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Identifying Asthma Triggers

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KEYWORDS

• Reflux • Paradoxic vocal fold dysfunction • Obesity • Asthma triggers • Sinusitis • Inhalant allergies • Food allergies

KEY POINTS

- Asthma may have one or many triggers.
- Identification and management of the trigger improves management.
- Common triggers include inhalants (allergens or irritants); food allergies (IgE and non-IgE mediated); gastroesophageal reflux; cyclooxygenase 1 inhibitors, such as aspirin in aspirin-exacerbated respiratory disease; and rhinosinusitis.
- Mimics of asthma include paradoxic vocal fold dysfunction.
- Comorbidities that exacerbate asthma include obesity.

INTRODUCTION

In medicine, the maxim that an ounce of prevention is worth a pound of cure plays a pivotal role in efficacious and cost-effective patient care. Asthma, with its pathogenesis rooted in atopy and airway hyperresponsiveness, can be treated in part by knowledge of and subsequent avoidance of the various triggers. Although asthma is associated with an allergic diathesis, an allergic trigger is only true or partly true in a subset of patients. This article reviews familiar allergic triggers and their management, and comorbid associations that worsen asthma or even mimic asthma without true bronchial hyperresponsiveness. In many patients there is more than one factor or trigger for the asthma, and optimal control is obtained when the patient and health care team work together to prevent exposure or ameliorate the aggravating condition, such as environmental allergens (pollen, dust mites, pet dander, and mold in the allergic patient with asthma). Other triggers or mimics of asthma symptoms are laryngopharyngeal reflux (LPR), also known as gastroesophageal reflux disease (GERD); exercise; irritants (tobacco smoke and industrial pollutants); food allergies; viral infections; pharmacologic agents (aspirin and β-blockers); and paradoxic vocal fold dysfunction (PVFD). Associations under investigation include obesity, stress, and hormonal status.

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INHALANT TRIGGERS

The initial assessment of a patient should follow a systematic series of questions to identify possible exacerbating factors (Fig. 1). Once preliminarily identified, specific triggers then elicit an appropriate algorithm of inquiry. It is necessary to identify the precipitating factors to optimally direct therapy or avoidance. When evaluating irritant

Inhalant allergens
Does the patient have symptoms year round? (If yes, ask the following questions. If no, see next set of questions).
Does the patient keep pets indoors? What type?
Does the patient have moisture or dampness in any room of his or her home (eg, basement)? (Suggests house dust mites, molds).
Does the patient have mold visible in any part of his or her home? (Suggests molds).
Has the patient seen cockroaches or rodents in his or her home in the past month? (Suggests significant exposure).
Assume exposure to house dust mites unless patient lives in a semiarid region. However, if a patient living in a semiarid region uses a swamp cooler, exposure to house dust mites must still be assumed.
Do symptoms get worse at certain times of the year? (If yes, ask when symptoms occur).
Early spring? (Trees).
Late spring? (Grasses).
Late summer to autumn? (Weeds).
Summer and fall? (Alternaria, Cladosporium, mites).
Cold months in temperate climates? (Animal dander).
Tobacco smoke
Does the patient smoke?
Does anyone smoke at home or work?
Does anyone smoke at the child's daycare?
Indoor/outdoor pollutants and irritants
Is a wood-burning stove or fireplace used in the patient's home?
Are there unvented stoves or heaters in the patient's home?
Does the patient have contact with other smells or fumes from perfumes, cleaning agents, or sprays?
Have there been recent renovations or painting in the home?

Workplace exposures
Does the patient cough or wheeze during the week, but not on weekends when away from work?
Do the patient's eyes and nasal passages get irritated soon after arriving at work?
Do coworkers have similar symptoms?
What substances are used in the patient's worksite? (Assess for sensitizers).
Rhinitis
Does the patient have constant or seasonal nasal congestion, runny nose, and/or postnasal drip?
Gastroesophageal reflux disease (GERD)
Does the patient have heartburn?
Does food sometimes come up into the patient's throat?
Has the patient had coughing, wheezing, or shortness of breath at night in the past four weeks?
Does the infant vomit, followed by cough, or have wheezy cough at night? Are symptoms worse after feeding?
Sulfite sensitivity
Does the patient have wheezing, coughing, or shortness of breath after eating shrimp, dried fruit, or processed potatoes or after drinking beer or wine?
Medication sensitivities and contraindications
What medications does the patient use now (prescription and nonprescription)?
Does the patient use eyedrops? What type?
Does the patient use any medications that contain beta-blockers?
Does the patient ever take aspirin or other nonsteroidal antiinflammatory drugs?
Has the patient ever had symptoms of asthma after taking any of these medications?

Fig. 1. Assessment questions for environmental and other factors that can make asthma worse. These questions are examples and do not represent a standardized assessment or diagnostic instrument. The validity and reliability of these questions have not been assessed. (*From* National Heart, Blood, and Lung Institute. Expert panel report 3 (EPR 3): guidelines for the diagnosis and management of asthma. NIH Publication no. 08-4051.)

or allergic exposures as triggers, include the amount of exposure; patient sensitivity to a specific allergen; place of exposure to the asthma trigger (home, work, school); and clinical significance of sensitivity in how it relates to the patient's medical history.[1]

Unlike environmental allergens, in which the clinician is in part guided by allergy test results, such irritants as workplace chemicals and cigarette smoke trigger asthma through non–IgE mediated mechanisms and it can often be difficult to definitively identify the culprit, beyond the fact that the patient develops symptoms on entering the workplace, which are relieved when at home or in another environment. Formaldehyde outgassing of new construction and carpets can also trigger symptoms in poorly ventilated areas in some patients and reaches particularly high levels in mobile homes.[2] Glutaraldehyde, commonly used as a disinfectant for endoscopes, can be a trigger in the workplace.[3]

INHALANT ALLERGY

Allergens play a key role in many patients' allergies as a trigger of acute exacerbations and as underlying long-term effects on control. Allergens activation of mast cells with bound IgE leads to the release of bronchoconstrictor mediators, which results in the bronchial narrowing that characterizes asthma and symptoms of allergic rhinitis.[4] The most common allergen triggers, with slight differences in their effects, include *Dermatophagoides* species (dust mites), which cause perennial low-grade chronic symptoms; domestic animals (cats, dogs, cockroaches) causing perennial symptoms; and grass, ragweed, tree pollen, and fungal spores, which are seasonal but more often cause allergic rhinitis rather than asthma symptoms.[1] Environmental factors, such as thunderstorms, can increase the amount of pollen in the air attributed to conditions at the beginning of the storm causing pollen grains to rupture and disperse into the air.[5]

Recommendations that can be applied generally to allergens as an asthma trigger follow a systematic approach. After identification of the allergen, the environmental controls range from the simple to the complex. If water damage exists in the patient's dwelling and the patient is reactive to mold, then correction of the water leak and damage and remediation of any mold is requisite to improving the patient's health. This can be quite expensive. However, if dust mite or cockroach is a trigger, then pillow and mattress allergen covers coupled with hot water weekly washings of bed coverings may suffice in the former, and a visit from a pest control company on a scheduled basis may resolve the latter. Except in the most obvious cases, allergy skin or in vitro testing for IgE to specific antigens is the best way to identify potential allergens. Not every positive test represents a clinically important allergen. For example, in the 2005 NHANES study, more than 50% of the population demonstrated skin allergy test positivity to dust mite, whereas only about 20% of the population is allergic.[6] Similarly, up to 30% of allergens noted clinically by patients and negative on skin testing are positive on nasal provocation or assessment of nasal-specific IgE to the allergen.

If complete avoidance is not possible, then limiting exposure should be attempted. If there is no way to completely avoid or limit exposure, then a third option is for the patient to take an extra dose of bronchodilator and antihistamine before predicted trigger exposure or to undergo desensitization therapy either with allergy shots or sublingual drops.[1]

VIRAL TRIGGERS

One of the most common triggers of acute exacerbation is an upper respiratory tract infection, such as rhinovirus, respiratory syncytial virus, or coronavirus.[4] These viral infections, by poorly understood mechanisms, result in an increase in the numbers of eosinophils and neutrophils. People with asthma additionally may have reduced

production of type 1 interferons by respiratory epithelial cells, thus increasing their susceptibility to viral infections and resulting in a greater inflammatory response when infection does occur. Patients may present with infections including colds, influenza, respiratory syncytial virus, and airway inflammation with concomitant increased mucus production. In patients with asthma, a viral infection can exacerbate inflammation that persists long after the viral part of the infection has resolved. Viral infections may also increase patient susceptibility to developing new allergic sensitivities.[7]

Patient recommendations to avoid infection follow advice that is applicable to all patients but that is especially important for people with asthma. Patients should be informed of the importance of washing their hands; avoiding sick contacts; getting adequate sleep; and using their prescribed medications for symptomatic treatment of the infection (intranasal glucocorticoids, decongestants).[8] It is recommended that people with asthma get yearly intramuscular flu vaccines; and there is evidence that people with asthma and others with chronic obstructive pulmonary disease may benefit from pneumococcal vaccine because of reductions in morbidity and mortality in these groups.[9,10]

GERD OR LPR

GERD or LPR is a commonly encountered comorbidity seen in people with asthma.[11,12] In one review of 28 studies GERD symptoms were seen in 59%, abnormal 24-hour pH tests in 51%, hiatal hernia in 51%, and esophagitis in 37%.[13] The symptoms of LPR include heartburn; regurgitation; dysphagia; chest pain; hoarseness; dental erosions; worsening in supine position; and worsening with such factors as eating, alcohol, theophylline, and systemic β-adrenergic agonists. Bronchodilators lower esophageal sphincter tone. Acid reflux may cause bronchoconstriction by three proposed mechanisms: (1) increased vagal tone, (2) sensitization of bronchial reactivity, and (3) microaspiration of gastric contents in the upper airway.[14–17]

Patient recommendations about the significance of LPR control and asthma symptoms have been variable in their outcomes in various trials. The recommendations can be split into two groups: patients with symptomatic LPR and patients that are asymptomatic. Patients with symptomatic LPR may benefit from a proton pump inhibitor (PPI) primarily in patients' subjective criteria based on studies quality of life questionnaires and in reducing the number of asthma exacerbations.[18] The studies that show improvement in pulmonary function in patients with asthma with GERD controlled with PPI showed only minor improvements.[19] In patients with asthma with clinically silent LPR, PPI therapy has not been shown to be of benefit in asthma outcomes, and it can be concluded that in these situations difficult-to-control asthma is not likely from GERD.[20,21] The approach should be to identify those patients most likely to benefit from PPI therapy, which are those with symptoms of regurgitation, nocturnal asthma, and most importantly concurrent symptoms of LPR and asthma. Patients should additionally follow the recommendations given to all patients with LPR, which include raising the head of the bed at night by 6 to 8 inches; not eating 2 to 3 hours before lying in supine position; avoiding fatty foods, chocolate, peppermint, and excessive alcohol; and reduction of abdominal obesity.[22] If clinical suspicion for LPR is high, then a trial of PPIs can be given. If the patient does not improve clinically, then further testing can be undertaken, such as 24-hour esophageal pH testing to help determine the cause.[23]

MEDICATION TRIGGERS AND ASPIRIN-EXACERBATED RESPIRATORY DISEASE

The most important medications to be aware of as triggering reactive airway are nonselective β-blockers, aspirin, and other nonsteroidal anti-inflammatory drugs

(NSAIDs). Although potentially nonselective β-blockers are contraindicated in all people with asthma, only about 5% of those with asthma or up to 40% of people with asthma with nasal polyps are triggered by aspirin or NSAIDs. These patients are classified as having aspirin-exacerbated respiratory disease (AERD), which is also commonly known as Samter triad: asthma, aspirin sensitivity, and nasal polyps.[24–27] Reactions to NSAIDs in those with AERD are classified as pseudoallergic because it is not a typical IgE-mediated reaction but rather is based on the common ability of NSAIDs and aspirin to inhibit the cyclooxygenase (COX)-1 enzyme. The pathophysiology of AERD is incompletely understood and most likely is related to overproduction of proinflammatory arachiadonic acid products, especially the leukotrienes. This is supported by the fact that medications that inhibit leukotriene synthesis and leukotriene receptor antagonists (eg, zileuton, montelukast) reduce or eliminate the bronchoconstrictive response to aspirin.[28–30] The diagnosis of AERD is based initially on clinical features being present. If Samter triad is present, the diagnosis can be relatively unambiguous, but more often only part of the triad is present or each part develops slowly over time making the association more difficult.[31] When suspicion of NSAID reaction is aroused, the physician should question the patient about any NSAID use after the first suspected reaction and whether any reaction occurred at that point, the reason being that NSAID sensitivity is acquired and thus prior nonreactivity is not as relevant.[26] Aspirin challenge is the only way to definitively diagnose NSAID sensitivity. There is an 80% likelihood of positive oral aspirin challenge with a history of a single NSAID reaction, which increases to 90% with history of two reactions.[32] Aspirin challenge is only needed in cases where a patient has ongoing regular need for NSAID therapy, such as rheumatologic disease or cardiovascular disease. These patients should be referred to an allergy or pulmonary specialist for the test.

Patient recommendations in AERD include typical asthma therapy with avoidance of all COX-1–inhibiting NSAIDs or aspirin desensitization followed by daily aspirin therapy. Pharmacologic therapy should include a leukotriene modifying agent, which can result in better asthma control than medium to high doses of glucocorticoids alone.[33] Alternative medications that can be used safely are acetaminophen at doses up to 650 mg, being aware that 20% of patients react to a dose of 1000 mg, or highly selective COX-2 inhibitors, such as celecoxib.[34] Aspirin desensitization in those instances where it is needed can be accomplished in nearly all patients with AERD, but once desensitized the patient must continue to take aspirin daily to maintain desensitized state.[35]

Nonselective β-blockers are another class of medication that present a problem to patients with asthma. In those with asthma, β-blockers cause increased bronchial obstruction and airway reactivity, and importantly blunt the effect of inhaled or oral β-receptor agonists, such as albuterol, which plays a key role in treatment of acute asthma exacerbations.[36] In most people with asthma without concomitant cardiovascular disease, routine use of even cardioselective β-blockers for treatment of hypertension is to be avoided.[37] Some studies have shown that in moderate and stable asthma, selective β-blockers may be used at low doses but require close physician supervision.[38] It is important for physicians to understand that although there is evidence to support using β-blockers to improve survival in patients with chronic obstructive pulmonary disease, possibly as a result of their cardiopulmonary protective properties, this does not currently apply to patients with asthma based on the most current review of the literature.[39]

Angiotensin-converting enzyme inhibitors deserve discussion because they relate to asthma triggers, primarily to point out that their most common side effect occurring

at 5% to 20%, a dry hacking cough, can easily be mistaken for worsening asthma symptoms.[40] It is independent from asthma, and these patients should be switched to an angiotensin receptor blocker, which has a lower incidence of dry cough.

There are a plethora of inhaled irritants and pollutants that people with asthma should be made aware of that increase asthma exacerbations. These include, but are not limited to, tobacco smoke, fireplace smoke and ash, aerosols, perfumes, cooking odors, musty odors, shower steam, traffic pollution, air pollution, dust, and workplace irritants.[8]

Cigarette smoke is a well-studied airway irritant known to cause those with asthma to have more severe symptoms, increased rates of hospitalization, accelerated decline in lung function, and impaired response to inhaled and systemic glucocorticoids compared with nonsmokers.[41] Interestingly, in most developed countries approximately 25% of adults with asthma are current cigarette smokers, which is similar to the rate in the general population. This patient population presents unique issues in treatment in their reduced response to short-term corticosteroid therapy, which normally plays an important role in the typical treatment regimen. The mechanism of glucocorticoid resistance is not fully explained, but it has been postulated that it is caused by changes in airway inflammatory cell phenotypes, changes in glucocorticoid receptor alpha to beta ratio, and reduced histone deacetylase activity.[42] The strongest recommendation for smokers with asthma is to educate the patient about the various methods that are available to them to help them quit smoking as this best efficacy. It has been shown that by 6 weeks after smoking cessation considerable improvement in lung function and a fall in sputum neutrophil count occurs.[43] Unfortunately, it still remains difficult to maintain smoking cessation in people with asthma, as it is in all chronic smokers, and the only avenue is often trials of asthma drugs other than or in addition to glucocorticoids. There is some preliminary data that leukotriene-receptor antagonists may benefit smokers with mild asthma.[44]

PARADOXIC VOCAL FOLD DYSFUNCTION

Patients with this disorder can be acutely symptomatic and have even required intubation in the emergency setting. Once intubated, monitoring of their pulmonary functions demonstrates absolute normality. This is because the pathology of this asthma imposter is not the pulmonary tree but rather a paradoxic closure or adduction of the vocal cords on inspiration. Once intubated, the obstruction is bypassed. PVFD is usually present intermittently and may not be observed on video endoscopy of the larynx unless triggered by exercise or stress. A helpful diagnostic question is, “are you more short of breath on inspiration or expiration?”. The patient with PVFD will answer “on breathing in,” whereas the patient with asthma has problems with expiration. Breathing exercises and voice therapy can be helpful in treating PVFD.

EMOTIONAL TRIGGERS

Emotional states, such as stress and depression, are known to influence the level of asthma control.[8] Various studies have shown that children that grow up in more chronically stressful environments have higher prevalence of asthma.[45,46] A stronger correlation is seen between atopic asthma and stress, anxiety, and depression versus nonatopic asthma.[47] It is recommended that the emotional triggers in the patients be recognized and managed accordingly with the appropriate medications, psychotherapy, or social work to best alleviate the stressors.[8]

OBESITY

There is a positive correlation between obesity and increased prevalence and incidence of asthma and reduced asthma control.[1,48,49] A prospective cohort study of 86,000 individuals demonstrated a linear correlation between body mass index and adult-onset asthma incidence.[50] The mechanism is incompletely understood, but a significant portion is attributed to chronic low-grade systemic inflammation as a function of increased amounts of functioning adipose tissue resulting in release of various cytokines, chemokines, and the soluble fractions of their receptors. A recent study showed that there is increased eosinophilic activity associated with high serum leptin and tumor necrosis factor-α levels in atopic obese children and adolescents with asthma compared with nonobese healthy volunteers.[51] Mechanically, obese individuals have reduced lung function mechanics with decreased functional residual capacity, lung volume, and tidal volumes.[1] There are additionally the myriad comorbid conditions associated with obesity, such as dyslipidemia, GERD, type 2 diabetes, and hypertension, which further complicate management. It is recommended that all patients, not just those with asthma, be counseled about the benefits of weight loss and methods that are available to them.

RHINOSINUSITIS

In the last 15 years the unified airway model, with interrelatedness between the pathophysiologic processes of the upper airway and its influence on the lower airway, has shaped the therapy directed at both targets. It is known that nasal obstruction triggers asthma exacerbations and this is particularly problematic for those patients with nasal polyps. In pre-endoscopic and postendoscopic sinus surgery, review of 70 patients with chronic rhinosinusitis and concomitant asthma, improvement in symptoms and reduction in emergency room visits and medications resulted, whereas only two patients did not improve and required revision surgery for nasal polyps.[52]

In addition, the intense accumulation of inflammatory material in the sinuses is hypothesized to feed the fuel of lower airway inflammation, so improvement in chronic rhinosinusitis, either by establishing nasal breathing or by reducing inflammatory drip, can improve symptomatic asthma.

SUMMARY

The patient armed with knowledge about the disease process and how to identify triggers and exacerbating factors is best able to partner with the health care team to prevent exposure to triggers of asthmatic exacerbations and to control their symptoms. Important in treating and preventing asthma is the understanding that for many patients there is more than one trigger and there may be multiple triggers.

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