been debate over whether this process is the cause or the consequence of these conditions; the current view is that it is the cause. Studies have found tissue eosinophilia in more than half of patients with chronic sinusitis undergoing surgery and eosinophils in the nasal secretions of patients with nasal polyps. A more recent study of chronic hypertrophic sinusitis identified cytokines, granulocyte-macrophage colony stimulating factor (GM-CSF), and interleukin-3 (IL-3) as contributing to local eosinophil accumulation.

**Sinusitis and asthma**
Chronic sinusitis and asthma share pathogenetic features and frequently occur as a continuum of eosinophilic respiratory inflammation.

Many patients with asthma (especially severe asthma) also have chronic sinusitis. Schwartz et al reported that 47% of 217 patients seen for acute asthma symptoms had sinusitis. Eosinophilia in the peripheral blood and in mucosal specimens is common to both chronic sinusitis and asthma and increases with disease severity. Although allergies play a role in both chronic sinusitis and asthma, eosinophilia may be present without inhalant allergies.
Treating the sinusitis can relieve the asthma. Rachelefsky et al\textsuperscript{14} studied 48 children with asthma and sinusitis. All received antimicrobial agents for 2 to 5 weeks. Thirty-nine experienced clinical and radiologic resolution of sinusitis; 38 were able to stop taking bronchodilators. Slavin\textsuperscript{15} followed up asthmatic patients with sinusitis 5 years after sinus surgery and found that asthma symptoms had decreased in 60%.

**Intubated patients at risk**

Nasal intubation places hospitalized patients at high risk of acquiring sinusitis. Caplan and Hoyt\textsuperscript{16} discovered nosocomial sinusitis in 32 patients hospitalized with severe trauma. All had high fever and most had leukocytosis. Forty-one pathogens, mostly gram-negative bacilli, were recovered from 25 patients. *Pseudomonas aeruginosa* was the most common isolate. The sinusitis resolved with treatment and with removal of the nasal tube in 20 patients.

In another study, maxillary sinusitis developed in 73% of patients who had nasogastric or nasotracheal tubes, compared with only 34% of patients with oral tubes. The incidence of sinusitis increased to 95.5% if the tube remained in place for a week. Overall, gram-negative bacteria were the organisms most commonly recovered on maxillary aspiration, but the gram-positive bacterium *S aureus* was the single organism most commonly recovered; *P aeruginosa* (which is gram-negative) was the second most common.\textsuperscript{17}

### CLINICAL DIAGNOSIS AND EVALUATION

Chronic sinusitis is common among the patients of internists, pediatricians, family physicians, allergists, pulmonologists, and otorhinolaryngologists. Many patients present with complaints of chronic sinus pain or drainage, and symptoms may last for years. The clinical history needs to probe the early phase of the patient's nasal symptoms. A history of intermittent seasonal rhinitis and conjunctivitis may precede year-round symptoms caused by nasal polyps or chronic sinusitis.

It is just as important to exclude sinusitis as a diagnosis as it is to rule it in. Many a patient with frequent "sinus headaches" has no radiographic evidence of sinusitis. Even patients with impressive histories of chronic nasal complaints, including congestion and drainage, may not have radiographic evidence of sinusitis and may not need antibiotics.

The historic, physical, and radiographic findings all help establish the diagnosis of chronic sinusitis and determine treatment.

**Clinical signs and symptoms unreliable**

The accuracy of clinical signs and symptoms in diagnosing sinusitis in the absence of radiographic proof is low. Williams et al\textsuperscript{18} calculated that the symptom of greatest sensitivity is colored nasal discharge, but its specificity was only 52%. The next most sensitive symptoms were cough and sneezing, but their specificities were only 44% and 34%, respectively. The symptom of greatest specificity was maxillary toothache (93%), but its sensitivity was only 18%. Sinus tenderness had a sensitivity of 43% and a specificity of 65%.

**Radiographic findings**

Radiographically, an air-fluid level in a paranasal cavity is interpreted as acute sinusitis (FIGURE 2). Mucosal thickening implies inflammation or at least edema of the mucosa of the sinus, but, in the absence of air-fluid levels or opacification, does not necessarily imply infection. Patients who have undergone maxillary antrostomy may still have mucosal thickening even if the antrostomy is patent, and endoscopic examination of the maxillary cavity may reveal hypertrophic or edematous mucosa with no evidence of infection.

**Advantages of CT.** CT scans provide far better anatomic information than do plain films of the sinuses. Plain films may even be misleading. McAlister et al\textsuperscript{19} obtained plain radiographs and CT scans in 70 infants and children who had recurrent sinusitis. If CT is the "gold standard," standard radiography had a false-negative rate of 45% and a false-positive rate of 35%.

CT scans frequently reveal anatomic abnormalities of the sinuses in children and adults with chronic upper respiratory symptoms. Nasal polyps, if present, nearly always show up on CT scans of the sinuses, since most nasal polyps originate in the paranasal sinuses.

On the other hand, positive CT findings do not always indicate bacterial infection. Gewaltney et al\textsuperscript{20} found abnormalities of the sinus cavities by CT in all but four of 31 adults with viral colds. In 79% of cases, another CT scan 2 weeks later showed resolution or marked improvement. None of the patients received antibiotics.
Computed tomographic scans of the paranasal sinuses, axial cuts. Top left, normal maxillary sinuses. Top right, thickened mucosa in the left and right maxillary sinuses. Bottom left, an air-fluid level in the left sphenoid sinus after ethmoidectomy. Bottom right, a cyst or polyp in the left maxillary sinus.

Nguyen et al. obtained CT scans in 91 children presenting to allergy clinics with chronic respiratory symptoms lasting longer than 3 months, and found that 63% had chronic sinusitis. This percentage is very similar to the results of CT scans in adults presenting to our allergy clinic with chronic upper respiratory symptoms. We reviewed 1000 CT scans and found that 61% of the cases had one or more abnormal sinus cavity. The maxillary sinuses were abnormal in 52%, the ethmoid sinuses were abnormal in 42%, the sphenoids were abnormal in 16%, and the frontals were abnormal in 15%.

**Recommendations for the use of CT.** CT
is widely available in the United States; the main factor limiting its use is that it costs more than plain radiography. This difference can be greatly reduced or eliminated by using limited axial or coronal views. A limited CT scan is sufficient for diagnosing sinusitis and costs no more than plain films of the sinuses. Four non-contiguous coronal cuts through the frontal, anterior ethmoid and maxillary, posterior and maxillary, and sphenoid sinuses has demonstrated 93% sensitivity and 89% specificity compared with standard contiguous 2- to 5-mm cuts.23

Limited axial cuts can also be used. The advantage of axial cuts is that they display the ethmoid complex in its entirety along the axial plane.

Obtaining screening films in the axial plane and subsequent films in the coronal plane provides maximum anatomic information.

If the patient does not improve with appropriate medical therapy, detailed coronal CT views may be obtained to provide the surgeon with more anatomic information about the ostiomeatal complex (the structures surrounding the drainage path of the frontal, maxillary, and anterior ethmoid sinuses). All of these sinuses drain into the space under the middle turbinate, the middle meatus. The ostia of these sinuses and the gap between the uncinate process and the middle turbinate are very small. Even mild mucosal swelling may obstruct drainage. If obstruction persists long enough, fluid accumulation and infection follow. Improving drainage through this area is one of the main goals of current sinus surgery.

Once a diagnosis of sinusitis is established on clinical and radiographic grounds, CT does not need to be repeated every time symptoms return. Repeat CT may be needed to evaluate complications such as extension of infection into the cranium or orbit, or to document improvement such as aeration of an opacified major sinus cavity.

Nasal endoscopy
The finding of purulent drainage from sinus ostia on nasal endoscopy is highly specific; however, infected sinuses do not drain constantly, and there may be no drainage from an infected sinus during examination. Patients with sinusitis failing to respond to antibiotic therapy should have a thorough nasal evaluation to look for polyps.

Immunologic evaluation
A variety of immunologic deficiencies, from absent IgA to AIDS, have been reported in chronic sinusitis. However, immunologic evaluation should begin with inhalant allergies, which are more common.24

Nasal challenge with allergens can acutely increase mucosal thickening or opacification in allergic patients with chronic maxillary sinusitis. The acute mucosal changes resolve in 24 hours for patients with an immediate-phase clinical response to the nasal challenge, while a late-phase clinical response requires 48 hours to resolve.25

TREATMENT

In most cases, treatment of presumed bacterial acute sinusitis can be deferred until the upper respiratory illness has lasted longer than a typical viral cold.

It is common practice to treat isolated episodes of acute sinusitis on the basis of clinical findings without radiographic confirmation. A 10-day course of an inexpensive antibiotic such as amoxicillin or trimethoprim-sulfamethoxazole may eliminate bacterial growth in acute sinusitis. However, in advanced chronic sinus, symptoms commonly return within 2 to 3 days after a 10-day course of antibiotics. Goodman and Slavin26 consider 3 weeks the minimum course of antibiotics for chronic sinusitis.

In addition, antibiotics effective against β-lactamase-producing organisms are needed in chronic sinusitis. Because prolonged treatment with β-lactam antibiotics is expensive, proving the diagnosis of chronic sinusitis radiographically is cost-effective. Since one course of antibiotics effective in chronic sinusitis costs more than do radiographic studies to prove the diagnosis, radiographic evidence should be obtained before prescribing a second course of antibiotics.

FIGURE 3 shows my strategy for treating chronic sinusitis.

Antibiotics
Although isolated acute cases of sinusitis may respond to amoxicillin, the increasing prevalence of β-lactamase producing bacteria has changed the optimal choice of antibiotics in chronic sinusitis (TABLE 2). Many patients receive multiple courses of antibiotics per year, further increasing the likelihood of antibiotic resistance.
**An algorithm for treating sinusitis.**

**Resistant organisms.** *H influenzae* produce β-lactamase in 30% to 35% of strains, are usually resistant to erythromycin, and are resistant to trimethoprim-sulfamethoxazole in 30% of strains. About 90% of *M catarrhalis* strains produce β-lactamase, up to 20% may be resistant to trimethoprim-sulfamethoxazole, and 10% may be erythromycin-resistant.

*S pneumoniae* are relatively resistant to penicillin; however, the resistance is mediated by alteration of penicillin-binding proteins rather than by elaboration of β-lactamase. Thus, clavulanate does not help with this organism. Up to 56% of *S pneumoniae* are resistant to erythromycin, and up to 30% are resistant to trimethoprim-sulfamethoxazole.

Group A streptococci are generally resistant to trimethoprim-sulfamethoxazole and a small percent are resistant to erythromycin.

*Staphylococcus aureus* almost always produce β-lactamase. Most *S aureus* strains are susceptible to trimethoprim-sulfamethoxazole, but erythromycin resistance is growing.27

**Amoxicillin with potassium clavulanate** (Augmentin) inhibits the β-lactamase enzymes. Another advantage is that anaerobic organisms such as *Bacteroides* species should respond to it.

**Erythromycin-sulfisoxazole** (Pediazole) is used in children. Erythromycin is not used alone because it does not cover *H influenzae*. Sulfas allergy may be a problem, and allergy skin testing is not available for sulfas drugs as it is for penicillin.

**Clarithromycin** (Biaxin) is particularly...
useful for patients with hypersensitivity to both sulfa and penicillin. In treating lower respiratory tract infections, clarithromycin also covers *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella pneumophila*, and *Bordetella pertussis.*

Erythromycin and clarithromycin should not be taken in combination with terfenadine (Seldane) or astemizole (Hismanal), because of the metabolic interaction resulting in possibly toxic levels of the antihistamines. Theophylline doses must be reduced if erythromycin or clarithromycin are given to patients already taking optimal levels of theophylline.

**Cephalosporins** are frequently used to treat sinusitis. However, first-generation cephalosporins, such as cephalexin (Keflex), do not adequately cover *H influenzae*, *M catarrhalis*, or penicillin-resistant pneumococci. Second-generation cefaclor (Ceclor) still does not cover some strains of *H influenzae* and *M catarrhalis*. In addition, cefaclor is more frequently associated with serum sickness-like reactions than other cephalosporins. Cefuroxime axetil (Ceftin) has the advantage of resistance to the β-lactamases of *H influenzae*, *M catarrhalis*, and *S aureus* and covers anaerobes.

Cefixime (Suprax) is a third-generation cephalosporin effective against β-lactamase-producing organisms, but has somewhat reduced activity against *S pneumoniae.* Cefpodoxime proxetil (Vantin) has improved activity against gram-positive organisms, including relatively penicillin-resistant pneumococci.

**Fluoroquinolones**, including ciprofloxacin (Cipro) and ofloxacin (Floxin) are avoided in children, owing to concern about damage to growing cartilage. Quinolones are active against *H influenzae* and *M catarrhalis*, but are poor against pneumococci. The quinolones reduce theophylline metabolism, necessitating reductions in theophylline doses.

**Anaerobic bacteria** have been cultured in chronic sinusitis in both adults and children. In one study of 40 children with chronic sinusitis, anaerobes were recovered in all 37 positive bacterial cultures. In 14 cases, anaerobes were mixed with aerobes. Response to treatment was more rapid with clindamycin than other antibiotics, including amoxicillin.

**Side effects.** Many of the broad-spectrum antibiotics used in treating sinusitis cause diarrhea. In many cases, the diarrhea is mild and can be controlled by eating yogurt or taking lactase tablets. If diarrhea becomes severe, pseudomembranous colitis must be considered. Detecting the toxin of *Clostridium difficile* in the stool requires stopping the offending antibiotic and then giving either vancomycin or metronidazole.

**Who should receive antibiotics?** Considerable art remains in deciding who should be treated with antibiotics at all. Most physicians agree with antibiotic treatment for patients with facial pain and purulent drainage. Most also agree with antibiotics for an air-fluid level on an x-ray or CT scan. Most other circumstances are open for debate.

Opacified maxillary sinuses yielded white blood cells and bacteria in 17 of 18 cases stud-
CHRONIC SINUSITIS

TABLE 3

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Brand name</th>
<th>Dosage</th>
</tr>
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<tbody>
<tr>
<td>Beclometasone</td>
<td>Vancenase</td>
<td>1 puff each side two to four times a day</td>
</tr>
<tr>
<td></td>
<td>Vancenase AQ</td>
<td>1-2 sprays each side twice a day</td>
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<tr>
<td></td>
<td>Vancenase AQ (double strength)</td>
<td>1-2 sprays each side daily</td>
</tr>
<tr>
<td></td>
<td>Beconase</td>
<td>1 puff each side two to four times a day</td>
</tr>
<tr>
<td></td>
<td>Beconase AQ</td>
<td>1-2 sprays each side twice a day</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>Nasacort</td>
<td>2-4 puffs each side daily</td>
</tr>
<tr>
<td></td>
<td>Nasacort AQ</td>
<td>1-2 sprays each side daily</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>Nasalide</td>
<td>2 sprays each side three times a day</td>
</tr>
<tr>
<td></td>
<td>Nasarel</td>
<td>2 sprays each side twice a day</td>
</tr>
<tr>
<td>Budesonide</td>
<td>Rhinocort</td>
<td>1-4 puffs each side daily</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>Flonase</td>
<td>1-2 sprays each side daily</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Dexacort</td>
<td>1-2 puffs each side two to three times a day</td>
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</tbody>
</table>

ied by Evans et al. However, patients with nasal polyps can have all their sinuses opacified and yet have long periods of time with no facial pain or purulent drainage to suggest infection. The diagnosis of structural abnormality of the mucosal lining of the paranasal sinuses, "sinusitis," is definitively made by the display of the anatomy on CT scans of the sinuses. Antral punctures are only practical for the maxillary sinuses and are too invasive for daily management of upper respiratory symptoms. The diagnosis of bacterial infection still must be made on the basis of the history and physical examination. A decrease in pain and resolution of yellow drainage after 2 or 3 days of antibiotic therapy confirms the diagnosis of bacterial infection.

How long to continue the antibiotic is difficult to predict. As few as 3 days may suffice in some patients with acute sinusitis, ie, those with a first episode of bacterial sinusitis and no structural damage to the sinuses.

There are no controlled studies of the optimal duration of antibiotic treatment in chronic sinusitis. For a patient with months or years of recurrent sinusitis and extensive mucosal damage, resolution of inflammation may take several weeks. The pain and purulent drainage may recur in 2 or 3 days after a 10-day course of antibiotics is completed. Three weeks of antibiotics has been suggested as the minimum for treatment in chronic sinusitis, but courses of 6 weeks are not rare. Bacterial growth probably does not take this long to suppress, but if the damaged mucosa is not allowed long enough to heal, the pathogenic bacteria rapidly return.

Ancillary treatment

Although controlled studies are again lacking, treatment of the eosinophilic inflammation seems appropriate.

Steroid nasal sprays

Several available sprays have potent topical steroid activity on the mucosa and minimal systemic activity (TABLE 3). These agents reduce inflammation around the sinus ostia to promote normal aeration and drainage of the sinus cavities. The steroid spray is continued throughout the course of antibiotics and afterward.

Continued use of steroid sprays is especially important in patients with nasal polyps. Corticosteroids are the only medicines available that have any chance of shrinking polyps. Systemic corticosteroids occasionally dramatically shrink polyps, but polyps last or recur for many years, and systemic steroids are too toxic for long-term use. Fortunately, topical steroids may help reduce the obstruction caused by polyps. In one study, intranasal budesonide, 400 μg/day was more effective than placebo in reducing nasal symptoms and increasing the peak nasal inspiratory flow rate.

Nasal saline may help remove crusts and help restore mucociliary function, especially when the mucosa has been damaged by very dry air.

Avoiding smoking is strongly encouraged, as it is in all respiratory conditions.

Oral decongestants may promote sinus drainage through vasoconstriction. Phenylpropanolamine and pseudoephedrine, the oral decongestants most frequently used, are safe for most patients who are not...
hypertensive and are not receiving monoamine oxidase inhibitors.

**Nasal decongestant sprays** promptly relieve nasal congestion, but rebound nasal congestion develops after only a few days.

**Surgery**

Surgery is considered when medical management cannot control recurrent infection, nasal polyps prevent nasal breathing, or there is reason to suspect a tumor of the sinuses rather than infection. Tumors of the paranasal sinuses, such as inverted papilloma, squamous carcinoma, and adenocarcinoma, extend beyond the confines of the sinus of origin. CT of the sinuses is very valuable in identifying this important distinction. Destruction of the bony walls of a sinus strongly suggests a process more destructive than the usual chronic sinusitis or nasal polyposis. Even in cases of opacification of all sinuses by polyp tissue, the bony walls are still visible on CT of the sinuses. Bacterial sinusitis may penetrate the walls of the sinuses, causing the medical and surgical emergency of infection of the orbit or of the intracranial space.

Unfortunately, surgery for nasal polyps cannot be considered curative. The usual polyp history is of multiple polypectomies and continued symptoms over many years. Ruhno et al studied 36 patients with nasal polyposis. Notably, the patients had undergone polypectomy a mean of 5.6 times. Use of steroid nasal sprays after polypectomy may slow the regrowth of polyps.

**REFERENCES**

1. National Institute of Allergy and Infectious Disease Profile FY1993 p. 52.