

Evidence-based approach to medical and surgical treatment of nasal polyposis

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Activity Objectives

1. To discuss the management of a case of nasal polyps.
2. To review risk factors for nasal polyps.
3. To discuss treatments of nasal polyps.
4. To review the role of aspirin in patients with aspirin-exacerbated respiratory disease.

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CLINICAL VIGNETTE

A 46-year-old African American woman was referred by her pulmonologist for evaluation of sinusitis. She had had sinus problems for many years, which were getting progressively worse. Her symptoms included postnasal drip that irritated her throat and worsened her asthma, dark yellow to greenish nasal discharge, and bilateral nasal congestion with a decreased sense of smell and taste. In the past, her nasal symptoms had generally been worse in the spring and summer, but by the time of presentation, they had worsened and were present year-round. The patient had severe persistent asthma and was currently being treated with zileuton, budesonide/formoterol (160-4.5), albuterol, and prednisone (40 mg/d). She was using her rescue inhaler 2 to 5

times per day and waking nightly. Medications for her nasal complaints included diphenhydramine nightly and both intranasal budesonide and azelastine daily. She had tried cetirizine, loratadine, and fexofenadine previously but thought that diphenhydramine worked better in minimizing her nasal symptoms. Her primary care physician prescribed multiple courses of oral antibiotics for recurrent sinus infections over the course of the past year. She stated that she felt a temporary improvement after taking the antibiotics, but symptoms quickly returned. Other symptoms included headaches located between her eyes and in the temples that ranged from mild to severe (rated approximately 8/10). On review of systems, she reported that her left ear felt blocked.

Past allergy testing showed positive reactions to several common allergens. Cystic fibrosis and immune deficiencies had been excluded by appropriate testing. Her total IgE level was 47 KU_A/L, and her fraction of exhaled nitric oxide was 111 parts per billion. Results of pulmonary function tests are shown in Table E1 in this article's Online Repository at www.jacionline.org.

The patient described a history of asthma and allergies in her parents and siblings. She had "cardiac arrest" after taking aspirin and subsequently avoided aspirin and all nonsteroidal

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anti-inflammatory drugs. Other parts of the medical history for this patient included obstructive sleep apnea on continuous positive airway pressure (CPAP), but recently, she has been unable to tolerate CPAP because of worsening nasal congestion. She was treated for morbid obesity with a gastric restrictive procedure, which consisted of gastric bypass and a short limb roux-en-y gastroenterostomy that led to an approximately 160-lb weight loss. The frequent use of prednisone induced type 2 diabetes mellitus and cataracts. She never smoked, and she abstained from alcohol.

Physical examination showed an edematous nasal mucosa on anterior rhinoscopy. Endoscopic examination showed bilateral

nasal polyps with mucus stasis (see Fig E1 in this article's Online Repository at www.jacionline.org). Polypoid changes of the uncinate process were observed.

Sinus computed tomographic scanning showed severe pansinusitis, with the exception of the left frontal sinus. There was an air-fluid level in the left maxillary sinus. Both osteomeatal units were obstructed (see Fig E2 in this article's Online Repository at www.jacionline.org).

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REVIEW

Nasal polyps have been reported to occur in between 0.5% and 4% of the population, with the majority being asymptomatic in older patients.^{E1} The polyps usually begin to develop at approximately 40 years of age and are particularly common in asthmatic patients. Among patients with aspirin sensitivity, 36% to 96% have chronic rhinosinusitis with polyps.

The clinical evaluation of patients with polyps begins with a detailed history. The primary complaints are nasal obstruction and olfactory dysfunction. Headaches are possible in this setting, but unlike the common belief among patients and some clinicians, severe headaches are not typical. The physical examination evaluates for signs of the sinus disease spreading beyond the sinus cavities, such as proptosis or double vision indicating involvement of the orbits by expansion of the sinuses or neurologic symptoms indicating involvement of the nearby part of the central nervous system. Endoscopic evaluation visualizes the nasal cavity better than an anterior examination with a nasal speculum, and it can be used for collection of cultures of purulent secretions to guide medical intervention or for diagnosis of small polyps. Beware of unilateral polyps because approximately 30% of such cases are tumors that require a distinct work-up and treatment.^{E1}

When patients have persistent symptoms despite optimal medical treatment or a complication is suspected based on the history or physical examination, a sinus computed tomographic scan is recommended. Magnetic resonance imaging overcalls typical inflammatory disease of the sinuses, including polyposis, but can be useful when the clinician is suspicious of malignancy, extrasinus involvement by inflammatory disease, or a severe headache initially suspected of not being of sinus origin.

Causative factors in patients with nasal polyposis

Many factors are postulated to play a role in nasal polyps.^{E2} We limit our discussion to 3: allergies, aspirin, and obesity. The incidence of positive allergy test results is greater in patients with polyps than in the healthy population, although it is high in both groups. A critical review of the literature shows that there is not strong support for the role of allergy in nasal polyps because many studies have methodological flaws. Thus we currently do not believe that immunotherapy is indicated in the treatment of nasal polyps because there are no available data to support its efficacy. One medical intervention for allergies, administration of glucocorticosteroids, works well in patients with nasal polyps and patients with allergies.

Ninety-six percent of aspirin-sensitive patients have radiographic evidence of sinus disease in their paranasal sinuses.^{E3} Patients with the combination of aspirin sensitivity, asthma, and nasal polyps are usually nonatopic, and the prevalence of this classic condition (Samter triad, which is currently referred to as aspirin-exacerbated respiratory disease) increases after the age of 40 years. Children of parents with asthma, nasal polyps, and aspirin sensitivity are more likely to have chronic sinusitis with nasal polyps than those children of parents without aspirin-exacerbated respiratory disease. Interestingly, IgE antibodies to staphylococcal enterotoxins can be found in the majority of patients with nasal polyps who are aspirin sensitive, indicating a potential role for locally produced IgE in polyps.^{E4}

The mechanism by which aspirin leads to disease in aspirin-exacerbated cases is unclear, despite major interest in this disease

entity.^{E3} This disease is not inherited in a typical fashion (eg, autosomal dominant or recessive), indicating a complex genetic inheritance. Environmental exposures are likely to contribute to the pathophysiology of this disease. The most notable causes are exposure to tobacco smoke and viral infection. Environmental tobacco smoke increases the chances of having aspirin-exacerbated respiratory disease in adulthood 5-fold, especially if exposure to smoke starts in childhood and extends into the third decade of life.^{E5} Many patients describe a prolonged period of excellent respiratory health, followed by the sudden onset of sinus symptoms, which seems consistent with a viral upper respiratory tract infection precipitating the disease. It is entirely possible that in susceptible subjects, particularly those whose respiratory tracts already have sustained an assault by environmental tobacco smoke, a viral infection stimulates an inflammatory syndrome that becomes self-propagating. There are direct data to refute or support such a hypothesis, although it remains a leading one.

After the inciting events that lead to the development of aspirin-exacerbated respiratory disease, the acute reactions involved in the severe mucosal inflammation revolve around the inhibition of the COX-1 enzyme by aspirin and nonsteroidal anti-inflammatory drugs.^{E6} The primary event is a rapid decrease in the synthesis of COX-1 products, including prostaglandin E₂ (PGE₂). PGE₂ inhibits 5-lipoxygenase and 5-lipoxygenase-activating protein, which are enzymes that generate potent proinflammatory mediators, such as leukotriene B₄ and leukotriene C₄. PGE₂ has a critical inhibitory effect that is reduced in the aspirin-sensitive patient, leading to a large increase in the synthesis of leukotrienes. Reduced PGE₂ synthesis also results in decreased mast cell stability and increased release of histamine and tryptase. In addition to increased synthesis of leukotrienes, most patients with aspirin-exacerbated respiratory disease have increased expression of cysteinyl leukotriene 1 receptors, which increase end-organ responses to leukotrienes.

Why the inhibition of PGE₂ formation, which occurs in all subjects after COX-1 inhibition, leads to dysregulated leukotriene production only in patients with aspirin-exacerbated respiratory disease remains unknown. This increase in leukotriene levels has led to the use of leukotriene modifiers in patients with nasal polyps and aspirin sensitivity. Thus despite a robust clinical relationship between nasal polyposis and aspirin-exacerbated respiratory disease, we have little knowledge about the underlying pathologic link at the molecular level.^{E3}

Obesity is an increasing problem both in the United States and worldwide in developed nations. Evidence suggests that obesity affects the development and severity of asthma, a disease related to nasal polyposis.^{E2} The mechanism by which obesity influences asthma has not been established, with possibilities including a modified inflammatory response, increased asthma symptoms caused by weight and deconditioning, functional effects on breathing mechanics, or a decreased response to inhaled corticosteroids.

How obesity affects aspirin-exacerbated respiratory disease is unknown, other than being another exacerbating factor of asthma. Whether obesity influences chronic rhinosinusitis in general is unknown. Unfortunately, the major weight loss of our patient did not significantly affect her asthma or chronic rhinosinusitis.

A role of sinus disease in asthmatic patients

The connection between chronic rhinosinusitis with nasal polyposis and asthma is well documented, and the mechanism

for the connection is likely to be multifactorial.^{E7,E8} At least 4 mechanisms have been postulated to account for the relationship. First, the nose warms, filters, and humidifies inhaled air. If this function is impaired, the process is shifted to the lower airway, where cooling and drying can cause bronchospasm. Second, inflammatory products from the upper airways can be aspirated directly into the lower airways. Third, nasal inflammation might result in local release of cytokines into the bloodstream, which eventually upregulates circulating cells, such that when they are recruited to the lower airways, they are primed to release greater quantities of inflammatory mediators. Fourth, a nasal bronchial reflex might exist.

Treatment options

Treatment of chronic rhinosinusitis with nasal polyps is a challenge because the disease is heterogeneous, with multiple mechanisms leading to the same clinical end point.^{E9} Additionally, few treatments have been studied in randomized trials. Apart from intranasal and oral steroids, most other treatment options have failed to prove efficacy. One must also note that children differ from adults in their pathophysiology because their immune system is not fully mature. Additionally, nasal polyposis in children warrants consideration of cystic fibrosis as a diagnosis.

The unifying theme for treatment of nasal polyps is that chronic, severe mucosal inflammation needs to be controlled; acute infections need to be treated with antibiotics (ideally culture directed); and surgery is reserved for medical failure to provide access for postoperative topical anti-inflammatory treatment.^{E10} The goals of treatment are to eliminate or reduce polyp size, restore nasal breathing, restore the sense of smell, reduce symptoms of rhinitis, reduce the number of bacterial infections, and prevent recurrence. Also, there is evidence that treatment of chronic rhinosinusitis with polyps improves not only the upper airways but also the status of concomitant asthma.^{E1}

Because of their anti-inflammatory properties, corticosteroids have been the mainstay of treatment of nasal polyposis. Topical intranasal corticosteroids are more effective for chronic rhinosinusitis with polyps than for chronic rhinosinusitis without polyps. Oral steroids have been shown to reduce temporarily polyp size and symptoms, but the optimum dose has not been established, and many regimens exist. The reduction in polyp size with oral steroids can be extended by the use of intranasal steroids after the systemic treatment is concluded.^{E11} Large-scale prospective studies are needed for determination of the role of newer targeted agents, such as anti-IL-5 mAb and anti-IgE mAb, in patients with nasal polyps.

Antibiotics are used to eliminate infection and reduce inflammation. Only 1 of 7 randomized, placebo-controlled studies of topical antibiotics showed a positive effect.^{E12} Short-term oral antibiotics have been used for the treatment of acute exacerbations of chronic rhinosinusitis. Studies on the long-term use of antibiotics for their anti-inflammatory properties have had mixed results. Doxycycline had a modest and significant effect on patients with nasal polyps, potentially because of dual antibacterial and anti-inflammatory effects.^{E13}

Surgery is clearly indicated for intracranial and intraorbital complications, mucocoeles, anatomic variations, allergic fungal disease, massive polyps with bony remodeling, and antrochoanal polyps. However, the category leading to the majority of surgical interventions is that of patients who are symptomatic despite

medical treatment. Smith et al^{E14} showed better improvement in quality of life using validated instruments in patients electing surgery compared with continued medical therapy in some of the only outcome data available of surgical outcomes in patients with chronic rhinosinusitis.

The surgical approach aims at removing inflamed sinus tissue and bony septae within the sinus cavities. A large audit of patients at 5 years after surgery in England and Wales showed a 20% revision rate overall but marked and persistent improvement in results on the Sino-Nasal Outcome Test, a quality-of-life measure.^{E15} Worse outcomes for surgery are found for patients who have aspirin-exacerbated respiratory disease, asthma, and frontal sinus disease.

A multitude of other strategies for nasal polyps have been suggested, all of which lack good evidence for efficacy, and the field in general suffers from a lack of replicated, well-conducted trials.

THE CASE REVISITED

Our patient had aspirin-exacerbated respiratory disease confounded by obesity, sleep apnea, and headaches. The last is always a concern in a patient with opacified sinuses because it might indicate more severe disease and extrasinus complications. In this case medical therapy was maximized, significant weight loss caused by gastric bypass did not make a difference, and nasal disease prevented the use of CPAP, worsening the patient's sleep and daytime performance.

Given medical failure and no prior surgery, we opted to operate. Oral steroids were instituted before surgery and tapered postoperatively. Bilateral endoscopic sinus surgery went smoothly, and we continued intranasal steroids and zileuton postoperatively after the mucosa had healed, 3 weeks after surgery. Although the polyps will inevitably recur, we hope that continued topical treatment with corticosteroids and zileuton will delay the recurrence, and in the interim the patient will have a better quality of life with a sense of smell, better tolerance of CPAP (with resultant improved function), and reduced need for oral steroids and antibiotics. We anticipate that her productivity (eg, missed days at work) will be improved.

Although allergen immunotherapy has been proved effective in the treatment of allergic rhinitis, its role in the treatment of a patient with positive allergy test results and nasal polyps has not been studied and was not considered for our patient.

Patients who are candidates for aspirin desensitization include those with uncontrolled nasal polyp disease requiring more than 1 operative intervention (we recall that this was our patient's first surgery), those with repeated systemic corticosteroid bursts, or those receiving continuous systemic corticosteroids.^{E3} Although this has not been studied, patients are thought to do better if the desensitization shortly follows sinus surgery that debulks the nasal polyps and reduces the inflammatory load. Lack of evidence tempers a strong recommendation on this point. However, our pulmonologists were reluctant to consider aspirin desensitization because of our patient's "cardiac arrest" after taking aspirin. For additional information on aspirin desensitization, please refer to Burnett et al^{E16} and White et al.^{E17}

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FIG E1. Endoscopic visualization of the right nasal cavity showing a nasal polyp and polypoid degeneration of the uncinate process.

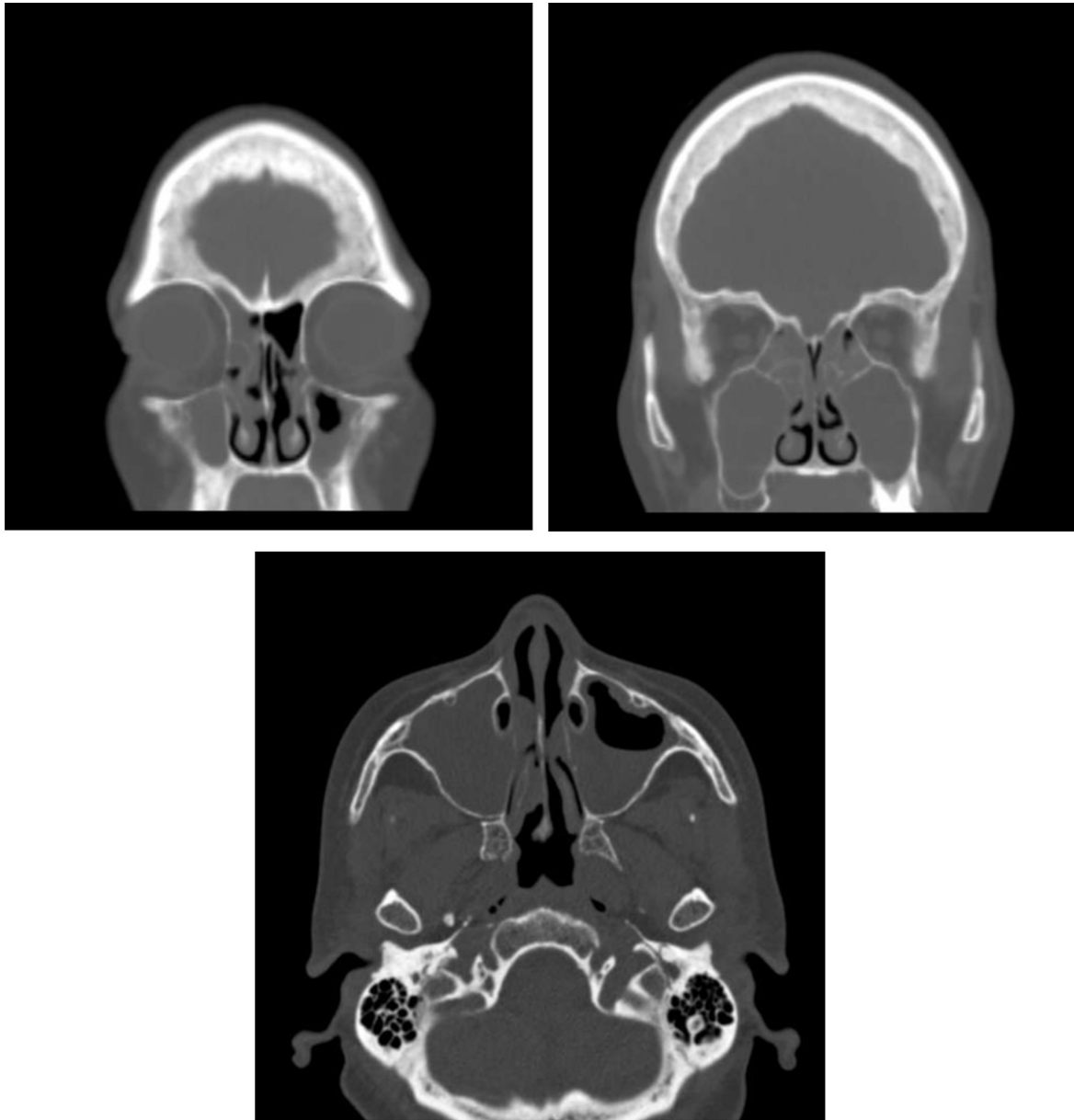


FIG E2. Sinus computed tomographic scans of the patient showing extensive inflammatory changes in the paranasal sinuses and an air fluid level in the left maxillary sinus.

TABLE E1. Pulmonary function test results

FVC (L)	2.73
FVC, predicted	3.34
FVC, % predicted	82
FEV ₁ (L)	1.72
FEV ₁ (L), predicted	2.71
FEV ₁ , % predicted	63
FEV ₁ /FVC ratio	0.63
FEV ₁ /FVC ratio, predicted	0.82
FEV ₁ /FVC ratio, % predicted	76

FVC, Forced vital capacity.