*Work Group Report**

American Academy of Allergy, Asthma & Immunology Work Group Report: Exercise-induced asthma

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It has long been recognized, even during biblical times, that physical exercise may induce asthma symptoms in susceptible individuals.[1] Nevertheless, the term *exercise-induced asthma* (EIA) only became popular in the 1960s and 1970s when several reports addressed the pattern of airway response to exercise and the influence of drugs on EIA, particularly in children.[2,3] Subsequently, reports of studies of the mechanisms causing EIA[4] often asserted that EIA represents a distinct clinical category of asthma. In fact, most if not all patients with asthma develop symptoms of asthma after a suitable exercise challenge.[5] Moreover, even cases of asthma in which exercise appears to be the only trigger of bronchial obstruction (pure EIA) may be manifestations of chronic inflammation of the airways.[6-8]

Abbreviations used

EIA:	Exercise-induced asthma
EIAna:	Exercise-induced anaphylaxis
EIB:	Exercise-induced bronchospasm
EILD:	Exercise-induced laryngeal dysfunction
EVH:	Eucapnic voluntary hyperventilation
FDEIAna:	Food-dependent exercise-induced anaphylaxis
GERD:	Gastroesophageal reflux disease

There is considerable controversy regarding the phenotypes of asthma, demonstrating apparent heterogeneity of the disorder that we call asthma.[9,10] For this report, we define EIA as the condition in which exercise induces symptoms of asthma in patients who have asthma. We do not view EIA as a unique condition separate from the

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condition we call asthma.[11] By definition, we use the term *exercise-induced bronchospasm* (EIB) to describe the airway obstruction that occurs in association with exercise[12] without regard to the presence of chronic asthma.

We recognize that this is a controversial position and that some authors suggest EIA seen in patients with chronic asthma is very different from EIA seen in athletes who do not otherwise have asthma because (1) a high percentage of patients with asthma experiences a decrease in EIB when treated with inhaled corticosteroids, whereas such a response may not be seen in elite athletes; (2) a reported 80% to 90% of patients with asthma with a positive methacholine challenge experience EIB, whereas Holzer et al showed that only 9 of 42 athletes with respiratory complaints had a positive methacholine challenge (with 25 of the 42 having a positive response to eucapnic hyperventilation); and (3) inflammation in asthma is usually associated with eosinophilia, whereas isolated EIB in elite athletes seems to be more associated with neutrophilic or mixed-type airway inflammation.[8,13-15] From these observations, it is possible to conclude that atopy causing chronic asthma and bronchial hyperresponsiveness to thermal, mechanical, or osmotic stimuli (seen more commonly in elite athletes) are not mutually exclusive.

One practical problem in defining EIA is in describing the type and intensity of the stimuli to cause asthma and the pulmonary function measurements to record whether asthma has occurred.[12] Some questions follow regarding these issues:

The type and intensity of exercise to cause asthma:

- Is a simple 10-minute, 1-km jog sufficient, or must a patient reach 90% to 95% of his or her predicted maximum heart rate (at the time when the patient reaches 40% to 60% of the maximum voluntary ventilation) during 6 to 8 minutes of exercise?[5]
- Is exercise on a treadmill sufficient, or it is necessary to visit the venue that normally produces symptoms to obtain objective data necessary to make a diagnosis?[16]
- Is a certain level of temperature and humidity essential in the least sensitive patients?
- Can an exercise challenge ever result in a false-positive, or does the presence of a positive test by definition mean that the patient has asthma?

The outcome measures to record if asthma has occurred:

- Is it sufficient for a patient to drop a predefined amount in FEV_1 from baseline values (eg, 10%) to make the diagnosis,[5] or must the patient also have symptoms accompanying this drop in FEV_1?
- Is there any benefit of using a 12%, 15%, or 20% drop instead of 10% drop in FEV_1?

EPIDEMIOLOGY AND PATHOGENESIS

Although the pathogenesis of EIA is not fully elucidated, it is probably caused by exercise-induced hyperventilation and corresponding changes in airway physiology.[4,17,18] An increased ventilatory rate is required to meet higher muscular oxygen requirements during exercise. This increased ventilatory rate challenges the ability of the airways to condition the inhaled air to the correct moisture and heat levels before the air reaches the alveoli. Vigorous exercise results in the inhalation of an increased volume of relatively cold and dry air and the loss of heat from the respiratory mucosa, which induces osmolarity changes in the airways surface[4] that can, in turn, activate mast cells and epithelial cells to release proinflammatory mediators such as histamine, leukotrienes, and chemokines.[17] Thus, treatments that block the activity of these mediators are logically used as effective therapies in controlling EIA.[19,20]

Various investigators have documented that exercising athletes have increased levels of chemical mediators as well as increases in the cellular markers of airway inflammation. The cellular markers include increased eosinophils,[21] neutrophils,[22,23] and/or columnar epithelial cells.[24] These inflammatory markers are not consistently related to airway bronchial hyperreactivity and do not respond to inhaled steroids as is characteristic of asthma.[23,25] The markers may, therefore, represent nonspecific indicators of inflammation secondary to exercise alone (with or without symptoms) and may improve with curtailment of exercise or with training in elite athletes.[26]

In addition to inflammatory mediators triggered by osmotic change, airway cooling stimulates cholinergic receptors in the airways, increasing airway tone and secretions. Cold air inhalation results in pulmonary vasoconstriction followed by secondary reactive hyperemia (airway rewarming) with vascular bronchial congestion, edema, and further airway narrowing.[6-8,18]

Other substances seem to play a role in triggering asthma, dependent on the sport. Competitive swimmers, who often swim at least 30 hours per week, inhale large amounts of contaminated air floating just above the water surface. This air contains compounds derived from either chlorine gas or hypochlorite liquid,[27] subjecting these athletes to ongoing irritation that may cause inflammation of the airways. Similarly, pollution created by ice grooming equipment can cause symptoms in figure skaters, perhaps explaining the high prevalence of asthma in these athletes.[28]

Exercise-induced asthma may be modulated by the baseline condition of the patient or by sport-specific characteristics. For instance, with pre-existent airway inflammation or bronchial hyperreactivity, such as in a patient with allergic asthma, an amplification of these mechanisms should be expected as a result of water loss with mucosal inflammation and because inflammatory cells respond to the hyperosmolar environment. The quality of inspired air may also be influenced by the type of exercise (indoor/outdoor)[29] and sport-specific conditions (eg, winter and water sports).[26]

The coexistence of rhinitis will also lower the air conditioning properties of upper airways in parallel with an increase in mouth breathing.[30] In 1998, Helenius[21] surveyed the incidence of allergic sensitization in a group of outdoor athletes competing in summer events. In this sample, clinical pollen allergy was significantly more common

in athletes than in the control group. Moreover, Katelaris et al[31] reported that among Australian elite athletes screened for allergic rhinitis in the context of an epidemiologic survey performed in preparation for the Olympic Games in Sidney, many were affected by allergic rhinoconjuctivitis.

Another individual and exercise-specific factor may be the autonomic deregulation associated with high-intensity and prolonged physical training.[32] The predominant parasympathetic drive of highly trained runners,[33] in addition to the well recognized low heart rate at rest, may also increase the bronchomotor tone of these athletes who are known to have an increased risk of EIA.[31]

CLINICAL PRESENTATION

The clinical features of EIA are cough, wheezing, chest tightness, and unusual shortness of breath or excess mucus occurring after a burst (eg, 6-8 minutes) of strenuous and continuous aerobic exercise.[34,35] In elite athletes such as female hockey players, Rundell et al[36] found that cough was the most frequent symptom and developed significantly more frequently than wheeze or excess mucus ($P < .05$). Symptoms were not highly correlated with having a positive exercise challenge; however, cough and chest tightness were the symptoms most suggestive of EIA. Rundell et al[37] also compared the presence of self-reported symptoms and exercise challenge positivity in a population of elite athletes and found that cough was the symptom most commonly reported by athletes who had positive exercise challenges. However, exercise challenge–negative athletes reported symptoms at least as often as those who had positive challenges. Other authors have also reported that the diagnosis of EIA using self-reported symptoms leads to unacceptable false-positive and false-negative rates.[12,38,39] Thus, we cannot recommend using self-reported symptoms to make a diagnosis of EIA without confirmatory objective evidence (eg, a positive exercise challenge).

Storms[40] also described more nonspecific symptoms such as poor performance or ''feeling out of shape,'' abdominal pain, headaches, muscle cramps, fatigue, and dizziness as symptoms suggesting EIA. Healthy children and adolescents may present with chest pain as a manifestation of EIA; the chest pain is almost never a symptom of cardiac disease in children.[41] Other more subtle symptoms include prolonged difficulty in eliminating upper respiratory illness; ''locker room cough''; difficulty sleeping because of nocturnal symptoms; the feeling of having heavy legs; seasonal fluctuations of asthma and asthma-like symptoms, especially related to humidity, pollen content, or concentration of airborne pollutants; avoidance of activity; and inability to keep up with peers. Seasonal change in fitness, sore throat in young children, and worsening problems with exposure to certain triggers during exercise may all be presenting symptoms of EIA.[12,38,39,42] Triggers that may worsen EIA include animal dander, house dust mites, molds, cigarette and other types of smoke, pollen, pollution, changes in weather, or airborne chemicals.

PREVALENCE

Prevalence of EIA varies from approximately 5% to 20% in the general population, to perhaps 30% to 70% in elite winter athletes and athletes who participate in summer endurance sports, to at least 90% in individuals with persistent asthma.[12,16,34,35,43] As noted, it is likely that almost all individuals who have chronic asthma will be triggered to have an asthma flare with an appropriate exercise challenge, even though some reports suggest a prevalence of EIA of only 50% to 90% in this population.[12,34] In individuals with intermittent asthma, EIA may be the only expression of asthma. However, most patients with asthma with EIA are felt to have underlying inflammation causing persistent asthma requiring daily therapy with anti-inflammatory medications.

It is important to reiterate that the prevalence of EIA in a population depends on the population surveyed (eg, elite vs recreational athletes), the method used to detect EIA (treadmill challenge vs exercise challenge in the specific venue in which the patient participates), and the intensity and duration of exercise as well as the humidity and temperature of the inspired air.[12,44] Prevalence in a population can vary depending on whether a cycle, treadmill, or free running is used for testing and whether an indirect surrogate test (eg, eucapnic voluntary hyperventilation [EVH], AMP, hypertonic saline, or mannitol challenge) or a direct surrogate test (histamine or methacholine) is used to suggest the diagnosis of EIA. In addition, pulmonary function criteria play an important role in determining whether an exercise challenge is positive.[34]

A numbers of authors have studied Olympic and other highly elite athletes. Voy[45] noted that 11% of 1984 US Summer Olympic team members reported having EIA. Weiler et al[46] reported that 17% of 1996 US Summer Olympic team members had a history of asthma, used asthma medications, or both. Weiler and Ryan[47] also reported that among US Olympic Winter athletes participating in the 1998 games, 22.4% had a history of asthma, used asthma medications, or both. The estimated prevalence increased to 28% when athletes who self-reported responses to asthma symptoms were included in the analysis. Rundell and Jenkinson[34] observed that the overall prevalence of EIA in Winter Olympic sports athletes was 23%, and as many as half of cross-country skiers had EIA. EIA is more prevalent in high-intensity aerobic sports, particularly with cold air exposure, such as ice hockey and cross-country skiing, and less prevalent in less strenuous sports, such as racquet sports or baseball. Others have reported a similar high prevalence of EIA in children and athletes.[48-50]

EVALUATION OF EIA

The clinical presentation of EIA includes cough, wheezing, shortness of breath and/or chest tightness, generally occurring within 5 to 30 minutes after intense exercise. In a recent worldwide study of more than 10,000

patients with asthma currently taking asthma medications or having had symptoms within the last year,[51] EIA symptoms were reported in a third to half of these patients. In adults who have had a previous diagnosis of asthma, the presence or appearance of EIA may be seen as a sign of suboptimal therapeutic control of asthma severity.[51] Many adult patients may admit they are not in the best physical condition because of asthma or may not seek treatment for the symptoms. In highly trained individuals, exercise-induced respiratory symptoms are usually poor predictors for EIA.[30,37] In these individuals, especially if involved in competitive sports, a diagnosis of EIA should be confirmed before starting treatment[52] because it is important that treatment not be given for a condition that does not exist.

Patients with suspected EIA should be evaluated with a detailed history and physical examination (including examination of the ears, nose, and throat and cardiac and chest examinations) and lung function measurements before and after a short-acting β-agonist is given.[35] In many patients, bronchial hyperresponsiveness should be evaluated with an exercise challenge or a surrogate challenge (eg, with cold air hyperventilation, methacholine, AMP, or mannitol challenge) to exclude asthma.[15,43,53-55] Currently mannitol challenge is not an approved procedure to predict a positive exercise challenge, but preliminary evidence suggests that it may become a useful test.[55] Direct challenges with histamine (also not an approved medication) or methacholine are suboptimal tests to assess EIA. Often, EIA can be prevented by use of a short-acting β-agonist inhaled within 15 minutes before exercise; some authors suggest that response to this therapy can serve as a basis for making the diagnosis of EIA.[35] In patients with a previous diagnosis of asthma, it is important to continue to follow a treatment plan with daily controller medicines and pre-exercise therapy as prescribed. If these treatments are not effective, further evaluation is required including an exercise challenge or a repeat exercise challenge if one has been performed (see differential diagnoses to follow).[35] Nonadherence or poor technique in taking medication must also be excluded as a cause for the lack of efficacy.

The most direct way to establish a diagnosis of EIA is to perform an exercise challenge. If possible, we recommend that a challenge be performed in the environment that usually causes EIA-type symptoms.[16] If symptoms (cough, wheezing, chest tightness) can be reproduced by running on a treadmill for 8 minutes, then this is a sufficient challenge if symptoms occur with a drop in FEV_1.[5,12] If symptoms cannot be reproduced by using a treadmill challenge, then a challenge should be performed under the conditions that the patient reports usually cause these symptoms and at the same exercise intensity (eg, in the sports venue).[16] If testing is being done to examine EIA in a patient who has not experienced EIA in the past, we recommend a treadmill test in which the patient is exercised for 8 minutes. During the first 2 minutes, the exercise is at such an intensity that the heart rate reaches at least 80% to 90% of predicted maximum, and during the remaining 6 minutes, exercise should continue at this heart rate. At this level of exercise, ventilation should reach 40% to 60% of maximum.[5] We also recommend that a drop of at least 10% in FEV_1 is sufficient to make the diagnosis of EIA, especially if symptoms accompany the drop in FEV_1.[5] It is important to recognize that the drop in FEV_1 after exercise is normally distributed in large population studies, meaning that there is no absolute FEV_1 cutoff that can be used to make the diagnosis of EIA.[56] Pulmonary functions should be followed for 30 minutes after the exercise is completed to assure that a delayed drop in FEV_1 is not missed.[57]

Office-based exercise challenges that use a free running asthma screening test are an extremely simple, efficient, and cost-effective way to screen for EIA in nonelite athlete children.[58] However, no similar simple, efficient diagnostic exercise challenge exists for adults with EIA, because the risk of coronary heart disease requires cardiac monitoring and immediate availability of resuscitation resources. Thus, practitioners often seek other types of challenges for adults. EVH is the surrogate challenge most similar to EIA because it replicates the hyperventilation part of the exercise challenge as a trigger of bronchospasm.[53] As in an exercise challenge, the fall in FEV_1 from the baseline value is measured after the patient breathes dry (or dry and cool) air, containing 5% CO_2 (to prevent respiratory alkalosis) for 6 minutes at 85% of predicted maximum voluntary ventilation. EVH correlates well with EIA in trained athletes,[15] and the International Olympic Committee Medical Commission has specified EVH as the preferred test for EIA for the purpose of obtaining approval for use of otherwise banned asthma medications (ie, β_2-agonists) by Olympic athletes.[59] However, EVH is not a satisfactory adult equivalent to the pediatric free running asthma screening test, nor can it be used in all adults, because it requires specialized equipment that limits its availability. Although elite athletes, in whom the test was studied, have no difficulty maintaining respiration at 85% of maximum voluntary ventilation for 6 minutes, a significant number of less physically fit children and adults might not be able to breathe at 85% of maximum voluntary ventilation for this length of time.

Exercise and EVH are 2 of a group of tests called *indirect airway challenges* that act by causing the release of endogenous mediators of airway smooth muscle contraction.[60] This is in contrast to the action of methacholine and histamine, which provoke bronchoconstriction by direct action on airway smooth muscle. Responses to challenge with different indirect-acting stimuli (mannitol, AMP, hypertonic saline, and cold dry air) tend to correlate with each other, and several have been studied as surrogate challenge agents for EIA.[54]

Recent years have seen the development of a number of rugged, accurate, inexpensive, and reproducible electronic devices that record peak flow and FEV_1.[61] Adults equipped with these devices can measure their FEV_1 before and after activities that are associated with symptoms, in the normal courses of their lives. Once these patients have established a predictable pre-exercise value, the values obtained associated with symptoms (eg, after

exercise) can be compared to determine whether the change in FEV_1 is compatible with EIA. FEV_1 should be measured before and 2.5, 5, 10, 15, and 30 minutes after exercise. Such testing does not subject the patient to the risks of a traditional exercise challenge.

In the past, peak flow measurements recorded outside of the clinic have been used to diagnose EIA; however, we do not recommend the use of peak flows in this setting because of large variability in this measure. Perhaps the inexpensive portable FEV_1 measurement devices used outside of the clinic will provide a more accurate basis to make the diagnosis of EIA,[61] but this remains to be shown. One important caveat is that some of these portable devices may not be as accurate or consistent or reproducible with results as reproducible as the more expensive equipment available in the clinician's office.[62-64] In addition, measurements made with devices that record numerical values for FEV_1 but do not record full flow-volume curves are subject to possible misinterpretation if the patient has laryngeal dysfunction.

We conclude this section by responding to the questions raised earlier regarding the type and intensity of exercise and the specific outcome measures to make a diagnosis of EIA. The exercise challenge itself must be of sufficient intensity for the patient to reach 40% to 60% of the maximum voluntary ventilation during no more than 6 to 8 minutes of exercise,[5] whether this is accomplished on a treadmill in a laboratory setting or in the venue that normally produces symptoms.[65] Temperature and humidity should be controlled so that the air breathed is dry (eg, from a dry air tank) and cool (15-20°C). A positive exercise challenge conducted in this manner denotes the presence of EIA by definition if there is at least a 10% drop in FEV_1 from baseline values that is reproducible in a patient who also has symptoms accompanying this drop in FEV_1. Although clinical research studies may require a larger drop in FEV_1, such large drops do not appear to be necessary to make a diagnosis in the vast majority of clinic patients if these criteria are met.[5]

EIA IN COMPETITIVE ATHLETES

The evaluation of EIA in competitive athletes poses several issues unique to this population.[66] We make the following observations and recommendations regarding competitive athletes:

The prevalence of EIA appears to be higher in competitive athletes than in other populations, and is particularly high in endurance sports such as swimming and winter sports.[21,45-47]

Participation in some sports involves exposure to particular environmental asthmogenic agents such as allergens (pollens, mites, and molds), polluted air, and cold and dry air, and involves high ventilation rates.[27,29,35]

Exercise challenge should be included among the evaluation tests for documenting the diagnosis of asthma in competitive athletes.[35] Athletes who do have asthma may be permitted to use some asthma drugs otherwise restricted by the World Anti-Doping Agency and the International Olympic Committee, such as β-adrenergic agents.[4,52,66,67] These restrictions should not impair the ability of athletes who clearly have asthma to be diagnosed and treated according to international guidelines applied to the general population.[68] Therefore, the criteria for evaluating EIA in competitive athletes should be carefully considered and based on sport-specific and environment-specific challenges performed at an intensity comparable with the intensity of competition.[65]

Self-reported symptoms of asthma and/or EIA are not reliable for evaluating EIA in competitive athletes.[37-39] Some athletes with asthma will fear that disclosure of their asthma will be detrimental, and so they will not disclose their symptoms and will participate without receiving proper treatment. Other athletes without asthma will try to secure asthma treatments in an attempt to gain a competitive advantage.

Baseline pulmonary function tests are also poorly predictive of EIA.[38,39]

Among bronchial provocation tests, field exercise challenges—preferably in the environment-specific and sport-specific conditions—have been reported to be more accurate than laboratory exercise challenges in revealing EIA in elite athletes.[16,34,64] However, there may be a different reference range for the drop in FEV_1 in elite athletes compared with the general population.[37] One study suggested that only a 7% drop in FEV_1 after treadmill exercise challenge in the laboratory is sufficient to make the diagnosis of EIA[65] compared with a greater drop in FEV_1 (eg, 15%) in a sports-specific setting.

Indirect challenge tests (such as with EVH and challenge with hypertonic aerosols) correlate better with exercise challenge than do direct challenges (that use a single pharmacological agonist such as methacholine).[53,54,69,70] However, if the goal of challenge testing is to identify asthma and not EIA, then indirect challenges may not be sensitive enough to reveal mild or subclinical asthma.[52,54]

DIFFERENTIAL DIAGNOSIS

The differential diagnoses of EIA include respiratory or cardiac conditions that can cause exertional dyspnea, exercise-induced laryngeal dysfunction (eg, vocal cord dysfunction, laryngeal prolapse), gastroesophageal reflux, exercise-induced hyperventilation, and exercise-induced anaphylaxis (EIAna). Although a thorough clinical history and physical examination, together with spirometry, bronchial hyperreactivity assessment, and physiological and cardiac monitoring of an exercise challenge can exclude most respiratory and cardiac disorders, some conditions will need a higher degree of clinical suspicion.

Exercise-induced laryngeal dysfunction (EILD) is an abnormal laryngeal response to exercise with different, but closely related, clinical entities: (1) exercise-induced (paradoxical) vocal cord dysfunction,[71] (2) exercise-induced laryngeal prolapse,[72] and/or (3) exercise-induced laryngomalacia.[73] All of these conditions present as

exercise-induced inspiratory stridor, with throat tightness during maximal exercise that resolves within 5 minutes of stopping, and are most common among young adult female patients.[74] This contrasts with EIA, in which case the dyspnea occurs after exercise, peaks 5 to 20 minutes after stopping, and involves expiration rather than inspiration. EILD is often not considered until a patient has failed several months of multiple asthma medications, but should be considered as the diagnosis from initial patient presentation, especially in patients with atypical EIA or EIA in the absence of obvious chronic asthma. These conditions (EILD and EIA) are not mutually exclusive.

The first form of EILD is vocal cord dysfunction, which causes dyspnea and an inspiratory stridor that is frequently mistaken for the wheeze of EIA. Direct observation of vocal cord adduction by laryngoscopy and flattening/truncation of the inspiratory limb of the spirometric flow-volume loop—the gold standards for vocal cord dysfunction diagnosis—are usually positive only when the patient is symptomatic. Moreover, the inconsistent occurrence of inspiratory stridor, for instance when inspiratory stridor is only present during stressful conditions, may render it difficult to reproduce these signs. It has recently been suggested[74] that vocal cord dysfunction might be identified in athletes by careful auscultation of the larynx and lung after exercise. Lack of resolution with β-agonist and a normal response to exercise provocation are typical of exercise induced laryngeal dysfunction. Again, vocal cord dysfunction, EIB,[74] and airway hyperresponsiveness to methacholine[75] are not mutually exclusive.

The second form of EILD is exercise-induced laryngeal prolapse, which has been found in otherwise healthy athletes,[72] where extreme exertion and a breathing pattern generating high inspiratory flows increase the negative pressure gradient in the hypopharynx, causing an abnormal movement of the arytenoid region and collapse of the upper airways.[76,77]

The final form of EILD is laryngomalacia, a condition that may be associated with inspiratory stridor during exercise.[78] Congenital laryngomalacia is the most common cause of inspiratory stridor in infants, but in a subset of patients it may present or recur later in childhood, typically after participation in competitive sports.[79] This syndrome has been called *exercise-induced laryngomalacia* and is often misdiagnosed as EIA;[80] endoscopic findings are described by some authors as *exercise-induced laryngeal prolapse*.

Gastroesophageal reflux disease (GERD) may be a cause of exercise-induced respiratory symptoms and a comorbid factor with vocal cord dysfunction.[71] Chronic cough and dyspnea are extraesophageal symptoms of GERD, and exercise may induce GERD through a low thoracic pressure during forced respiration combined with an increased abdominal pressure during exercise. In the videolaryngoscopic evaluation of patients with vocal cord dysfunction, Powell et al[72] noted that 19 of 22 (86%) had glottic changes (arytenoid and interarytenoid edema) commonly found in GERD. In another recent case series of paradoxical vocal cord dysfunction, laryngoscopic findings suggestive of GERD were seen in 19 of 30 cases (63%).[81] Although it is likely that laryngopharyngeal acid reflux is an important contributing factor in many EILD cases, there is very little evidence from controlled studies, primarily because of a lack of a gold standard test. The sensitivity and specificity of the laryngoscopic examination to diagnose laryngopharyngeal acid reflux is also controversial.[82]

Exercise-induced hyperventilation (pseudo-asthma syndrome) may be confused with EIA. Hyperventilation during exercise may be linked to exercise-induced respiratory symptoms (dyspnea and chest tightness) not directly related to bronchial obstruction,[83] but with hypocapnia and a possible abnormal ventilatory homeostasis during exercise, also suspected in other hyperventilation syndromes.[84] Chest pain associated with hyperventilation has also been shown in adults with negative cardiac testing by treadmill, and has been reproduced by the induction of hypocapnia with voluntary hyperventilation.[85]

Exercise-induced anaphylaxis may present with exertion-related respiratory distress, associated with pruritus, generalized urticaria, angioedema, and rapid development of vascular collapse. EIAna is characterized by the severity of its manifestations and onset precipitated by strenuous exercise, cold air, and medications such as aspirin. Food-dependent EIAna (FDEIAna) is a specific variant of EIAna that requires both vigorous physical activity and the ingestion of specific foods or, in rare cases, consumption of any food within the preceding several hours before exercise. Skin prick testing may identify food allergens that trigger FDEIAna such as celery, shellfish, and wheat.[86] The relationship of both food intake and exercise is usually evident on careful history taking. FDEIAna may be confirmed by subjecting the patient to an exercise challenge after ingestion of the identified food allergen, but the need for diagnostic certainty must be weighed against the risk of inducing anaphylaxis.

Other, even more rare conditions include idiopathic arterial hypoxemia of exercise, cystic fibrosis, atrial septal defect, and the mitochondrial defects.[40]

TREATMENT OF EIA

In treating elite athletes, clinicians must deal with the dilemma of providing relief from the disorder without using mediations that enhance performance in athletes who do not have asthma.[35,66,87,88]

Prophylaxis of EIA includes premedication and warm-up.[66,87,88] Warm-up of 10 to 15 minutes should include calisthenics with stretching exercises with an objective of reaching 50% to 60% of maximum heart rate.[35] A β-agonist should be used if asthma symptoms develop, and exercise should be restarted when symptoms clear.[35]

A refractory period may occur after exercise and may last as long as 2 to 3 hours, during which EIA is inhibited,[35] especially in children and patients with mild asthma. Although the amount of exercise required to induce this refractory period varies considerably among athletes and

over time, this nondrug maneuver may be used by some athletes to prevent attacks of EIA. Nevertheless, even when this maneuver is successful, it is usually only partially able to prevent symptoms of EIA in competitive athletes.

Breathing through the nose may allow cool dry air to be humidified and warmed. Underlying allergic and environmental nasal conditions should be treated to allow for nasal breathing.

In patients with chronic asthma, EIA may be a manifestation of poor asthma control. For these patients, it is important to assess overall treatment strategies to maximize therapy. In contrast, for patients who primarily have EIA without other manifestations of chronic asthma, it is important to determine that there is no underlying chronic asthma. This section provides an overview of treatment strategies for EIA in these patient populations.

Traditionally, premedication with inhaled β-agonists and mast cell stabilizers such as cromolyn or nedocromil 15 minutes before exercise improves EIA symptoms and exerts a protective effect.[89] Short-acting β-agonists are often used pre-exercise; however, long-acting β-agonists are also effective.[90] The onset of formoterol is rapid[91] and similar to albuterol, and can be used shortly before exercise. The onset of salmeterol is delayed, and as long as 90 minutes may be needed for full exercise protection.[92] Montelukast, a leukotriene receptor antagonist, has also been shown to benefit EIA when used prophylactically.[93]

Although short-acting and long-acting β-agonists are recognized to be effective for the prevention and treatment of EIA, there may be potential adverse events with the use of these agents, and health care providers should be aware of these concerns when β-agonists are used to prevent or treat EIA on a daily basis. If β-agonists are used daily, there is a potential for tachyphylaxis or partial loss of efficacy.[94-96] Loss of efficacy may be seen as a lessened bronchodilator response when β-agonists are used to treat symptoms, or as a shortening of the duration of effect of the β-agonist when used daily. Athletes who use albuterol, salmeterol, or formoterol as pretreatment before exercise may find that tachyphylaxis develops if they pretreat before exercise every day; the duration of action may decrease from about 12 hours to no more than 3 to 4 hours after a month of use.[97] In addition, in some genotypes of the β-receptor that occur in 15% to 20% of the population, regular use of both short-acting and long-acting β-agonists may be detrimental.[98]

Patients with EIA may need combination therapy.[66,88] The regular use of inhaled β-agonists alone, either short-acting or long-acting, should be discouraged because use of β-agonists leads to a reduction in the bronchodilator response for EIA.[94-96] When used regularly, β-agonists alone do not prevent exacerbations. In addition, the regular use of salmeterol leads to a small but statistically significant loss of bronchoprotection by albuterol to methacholine challenge. Nonetheless, regular use of long-acting β-agonists (formoterol or salmeterol) does have a role in the long-term treatment of asthma; patients receiving formoterol or salmeterol, in addition to budesonide or fluticasone, achieved asthma control 10 days sooner than those taking budesonide alone as defined by increased lung function, decreased symptoms, and improved quality of life including exercise and decreased exacerbations. Other treatments include leukotriene receptor anatonists[93] and zileuton.[99] Unlike with β-agonists, the benefits of montelukast or zileuton or zafirlukast are not reduced over time when they are used on a regular basis as monotherapy.[95] Theophylline and anticholinergics are third-line treatments and are rarely required or suggested.[66] Studies even suggest a role for vitamin C, inhaled furosemide, hydration, and heparin.[35,66]

Although there are no limitations in sport selection for patients with EIA, by selecting a sport based on its low asthmogenic potential, symptoms may be decreased. Breathing through the nose may allow cool dry air to be humidified and warmed. Underlying allergic and environmental nasal conditions should be treated to allow for nasal breathing. A warm down of 10 to 15 minutes post-exercise may avoid the rapid rewarming that may cause obstruction to occur. Most importantly, underlying chronic asthma should be controlled adequately with anti-inflammatory medications as specified in the Expert Panel Report from the National Heart Lung and Blood Institute.[89]

The possibility of poorly controlled refractory asthma also needs to be considered in patients who are unable to exercise.[89] If asthma is well controlled and if prophylactic treatment is not effective, then the diagnosis of EIA should be questioned and the patient should be referred to an asthma specialist. Consultation with an asthma specialist is indicated in patients with moderate or severe asthma, those with quality of life limitations, and those with inability to participate in exercise. Asthma specialists can assist in assessment of asthma when the diagnosis is uncertain, and can help to exclude other diseases in the athlete presenting with atypical symptoms. Even in mild asthma, monitoring of patients with spirometry is essential to determine that airway remodeling is not leading to progressive loss of lung function and to ensure that the underlying inflammation is adequately controlled.

Patients should also be evaluated for the presence of allergy by the use of skin testing or blood tests for specific IgE.[66] Skin testing is the preferred method because results are available immediately, sensitivity and specificity are high, and the cost of a skin test is less than the cost of an *in vitro* test for allergen sensitivity. Allergen triggers, when controlled, may lead to a decrease in the requirements for medications to treat EIA.[100] In some cases, control of symptoms with allergy vaccine may enhance the potential for an athlete to compete by reducing rhinitis and asthma symptoms. Refraining from exercise within a couple hours after receiving allergy vaccine is suggested. The use of allergy vaccine is not restricted by organizations that monitor elite athletes.

Finally, rhinitis should be treated in patients with rhinitis and EIA because nasal symptoms may have an impact of the severity of asthma associated with exercise.[30] Nasal congestion may directly limit performance as well as reduce quality of life and quality of sleep, even if it does not worsen EIA.[101] Nasal steroids and nonsedating

antihistamines should be used, and athletes should be told to avoid allergens if possible or to receive allergy vaccine if indicated.

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The Journal of Allergy and Clinical Immunology & *The Journal of Pediatrics* Announce a Shared Science Program

In the May 2007 issue of *The Journal of Pediatrics*, Constantin et al report the perspectives of parents of children who underwent adenotonsillectomy regarding the children's changes in sleep, breathing, quality of life, and neurobehavioral measures. The parents were more likely to report improvements in sleep, breathing, and quality of life, but not improvements in concentration, school performance, intellectual or developmental progress. Thus, healthcare professionals should advise parents that adenotenosillectomy may result in clinical improvements, but be cautious about promising improvement in behavior and development.

Constantin E, Kermack A, Nixon GM, Tidmarsh L, Ducharme FM, Brouillette RT. Adenotonsillectomy improves sleep, breathing and quality of life, but not behavior. *J Pediatr* 2007;150:540-6.

A report from Collins et al summarizes the practices and attitudes of pediatricians on controlling parental tobacco use and reducing environmental tobacco smoke (ETS). Pediatricians inconsistently intervened across treatment settings, and when treating different ETS-related illnesses (e.g., 60% "always" assessed during asthma visits, 13% during otitis visits). Less than 50% "always" explained ETS risks to smoking parents and less than 33% "always" advised about creating smoke-free homes. Most frequently cited barriers were lack of time and low confidence in effectiveness. Improving training for tobacco intervention skills is a good starting point that could have a wide public health impact.

Collins BN, Levin KP, Bryant-Stephens T. Pediatricians' practices and attitudes about environmental tobacco smoke and parental smoking. *J Pediatr* 2007;150:547-52.

Although children with type 1 diabetes (T1DM) are at increased risk for celiac disease (CD), the benefits of screening for antibodies to tissue transglutaminase (TG), a marker for CD, are unclear. Simmons et al report the impact of screening-identified CD on growth, bone mineralization, and diabetes control. They compared 71 children who were TG positive to 63 children with T1DM who were TG negative. In children with T1DM, screening-identified evidence of CD was associated with differences in weight and body mass index z-scores, but not bone mineral density or diabetes control. Further study is needed to determine the benefit of early diagnosis and treatment of CD in children with T1DM.

Simmons JH, Klingensmith GJ, McFann K, Rewers M, Taylor J, Emery LM, Taki I, Vanyi S, Liu E, Hoffenberg EJ. Impact of celiac autoimmunity on children with type 1 diabetes. *J Pediatr* 2007;150:461-6.

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