REVIEW

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Sinusitis: Allergies, antibiotics, aspirin, asthma

ABSTRACT

Sinusitis is very common, so it is important to understand its pathophysiology, diagnosis, and medical and surgical treatments. In cases of chronic sinusitis, adjunctive therapies and evaluation by subspecialists may be warranted. Some special testing is needed to diagnose allergic fungal sinusitis. Most important is to understand that sinusitis is not a single entity but is associated with many comorbid conditions, notably asthma.

KEY POINTS

Acute bacterial sinusitis should be treated with a 10-day course of an antibiotic active against *Streptococcus pneumoniae,* such as amoxicillin-clavulanate.

People with allergic fungal sinusitis have a hypersensitivity reaction involving an intense eosinophilic inflammatory response to fungi that colonize the sinuses. This allergic response is not invasive and should be distinguished from invasive fungal sinusitis, which is more common in patients with diabetes and immunocompromised patients.

Aspirin-sensitive asthma can initially present as nasal polyps or chronic sinusitis; its treatment includes avoidance of aspirin and nonsteroidal anti-inflammatory drugs (or desensitization protocols if aspirin therapy is necessary) and nasal steroids to shrink polyps.

MANY HAVE COLDS, but few need antibiotics. This is a good adage, but nevertheless some patients do develop bacterial sinusitis and would benefit from antibiotic treatment. Furthermore, there is a link, often unappreciated, between sinusitis, asthma, and aspirin, and treating the sinusitis (and avoiding aspirin) might improve the asthma. Complicating matters, some cases of chronic sinusitis are due to an allergy to fungi colonizing the sinuses.

SINUSITIS IS INFLAMMATION

Sinusitis is defined as inflammation of the usually air-filled sinuses of the skull. The inflammation can be caused by infectious (bacterial, viral, or fungal) or noninfectious (allergic) triggers. This inflammation can block the sinus ostia, leading to mucus retention, hypoxia, decreased mucociliary clearance, and predisposition to bacterial growth.

Sinusitis is categorized as:[1]

- *Acute* if symptoms have lasted less than 4 weeks
- *Subacute* if symptoms have lasted 4 to 8 weeks
- *Chronic* if symptoms have lasted longer than 8 weeks
- *Recurrent acute*, often defined as three or more episodes per year with each episode lasting less than 2 weeks.

MOST CASES ARE VIRAL

The most common cause of acute sinusitis is a viral upper respiratory tract infection. The viral infection may lead to sinus inflammation, but this usually resolves without treat-

Normal CT scan of the sinuses

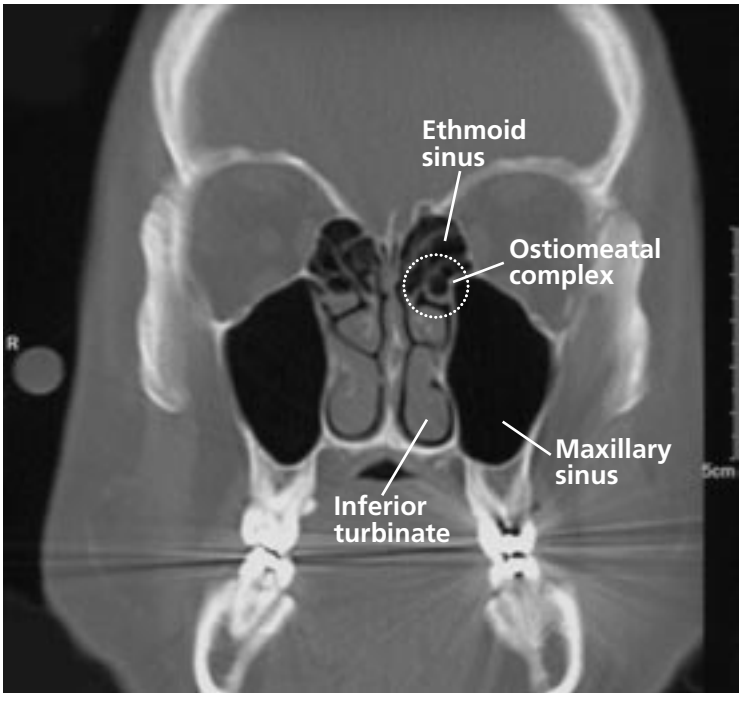

FIGURE 1. Computed tomographic scan of the sinuses, coronal view. The maxillary, anterior ethmoid, and frontal sinuses all drain into the ostiomeatal complex, which is easily obstructed.

ment in less than 2 weeks. Symptoms that worsen or persist for longer than 10 days suggest a secondary bacterial infection.

Inflammation creates environment for bacteria

The initial viral infection and inflammation set the stage for bacterial infection by blocking the ostia of the sinuses.

The sinuses most often involved in both acute and chronic sinusitis are the maxillary and the anterior ethmoid sinuses.[2] These sinuses, plus the frontal sinuses, all drain into the ostiomeatal complex, which is narrow and easily blocked (FIGURE 1).

Normally, cilia in the mucosa sweep the sinuses clear of mucus and debris. But in a viral infection, the nasal mucosa produces more mucus and recruits inflammatory mediators such as white blood cells, leading to congestion and swelling of the nasal passages. If the sinus ostium is blocked, air cannot get in and mucus cannot get out, creating an environment for bacterial growth.

If the acute sinusitis does not resolve, chronic sinusitis promotes continued recruitment of inflammatory infiltrates and mucosal thickening.

Bacterial pathogens

The most common organisms in acute bacterial sinusitis are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*.[1,3] In chronic sinusitis, the same organisms are involved, plus *Staphylococcus aureus*, coagulase-negative *Staphylococcus* species, and anaerobic bacteria.

These organisms are becoming resistant to antibiotics. For example, the reported rates of resistance to penicillin in *S pneumoniae* across the United States are 28% to 44%.[4] Resistant organisms are more common in patients who have received two or more recent courses of antibiotics, a common scenario in patients with chronic sinusitis.

Allergic fungal sinusitis is a distinct condition

Allergic fungal sinusitis is a distinct condition that occurs in nonimmunocompromised patients.[5] Fungi are ubiquitous in the environment, and most people tolerate exposure to mold spores in the air. However, people with allergic fungal sinusitis have a hypersensitivity reaction involving an intense eosinophilic inflammatory response to fungi that colonize the sinuses. This allergic response is not invasive and should be distinguished from invasive fungal sinusitis, which is more common in patients with diabetes and in immunocompromised patients.

The common fungi that cause this syndrome include *Bipolaris spicifera* and *Aspergillus*, *Curvularia*, and *Fusarium* species.[5]

The diagnostic criteria for allergic fungal sinusitis[6] include:

- Chronic sinusitis
- Computed tomography (CT) of the sinuses showing chronic mucosal thickening, opacification, polyps, and high-intensity signaling from the high protein content in the mucus
- Sinus secretions showing the characteristic allergic mucin with necrotic debris and eosinophils filled with Charcot-Leyden crystals and the presence of fungi, either on microscopic examination or by culture.

TABLE 1

Some treatment regimens for acute bacterial sinusitis

ANTIMICROBIAL	DOSAGE
First-line agents	
Amoxicillin	Mild-moderate cases: 500 mg every 12 hours for 10–14 days Severe cases: 875 mg every 12 hours for 10–14 days
Amoxicillin-clavulanate	Two 1,000-mg extended release (XR) tablets (each containing amoxicillin 1,000 mg and clavulanic acid 62.5 mg) every 12 hours for 10 days
Cefuroxime axetil	250 mg twice a day for 10–14 days
Cefpodoxime proxetil	200 mg every 12 hours for 10 days
Sulfamethoxazole-trimethoprim	One DS tablet (sulfamethoxazole 800 mg and trimethoprim 160 mg) daily for 10–14 days
Azithromycin	500 mg on day 1, then 250 mg on days 2–5
Clarithromycin	1,000 mg daily for 14 days
Second-line agents	
Gatifloxacin	400 mg daily for 10 days
Moxifloxacin	400 mg daily for 10 days
Levofloxacin	500 mg daily for 14 days, or 750 mg daily for 5 days
Telithromycin	800 mg daily for 5 days

Although magnetic resonance imaging (MRI) is overly sensitive for diagnosing sinusitis (see below), its excellent soft-tissue differentiation aids in diagnosing fungal sinusitis, with low signaling of fungal concretions in the sinus cavities.

Also, allergy testing can verify that these patients have a reaction to molds that is mediated by immunoglobulin E (IgE). Treatment is with oral steroids, allergy consultation, and surgery.

DIAGNOSIS OF ACUTE SINUSITIS

In a primary care setting, a good history and physical examination can provide a reliable diagnosis of acute sinusitis.

To avoid using antibiotics unnecessarily, one should try to determine if the patient truly has bacterial sinusitis or just a common viral upper respiratory tract infection. In viral infections, the mucus is typically thin, clear, and not persistently purulent. Purulent secretions have a high positive predictive value for bacterial sinusitis. Also, in viral infections, nasal congestion is a predominant symptom, but not persistent or worsening facial congestion, headache, facial pain, or fatigue. Again, symptoms of a viral upper respiratory tract infection should resolve in 7 to 10 days; symptoms lasting longer suggest bacterial sinusitis.

Most common in acute bacterial sinusitis: *S pneumoniae, H influenzae, M catarrhalis*

CT is the imaging study of choice

The two imaging studies most commonly used when acute sinusitis is suspected are plain radiography and computed tomography (CT). MRI is not recommended for this purpose because it does not distinguish air from bone.

However, plain radiographs do not adequately represent the anatomy of the individual ethmoid air cells, the extent of mucosal thickening, or the anatomy of the ostiomeatal complex.

Therefore, CT is the imaging procedure of choice (FIGURE 2). In fact, CT may not cost much more than plain radiography because limited coronal views (usually comprising approximately four to six views that include the maxillary, ethmoid, sphenoid, and frontal sinuses) are usually sufficient for ruling out sinusitis. More detailed coronal slices are useful for better viewing of sinus anatomy, such as the ostiomeatal complex, and for surgical mapping.

Acute sinusitis

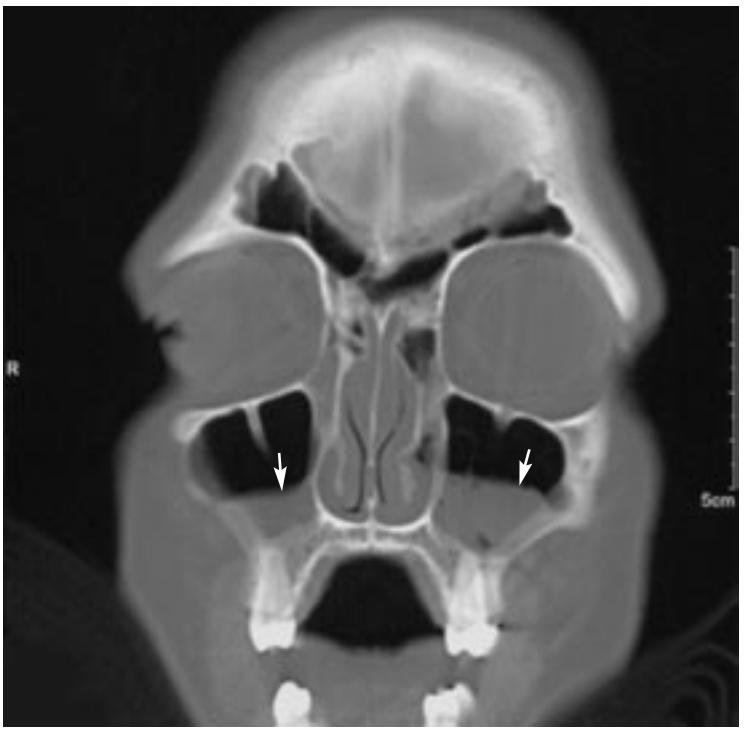

FIGURE 2. CT scan showing acute sinusitis. Note the fluid levels in the maxillary sinuses (arrows). Compare with the normal CT scan in FIGURE 1.

When to order. CT of the sinuses is not necessary if there is a high clinical suspicion of uncomplicated acute sinusitis. It can be ordered to confirm the suspicion of sinusitis before antibiotics are given, especially if complications are a concern. It is also performed preoperatively for visualization of the anatomy.

THERAPY FOR ACUTE SINUSITIS

The antibiotic chosen to treat uncomplicated acute sinusitis must cover *S pneumoniae*, *H influenzae*, and M *catarrhalis*.

Since *S pneumoniae* causes most of the intracranial and orbital complications of acute bacterial sinusitis (most commonly in immunocompromised patients), adequate coverage for this organism is important. Amoxicillin or amoxicillin-clavulanate for 10 to 14 days is an appropriate first-line treatment for uncomplicated acute sinusitis (TABLE 1).[7] The use of amoxicillin-clavulanate provides the additional benefit of clavulanic acid, which binds and inhibits beta-lactamases that inactivate amoxicillin, resulting in amoxicillin having a broader spectrum of activity.

In areas of high *S pneumoniae* resistance, dosages of amoxicillin as high as 90 mg/kg/day should be considered, up to a maximum of 1 g every 12 hours.[1] These dosages are effective because resistance in *S pneumoniae* is related to alterations in penicillin-binding proteins, a mechanism distinct from the beta-lactamase enzymatic inactivation of *H influenzae* and M *catarrhalis*.[7,8]

Other options are cephalosporins such as cefpodoxime proxetil and cefuroxime. Sulfamethoxazole-trimethoprim, clarithromycin, and azithromycin can be prescribed for patients allergic to beta-lactams but may not provide adequate coverage for *H influenzae* or resistant *S pneumoniae*.[7]

Penicillin, erythromycin, cephalexin, tetracycline, and cefixime are not recommended for acute sinusitis because they do not adequately cover the major organisms.

If treatment with one of these first-line agents fails—and lack of clinical response within 72 hours of starting therapy should be considered a treatment failure—antibiotics with a broader spectrum of activity should be considered. These include the fluoroquinolones gatifloxacin, moxifloxacin, and levofloxacin, especially if amoxicillin-clavulanate, cefpodoxime proxetil, and cefuroxime have already been tried.

Telithromycin (a ketolide) was most recently approved for treating acute bacterial sinusitis due to *S pneumoniae*, *H influenzae*, M *catarrhalis*, or *Staphylococcus aureus*.

TREATMENT OF CHRONIC SINUSITIS

Antibiotics are controversial in the treatment of chronic sinusitis. However, a patient may need antibiotics to treat an acute exacerbation of chronic sinusitis. The agent should cover not only organisms that cause acute sinusitis but also *Staphylococcus* species and anaerobes.[1] These antibiotics include amoxicillin-clavulanate, cefpodoxime proxetil, cefuroxime, gatifloxacin, moxifloxacin, and levofloxacin. Therapy may need to be for 3 to 6 weeks.

Nasal steroids have anti-inflammatory effects that reduce nasal congestion. Currently used nasal steroids such as fluticasone,

mometasone, budesonide, and triamcinolone have a favorable safety profile. Specifically, fluticasone and mometasone have very low bioavailability and are indicated for patients aged 2 years or older. Budesonide has a category B rating for use in pregnancy.

Oral steroids are commonly used for treating chronic sinusitis, especially when extensive mucosal thickening is seen on CT or there is congestion, although no well-controlled or blinded studies of these agents have been performed for this indication. However, nasal polyps, which are often present in patients with chronic sinusitis, have been shown to regress with the use of intranasal and systemic steroids.[1]

Antihistamines are not indicated for sinusitis but may be helpful to treat underlying allergic rhinitis.

Decongestant nasal sprays (eg, oxymetazoline and phenylephrine hydrochloride) can be used for 3 to 5 days to temporarily alleviate drainage and congestion. However, their long-term use can cause "rhinitis medicamentosa," ie, rebound congestion due to vasodilatation and inflammation.

Oral decongestants (eg, pseudoephedrine) are a reasonable alternative to topical decongestants if the patient has no contraindication such as hypertension.

Mucolytic agents (eg, guaifenesin) can help to decrease the viscosity of the mucus for better clearance and are often combined with decongestants. Some mucolytics are now available over the counter.

Saline spray or irrigation may help clear secretions.

Surgery

If medical therapy fails to control symptoms adequately or if complications are suspected, an otolaryngology consultation is warranted. The evaluation may begin with nasal endoscopy to better visualize the nasal cavity and ostiomeatal complex. Endoscopy may also allow for endoscopically guided sinus culture.

Endoscopic sinus surgery can clear the sinuses of chronic infection, inflammation, and polyps. Functional endoscopic sinus surgery focuses on removing mucosal disease while avoiding the stripping of mucosa from the dependent maxillary sinuses. Instead, bone is removed from involved ethmoid sinuses and sinus ostia. This current surgical approach, often done on an outpatient basis, emphasizes the importance of abnormalities in the ostiomeatal complex as predisposing to frontal, ethmoid, and maxillary sinusitis.

Chronic sinusitis

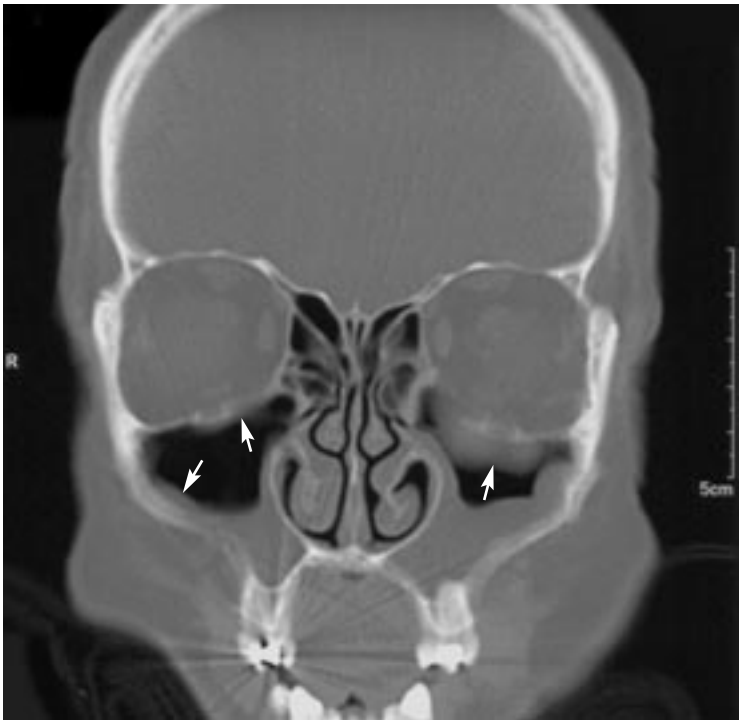

FIGURE 3. CT scan showing chronic sinusitis. Note the mucosal thickening in the maxillary sinuses (arrows).

Allergy consultation

Allergy consultation is recommended for any patient with recurrent acute or chronic sinusitis to rule out allergy to dust mites, mold, animal dander, and pollen, each of which can trigger allergic rhinitis.

An allergy consultation will provide immediate hypersensitivity skin testing to delineate which environmental aeroallergens may exacerbate allergic rhinitis and predispose to sinusitis. Medical management and environmental control measures are discussed, and treatment options such as medications and/or immunotherapy are considered. Other conditions associated with sinusitis such as asthma, immunodeficiencies, cystic fibrosis, and gastroesophageal reflux are looked for, assessed, and treated.

Allergy consultation is recommended for any patient with recurrent acute or chronic sinusitis

Allergists are also trained in aspirin desensitization to treat patients with the aspirin triad, ie, aspirin sensitivity, nasal polyps, and asthma (see below).

SINUSITIS AND ASTHMA

Special consideration should be given to patients with a history of sinusitis and asthma. The association between these two conditions was described as far back as 1870, when researchers induced bronchoconstriction in animals by stimulating the upper airway mucosa with chemicals.[9] Today, 50% of patients with severe asthma have radiographic evidence of sinusitis; the risk factors are steroid-dependent adult-onset asthma, aspirin sensitivity, and nasal polyps.[10]

If upper airway disease actually exacerbates lower airway disease, the exact mechanism has yet to be elucidated. Proposed mechanisms include:

- The nasopharyngobronchial reflex[11]
- Postnasal drip or drainage of inflammatory cells and mediators into the lung[12]
- Persistent mouth breathing, in which air is not warmed and filtered through the nasal passages before it enters the lungs[13]
- Cytokines and chemotactic factors released by inflamed sinus tissue into the circulation promoting inflammation and recruiting eosinophils into the upper and lower airway.[1]

A more likely explanation is that the same histopathologic processes take place in the upper and lower airways. Eosinophilic inflammation, epithelial damage, and basement membrane thickening, which are present in chronic rhinosinusitis,[14] are also present in asthma, suggesting a common process underlying at least some types of chronic sinusitis and asthma.

With this close association, one would expect that treatment of the upper airway would improve the lower airway. And indeed, in studies in adults and children with chronic sinusitis and asthma, those who underwent medical treatment of sinusitis were able to decrease or discontinue their use of bronchodilators and obtain normal results on their pulmonary function tests.[15–18]

Perform an aspirin challenge in patients in whom aspirin-sensitive asthma is suspected

On the other hand, the effects of surgical management of chronic rhinosinusitis on asthma have been mixed. But in some reports, functional endoscopic sinus surgery had beneficial effects on asthma: patients had less-frequent asthma symptoms, less-severe symptoms, fewer hospitalizations, and fewer acute care visits in the year following surgery.[19]

ASPIRIN-SENSITIVE ASTHMA

In 1968, Samter and Beers[20] described a triad consisting of asthma, aspirin sensitivity, and nasal polyps. This condition is frequently unrecognized by clinicians.

Based on patient history alone, the prevalence of aspirin sensitivity in asthmatic adults is 3% to 5%, but this percentage can be two to three times greater when adult asthmatic patients are challenged prospectively with aspirin.[21]

Aspirin intolerance is an independent risk factor for asthma.[21–23] However, even people not previously sensitive to aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) can develop aspirin-induced asthma as late as the third to fourth decade of life.[24]

Symptoms within 2 hours of ingestion

Patients with aspirin-induced asthma begin to experience wheezing, nasal congestion, rhinorrhea, and tearing 30 minutes to 2 hours after taking aspirin or NSAIDs. Other symptoms may include flushing, angioedema, and gastrointestinal distress.

Asthma is more severe in patients with aspirin-induced asthma than in those without aspirin sensitivity. Despite this increased severity, the initial presentation may be recurrent nasal polyps or chronic sinusitis.[24]

Disorder of leukotriene metabolism

Aspirin-sensitive asthma is not actually an allergy, ie, it is not an IgE-mediated reaction to aspirin. Instead, it is believed to be a disorder of leukotriene metabolism.

Higher concentrations of leukotrienes have been detected at baseline and after aspirin challenge in patients with aspirin-sensitive asthma than in patients with asthma not induced by aspirin.[25–27] In addition, aspirin-sensitive patients have greater

expression of the cysteinyl leukotriene receptor CysLT1 on leukocytes within the nasal epithelium compared with control patients,[28] and overexpression of the enzyme LTC4 synthase.

Aspirin challenge

Aspirin-induced asthma can be difficult to diagnose on the basis of the history alone, as the patient may not associate taking aspirin or an NSAID product with an asthma exacerbation. A definitive diagnosis may require an oral aspirin challenge in a closely monitored hospital setting with serial monitoring of pulmonary function tests.

Treatment of aspirin-induced asthma

The usual guidelines for asthma therapy also apply to patients with aspirin-induced asthma.

Avoiding aspirin and NSAIDs is also necessary. Acetaminophen is a generally safe substitute, but because it also inhibits cyclooxygenase (COX), although weakly, approximately 7% of patients who are aspirin-sensitive have an adverse reaction to acetaminophen if taken at high doses.[21,29,30] Magnesium salicylate and salicylic acid have weak to absent COX inhibitory properties and can be considered in these patients.[31] Additionally, studies with COX-2 inhibitors suggest that these drugs may be used in patients with aspirin-induced asthma.[32–34]

Aspirin desensitization. Patients who need aspirin can undergo desensitization. Protocols call for 1 to 3 days of inpatient treatment and continuous daily aspirin ingestion thereafter to maintain the desensitized state.[35,36]

Since aspirin desensitization has been reported to improve the upper airway disease as well as the lower airway disease of patients with asthma, it can significantly improve refractory symptoms of recurrent polyps and chronic sinusitis.[37]

Nasal steroids should be used aggressively to shrink polyps and possibly to prevent their regrowth after surgical polypectomy. Although surgical removal of polyps may improve nasal and sinus symptoms and decrease the occurrence of sinus infections, polyps almost always recur.

Prolonged antibiotic therapy is often necessary for adequate resolution of chronic sinus infections in aspirin-sensitive patients.

Inhibitors of leukotriene synthesis (eg, zileuton)[38,39] and **leukotriene receptor antagonists** (eg, montelukast) should both be considered in patients with aspirin-sensitive asthma.

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