

Management of Exercise-Induced Bronchoconstriction in Athletes



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Learning objectives:

1. To understand the mechanisms of exercise-induced bronchoconstriction (EIB) in athletes.
2. To understand the differences in response to inhaled corticosteroids.
3. To prevent drug doping according to the World Anti-Doping Agency code.

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Exercise-induced bronchoconstriction (EIB) is a phenomenon observed in asthma but is also seen in healthy individuals and frequently in athletes. High prevalence rates are observed in athletes engaged in endurance sports, winter sports, and swimming. The pathophysiology of EIB is thought to be related to hyperventilation, cold air, and epithelial damage caused by chlorine and fine particles in inspired air. Several diagnostic procedures can be used; however, the diagnosis of EIB based on self-reported symptoms is not reliable and requires an objective examination. The hyperosmolar inhalation test and eucapnic voluntary hyperpnea test, which involve indirect stimulation of the airway, are useful for the diagnosis of EIB. A short-acting β -agonist is the first choice for prevention of EIB, and an inhaled corticosteroid is essential for patients with asthma. Furthermore,

treatment should accommodate antidoping requirements in elite athletes. Tailoring of the therapeutic strategy to the individual case and the prognosis after cessation of athletic activity are issues that should be clarified in the future. © 2020 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). (*J Allergy Clin Immunol Pract* 2020;8:2183-92)

Key words: Exercise-induced bronchoconstriction; Athletes; Epithelial disorder; Eucapnic voluntary hyperpnea; Hyperosmolar challenge test; Short-acting β -agonist; Inhaled corticosteroids; World Anti-Doping Agency

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Abbreviations used

ASL- Airway surface liquid
 CC16- Clara cell secretory protein 16
 CRTH₂- Chemoattractant receptor-homologous molecule expressed on T-helper type 2 cells
 CysLT- Cysteinyl leukotriene
 EIB- Exercise-induced bronchoconstriction
 EVH- Eucapnic voluntary hyperpnea
 FEV₁- Forced expiratory volume in 1 second
 FVC- Forced vital capacity
 GINA- Global Initiative for Asthma
 ICS- Inhaled corticosteroid
 LABA- Long-acting β -agonist
 LTRA- Leukotriene receptor antagonist
 PC₂₀- Drug concentration required to reduce the FEV₁ by 20%
 PEF- Peak expiratory flow
 SABA- Short-acting β -agonist
 TUE- Therapeutic Use Exemption
 WADA- World Anti-Doping Agency

Exercise-induced bronchoconstriction (EIB) is defined as airway contraction associated with exercise.¹ This phenomenon was initially called exercise-induced asthma² but was subsequently renamed EIB because airway contraction may be observed in cases without asthma.³ EIB typically develops within 15 minutes, after at least 5 to 8 minutes of high-intensity aerobic training (>85% of maximal voluntary ventilation), although it can also occur during exercise, and resolves spontaneously within 60 minutes.⁴ EIB occurs in 70% to 90% of individuals with asthma.⁵⁻⁷ Recently, EIB was separated into EIB with asthma and EIB without asthma,¹ the latter being particularly common in athletes.⁸ EIB without asthma in athletes is thought to be the result of years of intensive training.⁹ Athletes who perform intense exercise on a daily basis require a large amount of ventilation, so are exposed to respiratory stress, including exposure to allergens (eg, pollen), air pollutants, inhalation of large volumes of cold dry air, and respiratory muscle loading.¹⁰ Furthermore, intensive physical training may induce transient immune downregulation with a shift toward a prevalent T-lymphocyte helper-2 response that is clinically associated with an increased prevalence of atopy and viral upper respiratory tract infections, both of which are risk factors for the onset and worsening of asthma.¹¹ EIB that occurs in athletes without other features of asthma has specific clinical and pathologic features.¹² Some elite athletes who are diagnosed with EIB do not have a personal or family history of asthma, suggesting that environmental factors are more important than genetic predisposition in such cases.¹³ These athletes seldom experience symptoms of asthma at rest but become symptomatic during high-intensity exercise.¹⁴ This article focuses on our current understanding of EIB in athletes with special emphasis on the mechanism of EIB, its treatment, and drug doping considerations.

PREVALENCE OF EXERCISE-INDUCED BRONCHOCONSTRICTION

The reported prevalence rates for EIB in athletes widely range from 3.7% to 54.8%¹⁵ depending on the study population and the diagnostic criteria used (ie, questionnaires, antidoping records, baseline spirometry, bronchial provocation challenge). In a previous report,¹⁶ we investigated more than 2000 young athletes (mean age 18 years) using a respiratory symptoms

questionnaire and pulmonary function tests to detect undiagnosed asthma. The forced expiratory volume in 1 second (%FEV₁), peak expiratory flow (%PEF), and FEV₁% (FEV₁/forced vital capacity [FVC]) values in the group with no history of an asthma diagnosis but with respiratory symptoms associated with exercise (possible bronchial asthma) were significantly lower than those in the group with no history of an asthma diagnosis or respiratory symptoms (nonbronchial asthma; Figure 1). Therefore, it was thought that there were a considerable number of cases with airway narrowing (clinical asthma) caused by repeated episodes of EIB in the “possible bronchial asthma” group.

The frequency of EIB was reported to be 16.7% in 1996 (summer event) and 21.9% in 1998 (winter event) in the US Olympic delegation.^{17,18} More recently, a 12-year study that included 4 cross-sectional surveys performed between 2000 and 2012, before the summer and winter Olympics, showed that the prevalence of asthma in 659 Italian Olympic athletes was 14.7%, with a significant increase from 2000 (11.3%) to 2008 (17.2%).¹⁹

The most common sports events are cycling, swimming, and marathons in summer and cross-country, ice hockey, and ice skating in winter (Table I).²⁰ There are several types of sports that have a high prevalence of EIB. Asthma is most commonly found in athletes performing endurance activities, such as long-distance running, cycling, triathlons, and pentathlons. Asthma in these athletes is attributed to long-term ventilation load through the mouth (bypassing the nasal filter) and exposure to allergens and air pollutants.^{21,22} For example, in the study by Robson-Ansley et al,²³ 32% of 208 runners in the 2010 London Marathon had asthma according to the validated Allergy Questionnaire for Athletes.²⁴ Cold hyperventilation load is also an important factor in the development of EIB. It has been reported that the prevalence of EIB is high in winter events such as cross-country and skating. More than half (54.8%) of Swedish cross-country skiers were shown to have EIB in the study of Larsson et al.²⁵ Similarly, the prevalence rates of bronchial hyperresponsiveness and clinical asthma were 42% and 43%, respectively, in 53 Swedish cross-country skiers investigated by Sue-Chu et al.²⁶ The high prevalence of EIB in athletes engaged in winter sports has been attributed to hyperpnea in cold dry air, which places significant environmental stress on the airways, and it has been reported that exposure to cold air causes parasympathetic stimulation of the airways, contributing to EIB.²⁷ Furthermore, elevated emission of pollutants from fossil-fueled ice resurfacing machines has been found to contribute to the onset of EIB in skating and ice hockey athletes.²⁸ Swimming has also been the subject of recent discussions. In the past, swimming was considered an activity that could be recommended for children with asthma because it is performed in a humid environment.²⁹ However, an increased risk of EIB has been reported in swimmers.³⁰ The association between EIB and indoor swimming facilities likely reflects the chemical disinfectants used in pools and the poor air circulation in these facilities.

MECHANISM OF EXERCISE-INDUCED BRONCHOCONSTRICTION

The hypothesized mechanism for EIB has been shown as a flowchart (Figure 2³¹) whereby EIB is roughly divided into an airway dehydration component and a mucosal cooling component as a result of loss of inhaled water, resulting in

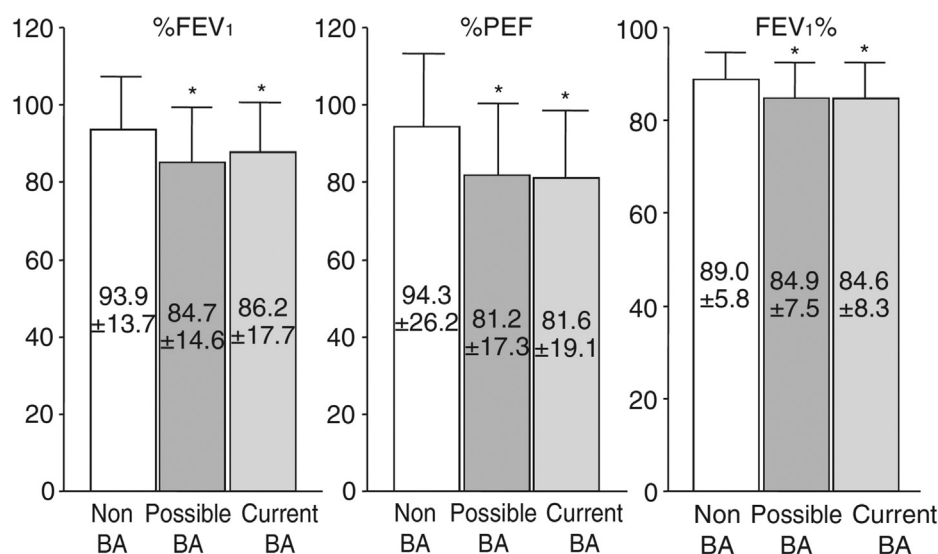


FIGURE 1. Obstructive indices on pulmonary function tests (%FEV₁, %PEF, and FEV₁%) in athletes.¹⁶ The medical history questionnaires and pulmonary function tests of 2111 athletes (1549 male, 562 female) were reviewed. The athletes were categorized as having current BA (confirmed and treated by a physician), possible BA (suspected based on history of allergy and/or symptoms), or no BA (control cases without current or possible BA). The data are shown as the mean ± standard deviation. **P* < .001, Kruskal-Wallis test. BA, Bronchial asthma; FEV₁, forced expiratory volume in 1 second; PEF, peak expiratory flow.

TABLE I. Sports with different levels of risk of exercise-induced bronchoconstriction²⁰

Risk	Characteristics	Examples of sports
Low	Sports in which the athlete performs a <5- to 8-min effort	Track and field: sprint (100, 200, and 400 m), middle distance (800 and 1500 m), hurdles (100, 110, and 400 m), jumps, throws, decathlon, heptathlon, tennis, fencing, gymnastics, downhill skiing, boxing, golf, body building, weightlifting, martial arts
Medium	Sports in which the continuous effort rarely lasts more than 5-8 min	Soccer, rugby, American football, basketball, volleyball, handball, baseball, cricket, field hockey
High	Sports in which the athlete performs a >5- to 8-min effort and/or in a dry/cold air environment, and/or in a noxious air environment (chlorine exposure, ultrafine particles, traffic air pollution)	Swimming, water polo Track and field: long distance (5000 and 10,000 m), 3000-m steeplechase, pentathlon (mixed), walks (20 and 50 km), marathon Cycling, cross-country skiing, ice hockey, ice skating, biathlon, high-altitude sports

increased vascular permeability and associated changes in bronchial reactivity. The concentration of water in inspired air is an important determinant of EIB.³² Loss of water by evaporation, in humidifying large volumes of air in a short time, is thought to cause a transient increase in the concentration of ions (eg, Na⁺, Cl⁻, Ca²⁺) in airway surface liquid (ASL).³³ This osmotic stimulus occurs after intense exercise when dry air of any temperature is inspired providing that the duration of exercise is sufficient. Changes in the osmolarity in ASL lead to intracellular movement of water, resulting in shrinkage of cells and release of inflammatory mediators that cause smooth muscle contraction and obstruction of the airway.³⁴ On the other hand, cooling of the airways, from heat lost through vaporization of water, was initially identified as a potential stimulus for EIB and to lead to vasoconstriction of the airway. Mucosal cooling of the airway also stimulates cholinergic airway receptors, increasing smooth muscle tone and secretions.³⁵ Chemical mediators, such as

cytokines and growth factors, released from epithelial cells, smooth muscle cells, and inflammatory cells in the airway are thought to further modify the disease state. Many mediators are involved in the pathogenesis of EIB, but some, such as prostaglandin E₂, act to dilate the airway and suppress inflammation.^{36,37} However, in the case of EIB, there are reports that expression of prostaglandin E₂ is reduced in the airway epithelium,³⁴ and many mediators, such as cysteinyl leukotrienes (CysLTs), prostaglandin D₂, and neurokinin, provoke narrowing and augment inflammation of the airway.³⁷ Mast cells are widely known to be involved in EIB and release chemical mediators, such as histamine, CysLTs, and prostaglandin D₂.³⁸

These chemical mediators act on smooth muscle and cause airway contraction.^{37,39} In particular, CysLTs are chemical mediators produced through the arachidonic acid cascade, and various cells, including mast cells, eosinophils, and epithelial cells, have been reported to be source cells.⁴⁰ Drugs targeting

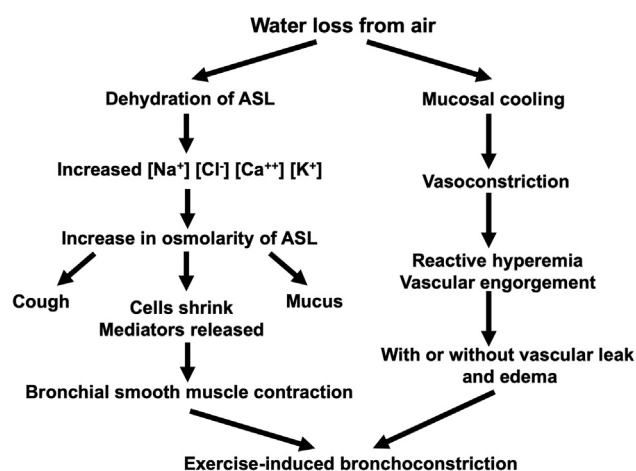


FIGURE 2. Both airway cooling and mucosal dehydration occur in response to evaporative water loss from the airway surface.³¹ These events lead to exercise-induced bronchoconstriction. ASL, Airway surface liquid. Published with permission from Rundell et al.³¹

CysLTs have been shown to be effective in preventing and suppressing EIB, including an inhibitor of 5-lipoxygenase,⁴¹ which is the key enzyme of the arachidonic acid cascade, and an antagonist of the CysLT1 receptor.³⁶ Furthermore, desensitization of the CysLT receptor has been reported to be the mechanism underpinning the refractory period in EIB.⁴² On the other hand, prostaglandin D₂ is mainly produced by mast cells, but its receptor is known as DP₁ and DP₂ (CRTH₂; chemo-attractant receptor-homologous molecule expressed on T-helper type 2 cells); especially CRTH₂ is known to be expressed on T-helper type 2 cells, type 2 innate lymphoid cell and eosinophil, and the role of the inhibitor of CRTH₂ in eosinophilic airway inflammation is now attracting research topic.⁴³ The DP₁ receptor may serve as the key receptor mediating bronchoconstriction and cough in EIB because it is a key activator of capsaicin-sensitive sensory neurons.⁴⁴ Mast cell stimulation and airway contraction by substance P and neurokinin, which are neurogenic mediators for nerves involved in the airways, are also important mechanisms.⁴⁵

Moreover, the effects of excessive athletic activity and long-term load on the autonomic nervous system should be considered. One study found a parasympathetic-dominant state in endurance athletes (long-distance runners) when compared with a control group.⁴⁶ The cholinergic parasympathetic nerves stimulate bronchoconstriction, and this is the predominant type of innervation at the bronchial level in humans.³⁵ Furthermore, type 2 cytokines and growth factors, such as vascular endothelial growth factor, are factors that complicate inflammation in cases with conventional asthma.⁴⁷ Recently, respiratory epithelial disorder has been recognized as an important cause of EIB in athletes with severe respiratory conditions.⁴⁸ There are several processes via which airway epithelial cells can become disordered, including damage to the cells themselves, impairment of the barrier function of the epithelial cells (ie, impaired tight junctions), and a change in the osmolarity of ASL.¹⁰ Shedding of epithelial cells into the airway lumen after exercise challenge has been demonstrated in individuals with asthma and EIB.⁴⁹ In

endurance sports, inhalation of large volumes of dry cold air makes it easier for the epithelium of the narrow airways (diameter <1 mm) to be damaged.⁵⁰ This damage was found to proceed promptly in the repair direction with infiltration of leukocytes into the walls of the airway in a mouse model.⁵¹ Athletes undergo these injury-repair processes many times during a season. One study found that competitive cross-country skiers without a diagnosis of asthma often showed airway hyper-responsiveness to methacholine and had increased deposition of tenascin, an extracellular matrix protein, in endobronchial biopsy specimens.⁵² Repeated prolonged exposure of the airways to harsh air conditions may be responsible for these early changes in airway remodeling. Clara cell secretory protein 16 (CC16) is a peripheral marker that can be used to assess epithelial barrier injury in the lower airways. Acute exercise stress-induced epithelial barrier injury can be confirmed by demonstrating increased CC16 levels in urine^{53,54} and serum⁵⁵ after exercise. Epithelial barrier injury occurs when tight junctions in the epithelium are destroyed and facilitates invasion of various foreign antigens and toxins, thereby strongly augmenting immune reactions and inflammation.¹⁰ Epithelial damage may also affect sensitization to pollens. The increased IgE production that occurs after acquisition of an atopic predisposition causes EIB by acting directly on airway smooth muscle or by contraction of airway smooth muscle in response to release of a chemical mediator from mast cells via IgE.^{56,57}

Although there have been few studies on changes in EIB after cessation of sport, it has been reported that swimmers show improvements in symptoms, airway hyperresponsiveness, and airway inflammation after retirement.⁵⁸ This suggests that airway hyperresponsiveness, which is the hallmark of EIB, may be reversible. Bougault et al⁵⁹ performed a study in competitive swimmers in which they performed a methacholine challenge test and a eucapnic voluntary hyperpnea (EVH) test during a period of intense training and after a rest period of 2 weeks. They found that the PC₂₀ (the drug concentration required to reduce the FEV₁ by 20%) was significantly higher after a nontraining period and that the decrease in FEV₁ after EVH was clearly lower than that during the training period. Therefore, airway hyperresponsiveness in competitive swimmers might be reversible after temporary cessation of training.

DIAGNOSIS OF EXERCISE-INDUCED BRONCHOCONSTRICTION

It is important to have a reliable method for diagnosing EIB or asthma in athletes that takes into account antidoping requirements.⁶⁰ The methods used to diagnose EIB include self-reported symptoms (questionnaire), biomarkers, respiratory function tests, and provocation tests. The questionnaire asks about symptoms during exercise, but these are difficult to determine.⁶⁰ According to Rundell et al,⁶¹ the diagnosis of EIB by self-reported symptoms is unreliable when the diagnosis can be confirmed by a provocation test (eg, an exercise test). The Allergy Questionnaire for Athletes, which is used to screen for allergic diseases in athletes, has been reported to have a positive predictive value of only 26% for the diagnosis of EIB; however, the negative predictive value is 92%, which suggests that this questionnaire is useful for excluding a diagnosis of EIB.⁶²

The markers used for the diagnosis of asthma, such as eosinophils (peripheral blood and sputum) and exhaled nitric

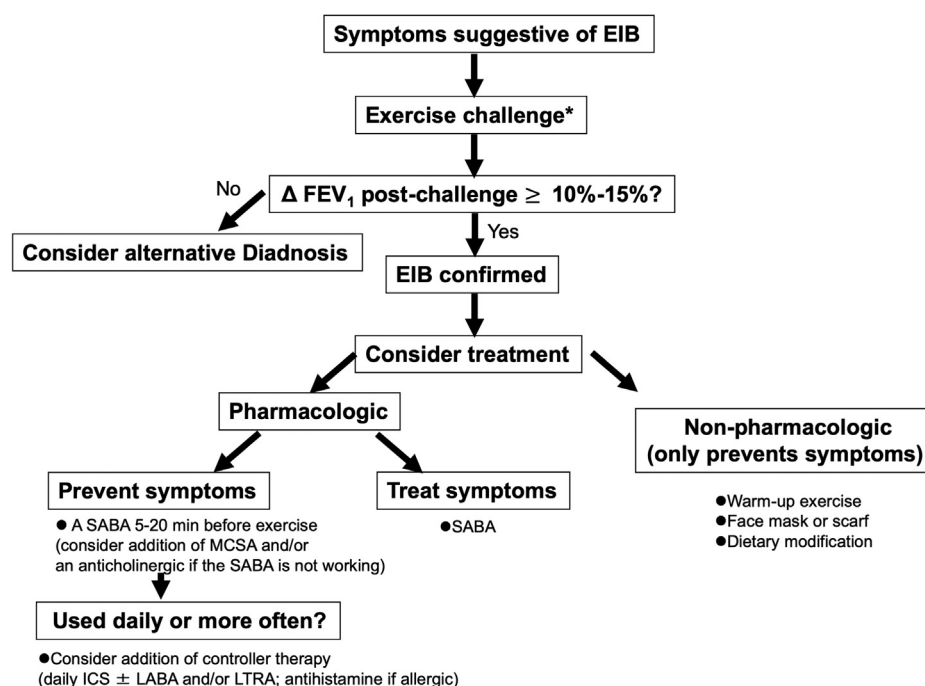


FIGURE 3. Diagnostic and treatment algorithm for EIB. *or surrogate challenge, for example, hyperpnea or mannitol. *EIB*, Exercise-induced bronchoconstriction; *FEV*₁, forced expiratory volume in 1 second; *ICS*, inhaled corticosteroid; *LABA*, long-acting β -agonist; *LTRA*, leukotriene receptor antagonist; *MCSA*, mast cell stabilizing agent; *SABA*, short-acting β -agonist. Reprinted with permission of the American Thoracic Society. Copyright © 2020 American Thoracic Society. Parsons et al.¹ The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society.

oxide, are useful for cases with an allergic predisposition. However, there are few data on the use of these parameters in athletes, and their clinical relevance is not well established.⁶³ According to Haahtela et al,⁶⁴ the diagnostic value of blood eosinophils and fraction of exhaled nitric oxide in EIB depends on whether or not it is accompanied by asthma, indicating that the value of these markers differs according to the type of disease. In a previous study, we performed a cluster analysis based on the pretreatment data for respiratory function tests and biomarkers in athletes with asthma diagnosed by respiratory symptoms on exercise and airway provocation test with methacholine, and separated the athletes into several clusters.⁶⁵ One of the clusters included athletes with limited predisposition to atopy and mild symptoms in whom the %FEV₁ value was significantly lower than that in the other clusters. Presumably, there would be a structural change in the airway after repeated episodes of EIB accompanying athletic activity.^{52,66}

Spirometry is mainly used to detect obstructive impairment (FEV₁/FVC < 70%), which is unusual in athletes.⁶⁷ However, subclinical airway obstruction is present in a number of individuals in whom all diagnostic criteria for obstructive disorder are not met; the airway reversibility test with inhalation of an aerosolized β_2 -agonist such as albuterol or salbutamol is useful for confirmation of airway obstruction in these cases. This test is judged to be positive when an FEV₁ increase of 12% or more than 200 mL is observed after the use of the β_2 -agonist. However, the reversibility test measures the reversibility by a bronchodilator in the airways, so it is useful for diagnosing asthma but not EIB.

Bronchial provocation tests can be broadly divided into direct provocation of the airway by inhalation of methacholine or histamine and indirect stimulation by exercise provocation tests, hypertonic saline or mannitol inhalation tests, or an EVH test.⁶⁸ Although the feasibility of EVH testing is well established, the practicalities and associated costs are substantial; therefore, this test is not widely available as part of a routine diagnostic examination in primary or secondary care.

Direct challenge with methacholine, an approved agonist, is frequently used for the diagnosis of asthma. This procedure is described in detail in the consensus statement by the American Thoracic Society.⁶⁹ This test provides an index of bronchial hyper-responsiveness and is expressed as the PC₂₀. A PC₂₀ of <4 mg/mL is judged to be positive, although a value of up to 16 mg/mL is considered positive in individuals who are established on inhaled corticosteroids (ICS). However, given that methacholine acts directly on airway smooth muscle, the bronchoconstriction by methacholine is far from the EIB mechanism. In practice, the methacholine challenge test can diagnose EIB reliably in athletes engaged in winter competition, but its sensitivity in those engaged in summer competition is as low as 40%.⁷⁰ Therefore, it can rule out asthma but is not recommended as a method for diagnosing EIB.⁷¹

Indirect stimulation tests, such as an exercise challenge test, hypertonic saline or mannitol powder inhalation test, and EVH, may stimulate inflammatory cells in the respiratory tract, release chemical mediators such as histamine and leukotrienes, and cause the smooth muscle in the airway to contract. These tests are thought to be reasonable for the diagnosis of EIB, and EVH is considered the gold standard for this purpose.⁶⁰

There are 2 types of exercise challenge tests: a test using a treadmill or ergometer in the laboratory and a test in the field where the individual is monitored while performing an outdoor activity (running or actual competition). Field tests have been reported to be more sensitive than indoor exercise tests⁷²; however, weather conditions and exercise loads are not constant and evaluation is difficult. More commonly used is the indoor exercise test performed according to the American Thoracic Society protocol,¹ that is, exercise stimulation with 80% to 90% of the predicted maximum heart rate under normal conditions (20°C to 25°C, humidity less than 50%) for 6 to 8 minutes. If the FEV₁ after exercise decreases by $\geq 10\%$ in comparison with the FEV₁ before exercise, the test is deemed positive.

Hypertonic saline and mannitol powder inhalation tests (also known as hyperosmolar inhalation tests) cause smooth muscle contraction in the airway by a mechanism that involves evaporation and dehydration of water in the airways. The hypertonic saline provocation test can be performed with 4.5% saline using an ultrasonic nebulizer (with an output of ≥ 1 mL/mL).⁷³ Furthermore, if sputum is collected in a nebulizer, inflammatory cells such as eosinophils and neutrophils can be analyzed. Using the mannitol powder inhalation test, the concentration of mannitol powder to be inhaled is increased stepwise, and FEV₁ is measured after each increment to determine the degree of airway contraction. However, the mannitol powder used in this test is currently approved only in the United States, European Union countries, Australia, South Korea, and a few other countries.⁷⁴ In both provocation tests, if a decrease in FEV₁ of $\geq 15\%$ is observed after inhalation, the result is judged to be positive.⁷¹

EVH is a provocation test based on the theory that an increased ventilation rate causes bronchoconstriction in susceptible individuals. The mechanism is thought to involve drying of the ASL and increased osmolarity, similar to what occurs during exercise.⁶⁸ The general procedure involves voluntary breathing of hypercapnic air (5% CO₂, 21% O₂, balance N₂) at a predetermined rate of 60% to 85% maximal voluntary ventilation.⁷⁵ The recommended ventilation rate is $30 \times \text{FEV}_1$ (estimated 85% maximal voluntary ventilation) for 6 minutes.⁷⁶ After 6 minutes of ventilation, spirometry is performed to measure FEV₁; if it is 10% lower than before ventilation, the test is judged as positive. The International Olympic Committee considers EVH to be the best of the airway provocation tests for athletes.⁷⁷

The differential diagnosis of EIB should take into account physiologic limitations, anxiety, exercise-induced laryngeal dysfunction, hyperventilation, and hypoxemia as a result of a lung disease other than asthma, and cardiac disease.¹

MANAGEMENT OF EXERCISE-INDUCED BRONCHOCONSTRICTION

Nonpharmacologic preventive strategies for EIB in athletes, including pre-exercise warm-up, wearing a face mask, and avoiding inhalation of cold air, are important given the harsh conditions in which athlete activity may be performed.^{78,79} It has often been suggested that the refractory period induced after a first bout of exercise explains why high-intensity warm-up activity protects against EIB. There is some evidence that weight loss⁸⁰ and dietary measures, such as a low sodium intake (<1500 mg per day),⁸¹ a diet rich in omega-3 polyunsaturated fatty

acids,^{82,83} and supplementation with ascorbic acid (1500 mg per day for 2 weeks),⁸⁴ may help to decrease the risk of EIB and its severity. In some cases, it may be necessary to advise that training be discontinued.

Short-acting β -agonists (SABAs) are now considered the first-line pharmacologic agents for protection against EIB based on consistent results across multiple meta-analyses of head-to-head comparisons with all other classes of medication commonly used in this condition and the consensus guidelines.^{1,71,85} SABAs are the most effective therapeutic agents for prevention of EIB.⁷¹ Use of a SABA 15 minutes before exercise is very effective.⁸⁶ SABAs stimulate β_2 receptors on the surface of the airway smooth muscle causing relaxation and bronchodilation.¹ However, it has been reported that the regular use of a SABA alone not only diminishes the efficacy of bronchodilation but also increases airway hypersensitivity.^{77,87} The mechanism for the development of tolerance is suspected to be downregulation of β_2 receptors on mast cells and airway smooth muscle.⁸⁸ Therefore, the current guidelines suggest that if a SABA is needed daily for EIB, an additional agent, preferably an ICS, should be added to decrease the frequency of use of the SABA.^{1,89}

In individuals of EIB with asthma, EIB is often a sign of poor asthma control; therefore, the treatment for asthma should be strengthened. The treatment components are adjusted depending on the guideline used, which is typically the one published by Global Initiative for Asthma (GINA). An ICS is the standard treatment for asthma. ICS therapy does not act rapidly in EIB but has been proven to decrease its severity⁹⁰ and is the first-line treatment for athletes with asthma.⁸⁶ However, the results of the only relevant long-term study in EIB, which was performed in competitive cross-country skiers, suggested that daily treatment with an ICS does not have any beneficial effect on respiratory symptoms, airway inflammation, or airway responsiveness to methacholine.⁹¹ In our study, there were a considerable number of athletes with asthma who had less atopic predisposition and eosinophilic inflammation in whom an ICS was ineffective.⁹² Moreover, it is thought that there is a “sports asthma” syndrome, defined by the presence of exercise-induced respiratory symptoms and airway hyperresponsiveness in the absence of allergic features.⁹³ Treatment with an ICS has a significant effect on allergic eosinophilic airway inflammation but has been reported to be less effective in types of disease with less eosinophilic inflammation.⁹⁴ Therefore, it is reasonable to suspect that ICS would not be so effective for “sports asthma.” The development of this pathophysiology is associated with specific training and environmental conditions, especially exposure to cold dry air and long exercise durations.⁹³ However, it is still unclear whether or not athletes with the phenotype that involves less eosinophilic inflammation can be treated with a bronchodilator without using an ICS.

An ICS combined with a long-acting β -agonist (LABA) is often used to treat patients with asthma in GINA step 3 or higher and is recommended for use on demand in GINA step 1 or 2.⁸⁶ A combination of budesonide and formoterol on demand has been reported to be extremely successful for reducing EIB.⁹⁵ Athletes with EIB who respond poorly to ICS alone often show improvement when switched to an ICS/LABA combination.⁶⁵ Although a LABA used alone has a preventive effect in EIB,⁹⁶ the US Food and Drug Administration has issued a warning against the use of LABA without an ICS for EIB.⁹⁷

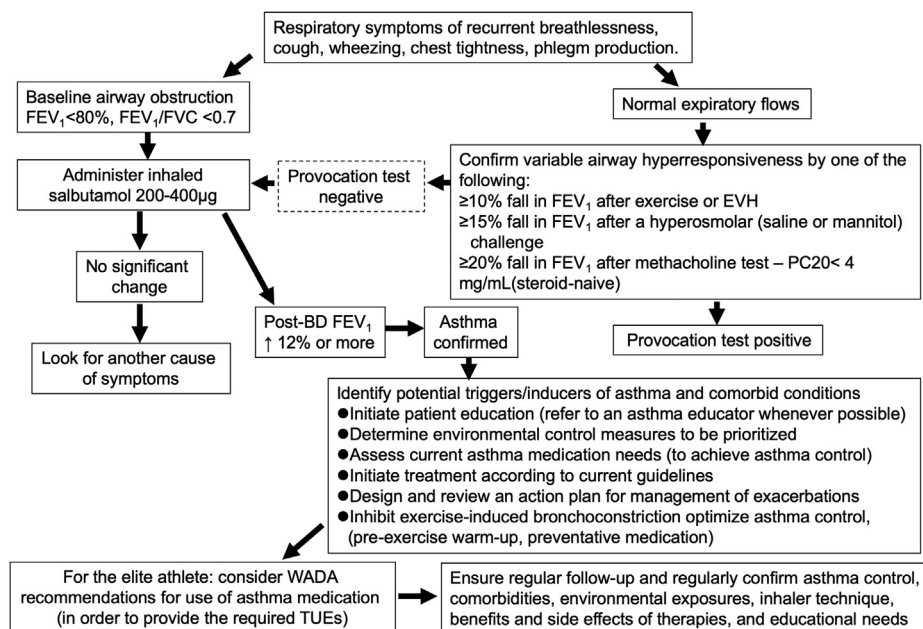


FIGURE 4. Management of asthma in the athlete.⁶⁰ BD, Bronchodilator; EVH, eucapnic voluntary hyperpnea; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; PC₂₀, drug concentration required to reduce the FEV₁ by 20%; TUE, Therapeutic Use Exemption; WADA, World Anti-Doping Agency. From Fitch et al.⁶⁰

TABLE II. Relationship between asthma medication and availability and need for a TUE application

Agent	Route	Use	TUE	Attention
Glucocorticoid*	Oral or injected	OK	Required	Retrospective TUE application required
	Inhalation	OK	Not required	—
β ₂ stimulant	Inhalation	OK	Required	No TUE application required for salbutamol, salmeterol, or formoterol†
	Oral, injected, or pasted	NO	Required	Normally TUE applications are not approved. In particular, clenbuterol, which is used as a bronchodilator in Asia, is classified as an anabolic agent
Leukotriene receptor antagonist	Oral	OK	Not required	—
Theophylline	Oral or injected	OK	Not required	—
Anticholinergic agent	Inhalation	OK	Not required	—
Cromone	Oral or inhalation	OK	Not required	—
Anti-IgE, anti-IL-5, anti-IL-5R antibody	Injection	OK	Not required	—

TUE, Therapeutic Use Exemption.

*Systemic (eg, oral or intravenous) administration of a glucocorticoid is prohibited in competition only and requires a TUE if the athlete competes before the drug has ceased to be identifiable in his or her urine. In emergency situations, a retrospective TUE application should be submitted as soon as possible to the appropriate antidoping organization if the athlete intends to compete while taking the systemic glucocorticoid or soon afterward.

†Maximum inhaled dose allowed. Salbutamol: 1600 µg over 24 hours and in divided doses of 800 µg over 12 hours. Salmeterol: 200 µg over 24 hours. Formoterol: 54 µg over 24 hours.

Alternatively, a leukotriene receptor antagonist (LTRA) can be used. LTRAs are theoretically effective because the CysLT pathway has been demonstrated to be involved in the pathophysiology of EIB.^{36,98} Although LTRAs are not as effective as β-agonists,⁹⁹ tolerance does not develop with long-term use.^{100,101} Allergic rhinitis is a common finding in atopic patients with asthma, and LTRAs are also an effective treatment allergic rhinitis¹⁰²; therefore, the use of these agents is convenient

in EIB with rhinitis. LTRAs can be used easily by athletes because they are not prohibited by the World Anti-Doping Agency (WADA).¹⁰³ Montelukast was shown to protect against EIB in college hockey players in environments containing low and high particulate matter.¹⁰⁴ However, Helenius et al¹⁰⁵ reported that LTRA was ineffective in hockey players, and data reported by our group and others show that montelukast is not as effective as an ICS in EIB with asthma.^{106,107}

TABLE III. Characteristics of exercise-induced bronchoconstriction with and without asthma

Feature	EIB with asthma	EIB without asthma
Pediatric asthma ^{65,92}	Often	Few
Comorbid allergic disease ^{65,92,93}	Often	Few
FeNO ^{65,92,93}	Elevated	Normal
Airway hyperresponsiveness ⁶⁴	+ (methacholine)	+ (EVH)
Response to ICS ^{65,92}	Good	Poor
Sports ^{30,64,66,91}	Any	Winter, swimming
Disease prognosis after retirement ^{58,59}	Persist treatment	Possible to quit treatment

EIB, Exercise-induced bronchoconstriction; EVH, eucapnic voluntary hyperpnea; FeNO, fraction of exhaled nitric oxide; ICS, inhaled corticosteroid.

Inhaled cromolyn sodium and nedocromil sodium (available in the United Kingdom, Austria, and Italy), which have no bronchodilator activity, attenuate EIB when used before exercise but have a short duration of action of only 1 to 2 hours and are not as potent as a SABA.¹⁰⁸ Cromolyn sodium is thought to alleviate EIB by suppressing the release of prostaglandin D₂ from mast cells.¹⁰⁹ Long-term use of either drug is not accompanied by tolerance.¹⁰⁸

Short-acting muscarinic antagonists, including ipratropium, target the muscarinic receptors on bronchial smooth muscle and provide bronchoprotection and bronchodilation in EIB.¹¹⁰ Ipratropium is not as effective a bronchodilator as a SABA but may be effective in cases of SABA tolerance.^{110,111} An inhaled long-acting muscarinic antagonist containing tiotropium has been reported to suppress exacerbations and improve quality of life in patients with moderate or severe asthma that cannot be controlled by medium to high doses of ICS and LABA.^{112,113} However, there are no data to evaluate the effectiveness of bronchoprotection in EIB.

The diagnosis and treatment of EIB have been described above. Figure 3 shows the algorithm, which summarizes the diagnosis and treatment of EIB. Of importance, although the algorithm provides a reliable diagnosis and identifies appropriate treatment, in clinical practice, it is often difficult to reliably diagnose EIB and evaluate treatment efficacy. Moreover, medical treatments are commonly interrupted even in cases that require continuous treatment.

In the survey of athletes who died from asthma attacks during sports activities, there were many cases of teenagers.¹¹⁴ A survey of asthma treatment history has shown that most cases do not use long-term management agents.¹¹⁴ With the use of appropriate therapeutics, the worst situation of asthma death might be avoided.

MANAGEMENT FOR ANTIDOPING

Medication for athletes with EIB requires compliance with the rules of WADA regardless of whether or not asthma is diagnosed. Even prohibited agents can be used by applying for a Therapeutic Use Exemption (TUE) because some have exemptions for treatment purposes and certain routes of administration.¹⁰³ Therefore, athletes can receive systemic steroids when they have an exacerbation of asthma with an appropriate application for TUE. However, a TUE application requires an objective diagnosis of asthma (after taking of a medical history, physical examination, pulmonary function, and airway responsiveness). The WADA provides a chart for management of asthma in athletes (Figure 4). Table II shows a list of the agents that are allowed under the current WADA regulations. For

bronchodilators, an inhaled SABA (salbutamol; also known as albuterol) and an inhaled LABA (salmeterol and formoterol) are allowed. More information is available online at www.wada-ama.org.

CONCLUSIONS

The following points are important when treating athletes with EIB: (1) prevention of sudden death during exercise; (2) avoiding use of ineffective drugs; (3) compliance with doping standards; and (4) prevention of a decline in athletic performance as a result of EIB symptoms. Although there are differences between EIB with and without asthma, it is important that athletes deal with EIB appropriately (Table III). According to statistics from the 2000 to 2006 Olympics (Sydney, Salt Lake City, Athens, Turin), the percentage of medalists with asthma was higher than that of those without asthma, especially in winter sports.⁶⁰ Therefore, it should be possible for athletes with EIB to maintain a level of performance comparable with that of athletes without EIB, if EIB is diagnosed as early as possible and treated appropriately.

REFERENCES

- Parsons JP, Hallstrand TS, Mastrorade JG, Kaminsky DA, Rundell KW, Hull JH, et al. An official American Thoracic Society clinical practice guideline: exercise-induced bronchoconstriction. *Am J Respir Crit Care Med* 2013;187:1016-27.
- McNeill RS, Nairn JR, Millar JS, Ingram CG. Exercise-induced asthma. *Q J Med* 1966;35:55-67.
- Weiler JM, Anderson SD, Randolph C, Bonini S, Craig TJ, Pearlman DS, et al. Pathogenesis, prevalence, diagnosis, and management of exercise-induced bronchoconstriction: a practice parameter. *Ann Allergy Asthma Immunol* 2010;105:S1-47.
- Smoliga JM, Weiss P, Rundell KW. Exercise induced bronchoconstriction in adults: evidence based diagnosis and management. *BMJ* 2016;352:h6951.
- Anderson SD, Silverman M, Konig P, Godfrey S. Exercise-induced asthma. *Br J Dis Chest* 1975;69:1-39.
- Storms WW. Review of exercise-induced asthma. *Med Sci Sports Exerc* 2003; 35:1464-70.
- McFadden ER Jr, Gilbert IA. Exercise-induced asthma. *N Engl J Med* 1994; 330:1362-7.
- Carlsen KH, Anderson SD, Bjerner L, Bonini S, Brusasco V, Canonica W, et al. Exercise-induced asthma, respiratory and allergic disorders in elite athletes: epidemiology, mechanisms and diagnosis: part I of the report from the Joint Task Force of the European Respiratory Society (ERS) and the European Academy of Allergy and Clinical Immunology (EAACI) in cooperation with GA2LEN. *Allergy* 2008;63:387-403.
- Boulet LP, O'Byrne PM. Asthma and exercise-induced bronchoconstriction in athletes. *N Engl J Med* 2015;372:641-8.
- Kippelen P, Anderson SD, Hallstrand TS. Mechanisms and biomarkers of exercise-induced bronchoconstriction. *Immunol Allergy Clin North Am* 2018; 38:165-82.
- Lakier Smith L. Overtraining, excessive exercise, and altered immunity: is this a T helper-1 versus T helper-2 lymphocyte response? *Sports Med* 2003;33:347-64.

12. Couto M, Kurowski M, Moreira A, Bullens DMA, Carlsen KH, Delgado L, et al. Mechanisms of exercise-induced bronchoconstriction in athletes: current perspectives and future challenges. *Allergy* 2018;73:8-16.
13. Wenzel SE. Asthma: defining of the persistent adult phenotypes. *Lancet* 2006;368:804-13.
14. Lund TK, Pedersen L, Anderson SD, Sverrild A, Backer V. Are asthma-like symptoms in elite athletes associated with classical features of asthma? *Br J Sports Med* 2009;43:1131-5.
15. Bonini M, Silvers W. Exercise-induced bronchoconstriction: background, prevalence, and sport considerations. *Immunol Allergy Clin North Am* 2018;38:205-14.
16. Tanaka J, Hasegawa T, Koya T, Hashiba M, Omori G, Gejyo F, et al. Pulmonary function analysis of Japanese athletes: possibly even more asthmatics in the field. *Allergol Int* 2010;59:53-7.
17. Weiler JM, Layton T, Hunt M. Asthma in United States Olympic athletes who participated in the 1996 Summer Games. *J Allergy Clin Immunol* 1998;102:722-6.
18. Weiler JM, Ryan EJ III. Asthma in United States Olympic athletes who participated in the 1998 Olympic Winter Games. *J Allergy Clin Immunol* 2000;106:267-71.
19. Bonini M, Palange P. Exercise-induced bronchoconstriction: new evidence in pathogenesis, diagnosis and treatment. *Asthma Res Pract* 2015;1:2.
20. Del Giacco SR, Firinu D, Bjerrmer L, Carlsen KH. Exercise and asthma: an overview. *Eur Clin Respir J* 2015;2:27984.
21. Helenius I, Haahtela T. Allergy and asthma in elite summer sport athletes. *J Allergy Clin Immunol* 2000;106:444-52.
22. McCreanor J, Cullinan P, Nieuwenhuijsen MJ, Stewart-Evans J, Malliarou E, Jarup L, et al. Respiratory effects of exposure to diesel traffic in persons with asthma. *N Engl J Med* 2007;357:2348-58.
23. Robson-Ansley P, Watson G, Tallent J, Mitcheson K, Walshe I, Toms C, et al. Prevalence of allergy and upper respiratory tract symptoms in runners of the London marathon. *Med Sci Sports Exerc* 2012;44:999-1004.
24. Bonini M, Braido F, Baiardini I, Del Giacco S, Gramiccioni C, Manara M, et al. AQUA: Allergy Questionnaire for Athletes. Development and validation. *Med Sci Sports Exerc* 2009;41:1034-41.
25. Larsson K, Ohlson P, Larsson L, Malmberg P, Rydstrom PO, Ulriksen H. High prevalence of asthma in cross country skiers. *BMJ* 1993;307:1326-9.
26. Sue-Chu M, Larsson L, Bjerrmer L. Prevalence of asthma in young cross-country skiers in central Scandinavia: differences between Norway and Sweden. *Respir Med* 1996;90:99-105.
27. McFadden ER Jr, Ingram RH Jr. Exercise-induced asthma: observations on the initiating stimulus. *N Engl J Med* 1979;301:763-9.
28. Rundell KW. High levels of airborne ultrafine and fine particulate matter in indoor ice arenas. *Inhal Toxicol* 2003;15:237-50.
29. Goodman M, Hays S. Asthma and swimming: a meta-analysis. *J Asthma* 2008;45:639-47.
30. Andersson M, Hedman L, Nordberg G, Forsberg B, Eriksson K, Ronmark E. Swimming pool attendance is related to asthma among atopic school children: a population-based study. *Environ Health* 2015;14:37.
31. Rundell KW, Anderson SD, Sue-Chu M, Bougault V, Boulet LP. Air quality and temperature effects on exercise-induced bronchoconstriction. *Compr Physiol* 2015;5:579-610.
32. Strauss RH, McFadden ER, Ingram RH, Deal EC, Jaeger JJ. Influence of heat and humidity on airway-obstruction induced by exercise in asthma. *J Clin Invest* 1978;61:433-40.
33. Anderson SD. Is there a unifying hypothesis for exercise-induced asthma? *J Allergy Clin Immunol* 1984;73:660-5.
34. Anderson SD, Kippelen P. Exercise-induced bronchoconstriction: pathogenesis. *Curr Allergy Asthma Rep* 2005;5:116-22.
35. Barnes PJ. Cholinergic control of airway smooth-muscle. *Am Rev Respir Dis* 1987;136:S42-5.
36. Hallstrand TS, Moody MW, Wurfl MM, Schwartz LB, Henderson WR Jr, Aitken ML. Inflammatory basis of exercise-induced bronchoconstriction. *Am J Respir Crit Care Med* 2005;172:679-86.
37. Hallstrand TS. New insights into pathogenesis of exercise-induced bronchoconstriction. *Curr Opin Allergy Clin Immunol* 2012;12:42-8.
38. Godfrey S. Exercise-induced asthma: application to clinical trials [proceedings]. *Br J Dis Chest* 1977;71:232-3.
39. Kippelen P, Larsson J, Anderson SD, Brannan JD, Dahlen B, Dahlen SE. Effect of sodium cromoglycate on mast cell mediators during hyperpnea in athletes. *Med Sci Sports Exerc* 2010;42:1853-60.
40. Hay DW, Torphy TJ, Udem BJ. Cysteinyl leukotrienes in asthma: old mediators up to new tricks. *Trends Pharmacol Sci* 1995;16:304-9.
41. Hallstrand TS, Henderson WR Jr. Role of leukotrienes in exercise-induced bronchoconstriction. *Curr Allergy Asthma Rep* 2009;9:18-25.
42. Larsson J, Anderson SD, Dahlen SE, Dahlen B. Refractoriness to exercise challenge: a review of the mechanisms old and new. *Immunol Allergy Clin North Am* 2013;33:329-45.
43. White C, Wright A, Brightling C. Fevipiprant in the treatment of asthma. *Expert Opin Investig Drugs* 2018;27:199-207.
44. Maher SA, Birrell MA, Adcock JJ, Wortley MA, Dubuis ED, Bonvini SJ, et al. Prostaglandin D2 and the role of the DP1, DP2 and TP receptors in the control of airway reflex events. *Eur Respir J* 2015;45:1108-18.
45. Rosa AC, Fantozzi R. The role of histamine in neurogenic inflammation. *Br J Pharmacol* 2013;170:38-45.
46. Filipe JA, Falcao-Reis F, Castro-Correia J, Barros H. Assessment of autonomic function in high level athletes by pupillometry. *Auton Neurosci* 2003;104:66-72.
47. Kanazawa H, Hirata K, Yoshikawa J. Involvement of vascular endothelial growth factor in exercise induced bronchoconstriction in asthmatic patients. *Thorax* 2002;57:885-8.
48. Anderson SD, Kippelen P. Airway injury as a mechanism for exercise-induced bronchoconstriction in elite athletes. *J Allergy Clin Immunol* 2008;122:225-35.
49. Hallstrand TS, Moody MW, Aitken ML, Henderson WR Jr. Airway immunopathology of asthma with exercise-induced bronchoconstriction. *J Allergy Clin Immunol* 2005;116:586-93.
50. Chimenti L, Morici G, Paterno A, Santagata R, Bonanno A, Profita M, et al. Bronchial epithelial damage after a half-marathon in nonasthmatic amateur runners. *Am J Physiol Lung Cell Mol Physiol* 2010;298:L857-62.
51. Chimenti L, Morici G, Paterno A, Bonanno A, Siena L, Licciardi A, et al. Endurance training damages small airway epithelium in mice. *Am J Respir Crit Care Med* 2007;175:442-9.
52. Karjalainen EM, Laitinen A, Sue-Chu M, Altraja A, Bjerrmer L, Laitinen LA. Evidence of airway inflammation and remodeling in ski athletes with and without bronchial hyperresponsiveness to methacholine. *Am J Respir Crit Care Med* 2000;161:2086-91.
53. Bolger C, Tufvesson E, Anderson SD, Devereux G, Ayres JG, Bjerrmer L, et al. Effect of inspired air conditions on exercise-induced bronchoconstriction and urinary CC16 levels in athletes. *J Appl Physiol* (1985) 2011;111:1059-65.
54. Romberg K, Bjerrmer L, Tufvesson E. Exercise but not mannitol provocation increases urinary Clara cell protein (CC16) in elite swimmers. *Respir Med* 2011;105:31-6.
55. Seys SF, Hox V, Van Gerven L, Dillissen E, Marijse G, Peeters E, et al. Damage-associated molecular pattern and innate cytokine release in the airways of competitive swimmers. *Allergy* 2015;70:187-94.
56. Brutsche M, Britschgi D, Dayer E, Tschopp JM. Exercise-induced bronchospasm (EIB) in relation to seasonal and perennial specific IgE in young adults. *Allergy* 1995;50:905-9.
57. Helenius IJ, Tikkanen HO, Haahtela T. Occurrence of exercise induced bronchospasm in elite runners: dependence on atopy and exposure to cold air and pollen. *Br J Sports Med* 1998;32:125-9.
58. Helenius I, Ryttila P, Sarna S, Lumme A, Helenius M, Remes V, et al. Effect of continuing or finishing high-level sports on airway inflammation, bronchial hyperresponsiveness, and asthma: a 5-year prospective follow-up study of 42 highly trained swimmers. *J Allergy Clin Immunol* 2002;109:962-8.
59. Bougault V, Turmel J, Boulet LP. Airway hyperresponsiveness in elite swimmers: is it a transient phenomenon? *J Allergy Clin Immunol* 2011;127:892-8.
60. Fitch KD, Sue-Chu M, Anderson SD, Boulet LP, Hancox RJ, McKenzie DC, et al. Asthma and the elite athlete: summary of the International Olympic Committee's consensus conference, Lausanne, Switzerland, January 22-24, 2008. *J Allergy Clin Immunol* 2008;122:254-60. 260.e1-7.
61. Rundell KW, Im J, Mayers LB, Wilber RL, Szmedra L, Schmitz HR. Self-reported symptoms and exercise-induced asthma in the elite athlete. *Med Sci Sports Exerc* 2001;33:208-13.
62. Allen H, Hull JH, Backhouse SH, De Carne T, Dimitriou L, Price OJ. The Allergy Questionnaire for Athletes provides value in ruling-out exercise-induced bronchoconstriction. *Allergy* 2019;74:1794-6.
63. Cote A, Turmel J, Boulet LP. Exercise and asthma. *Semin Respir Crit Care Med* 2018;39:19-28.
64. Haahtela T, Malmberg P, Moreira A. Mechanisms of asthma in Olympic athletes—practical implications. *Allergy* 2008;63:685-94.
65. Tsukioka K, Koya T, Ueno H, Hayashi M, Sakagami T, Hasegawa T, et al. Phenotypic analysis of asthma in Japanese athletes. *Allergol Int* 2017;66:550-6.
66. Sue-Chu M. Winter sports athletes: long-term effects of cold air exposure. *Br J Sports Med* 2012;46:397-401.

67. Bonini M, Lapucci G, Petrelli G, Todaro A, Pamich T, Rasi G, et al. Predictive value of allergy and pulmonary function tests for the diagnosis of asthma in elite athletes. *Allergy* 2007;62:1166-70.
68. Rundell KW, Slee JB. Exercise and other indirect challenges to demonstrate asthma or exercise-induced bronchoconstriction in athletes. *J Allergy Clin Immunol* 2008;122:238-46.
69. Crapo RO, Casaburi R, Coates AL, Enright PL, Hankinson JL, Irvin CG, et al. Guidelines for methacholine and exercise challenge testing-1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. *Am J Respir Crit Care Med* 2000;161:309-29.
70. Holzer K, Anderson SD, Douglass J. Exercise in elite summer athletes: challenges for diagnosis. *J Allergy Clin Immunol* 2002;110:374-80.
71. Weiler JM, Brannan JD, Randolph CC, Hallstrand TS, Parsons J, Silvers W, et al. Exercise-induced bronchoconstriction update-2016. *J Allergy Clin Immunol* 2016;138:1292-1295.e36.
72. Rundell KW, Wilber RL, Szmedra L, Jenkinson DM, Mayers LB, Im J. Exercise-induced asthma screening of elite athletes: field versus laboratory exercise challenge. *Med Sci Sports Exerc* 2000;32:309-16.
73. Anderson SD, Brannan JD. Methods for "indirect" challenge tests including exercise, eucapnic voluntary hyperpnea, and hypertonic aerosols. *Clin Rev Allergy Immunol* 2003;24:27-54.
74. Aridol. Mannitol bronchial challenge test; 2019. Available from: <http://www.aridol.info>. Accessed November 15, 2019.
75. Anderson SD, Argyros GJ, Magnussen H, Holzer K. Provocation by eucapnic voluntary hyperpnea to identify exercise induced bronchoconstriction. *Br J Sports Med* 2001;35:344-7.
76. Rundell KW, Anderson SD, Spiering BA, Judelson DA. Field exercise vs laboratory eucapnic voluntary hyperventilation to identify airway hyper-responsiveness in elite cold weather athletes. *Chest* 2004;125:909-15.
77. Anderson SD, Sue-Chu M, Perry CP, Gratzou C, Kippelen P, McKenzie DC, et al. Bronchial challenges in athletes applying to inhale a beta2-agonist at the 2004 Summer Olympics. *J Allergy Clin Immunol* 2006;117:767-73.
78. Stickland MK, Rowe BH, Spooner CH, Vandermeer B, Dryden DM. Effect of warm-up exercise on exercise-induced bronchoconstriction. *Med Sci Sports Exerc* 2012;44:383-91.
79. Millqvist E, Bengtsson U, Lowhagen O. Combining a beta2-agonist with a face mask to prevent exercise-induced bronchoconstriction. *Allergy* 2000;55:672-5.
80. Moreira A, Bonini M, Garcia-Larsen V, Bonini S, Del Giacco SR, Agache I, et al. Weight loss interventions in asthma: EAACI evidence-based clinical practice guideline (part I). *Allergy* 2013;68:425-39.
81. Mickleborough TD, Gotshall RW, Cordain L, Lindley M. Dietary salt alters pulmonary function during exercise in exercise-induced asthmatics. *J Sports Sci* 2001;19:865-73.
82. Mickleborough TD, Murray RL, Ionescu AA, Lindley MR. Fish oil supplementation reduces severity of exercise-induced bronchoconstriction in elite athletes. *Am J Respir Crit Care Med* 2003;168:1181-9.
83. Mickleborough TD, Lindley MR, Ionescu AA, Fly AD. Protective effect of fish oil supplementation on exercise-induced bronchoconstriction in asthma. *Chest* 2006;129:39-49.
84. Tecklenburg SL, Mickleborough TD, Fly AD, Bai Y, Stager JM. Ascorbic acid supplementation attenuates exercise-induced bronchoconstriction in patients with asthma. *Respir Med* 2007;101:1770-8.
85. Carlsen KH, Anderson SD, Bjerner L, Bonini S, Brusasco V, Canonica W, et al. Treatment of exercise-induced asthma, respiratory and allergic disorders in sports and the relationship to doping: part II of the report from the Joint Task Force of European Respiratory Society (ERS) and European Academy of Allergy and Clinical Immunology (EAACI) in cooperation with GA(2)LEN. *Allergy* 2008;63:492-505.
86. GINA. Global Strategy for Asthma Management and Prevention; 2019. Available from: <https://ginasthma.org/wp-content/uploads/2019/06/GINA-2019-main-report-June-2019-wms.pdf>. Accessed November 15, 2019.
87. Hancox RJ, Subbarao P, Kamada D, Watson RM, Hargreave FE, Inman MD. Beta2-agonist tolerance and exercise-induced bronchospasm. *Am J Respir Crit Care Med* 2002;165:1068-70.
88. Finney PA, Belvisi MG, Donnelly LE, Chuang TT, Mak JC, Scorer C, et al. Albuterol-induced downregulation of Gsalpha accounts for pulmonary beta(2)-adrenoceptor desensitization in vivo. *J Clin Invest* 2000;106:125-35.
89. Salpeter SR, Ormiston TM, Salpeter EE. Meta-analysis: respiratory tolerance to regular beta2-agonist use in patients with asthma. *Ann Intern Med* 2004;140:802-13.
90. Stelmach I, Grzelewski T, Majak P, Jerzynska J, Stelmach W, Kuna P. Effect of different antiasthmatic treatments on exercise-induced bronchoconstriction in children with asthma. *J Allergy Clin Immunol* 2008;121:383-9.
91. Sue-Chu M, Karjalainen EM, Laitinen A, Larsson L, Laitinen LA, Bjerner L. Placebo-controlled study of inhaled budesonide on indices of airway inflammation in bronchoalveolar lavage fluid and bronchial biopsies in cross-country skiers. *Respiration* 2000;67:417-25.
92. Hoshino Y, Koya T, Kagamu H, Tsukioka K, Toyama M, Sakagami T, et al. Effect of inhaled corticosteroids on bronchial asthma in Japanese athletes. *Allergol Int* 2015;64:145-9.
93. Couto M, Stang J, Horta L, Stensrud T, Severo M, Mowinckel P, et al. Two distinct phenotypes of asthma in elite athletes identified by latent class analysis. *J Asthma* 2015;52:897-904.
94. Lazarus SC, Krishnan JA, King TS, Lang JE, Blake KV, Covar R, et al. Mometasone or tiotropium in mild asthma with a low sputum eosinophil level. *N Engl J Med* 2019;380:2009-19.
95. Lazarinis N, Jorgensen L, Ekstrom T, Bjerner L, Dahlen B, Pullerits T, et al. Combination of budesonide/formoterol on demand improves asthma control by reducing exercise-induced bronchoconstriction. *Thorax* 2014;69:130-6.
96. Newnham DM, Ingram CG, Earnshaw J, Palmer JB, Dhillon DP. Salmeterol provides prolonged protection against exercise-induced bronchoconstriction in a majority of subjects with mild, stable asthma. *Respir Med* 1993;87:439-44.
97. U.S. Food and Drug Administration. Available from: <https://www.fda.gov>. Accessed November 15, 2019.
98. Leff JA, Busse WW, Pearlman D, Bronsky EA, Kemp J, Hendeles L, et al. Montelukast, a leukotriene-receptor antagonist, for the treatment of mild asthma and exercise-induced bronchoconstriction. *N Engl J Med* 1998;339:147-52.
99. Raissy HH, Harkins M, Kelly F, Kelly HW. Pretreatment with albuterol versus montelukast for exercise-induced bronchospasm in children. *Pharmacotherapy* 2008;28:287-94.
100. Villaran C, O'Neill SJ, Helbling A, van Noord JA, Lee TH, Chuchalin AG, et al. Montelukast versus salmeterol in patients with asthma and exercise-induced bronchoconstriction. Montelukast/Salmeterol Exercise Study Group. *J Allergy Clin Immunol* 1999;104:547-53.
101. Edelman JM, Turpin JA, Bronsky EA, Grossman J, Kemp JP, Ghanam AF, et al. Oral montelukast compared with inhaled salmeterol to prevent exercise-induced bronchoconstriction. A randomized, double-blind trial. *Exercise Study Group. Ann Intern Med* 2000;132:97-104.
102. Dykewicz MS, Wallace DV, Baroody F, Bernstein J, Craig T, Finegold I, et al. Treatment of seasonal allergic rhinitis: an evidence-based focused 2017 guideline update. *Ann Allergy Asthma Immunol* 2017;119:489-511.e41.
103. World Anti-Doping Agency; 2019. Accessed November 15, 2019. Available from: <https://www.wada-ama.org>. Accessed November 15, 2019.
104. Rundell KW, Spiering BA, Baumann JM, Evans TM. Effects of montelukast on airway narrowing from eucapnic voluntary hyperventilation and cold air exercise. *Br J Sports Med* 2005;39:232-6.
105. Helenius I, Lumme A, Ounap J, Obase Y, Ryttilä P, Sarna S, et al. No effect of montelukast on asthma-like symptoms in elite ice hockey players. *Allergy* 2004;59:39-44.
106. Vidal C, Fernandez-Ovide E, Pineiro J, Nunez R, Gonzalez-Quintela A. Comparison of montelukast versus budesonide in the treatment of exercise-induced bronchoconstriction. *Ann Allergy Asthma Immunol* 2001;86:655-8.
107. Koya T, Hasegawa T, Tanaka J, Kawakami H, Hayashi M, Kagamu H, et al. Effect of ciclesonide on bronchial asthma in athletes. *J Asthma* 2009;46:1032-6.
108. Spooner CH, Spooner GR, Rowe BH. Mast-cell stabilising agents to prevent exercise-induced bronchoconstriction. *Cochrane Database Syst Rev* 2003;4:CD002307.
109. Brannan JD, Gulliksson M, Anderson SD, Chew N, Seale JP, Kumlin M. Inhibition of mast cell PGD2 release protects against mannitol-induced airway narrowing. *Eur Respir J* 2006;27:944-50.
110. Boulet LP, Turcotte H, Tennina S. Comparative efficacy of salbutamol, ipratropium, and cromoglycate in the prevention of bronchospasm induced by exercise and hyperosmolar challenges. *J Allergy Clin Immunol* 1989;83:882-7.
111. Haney S, Hancox RJ. Overcoming beta-agonist tolerance: high dose salbutamol and ipratropium bromide. Two randomised controlled trials. *Respir Res* 2007;8:19.
112. Peters SP, Kunselman SJ, Icitovic N, Moore WC, Pascual R, Ameredes BT, et al. Tiotropium bromide step-up therapy for adults with uncontrolled asthma. *N Engl J Med* 2010;363:1715-26.
113. Kerstjens HA, Engel M, Dahl R, Paggiaro P, Beck E, Vandewalker M, et al. Tiotropium in asthma poorly controlled with standard combination therapy. *N Engl J Med* 2012;367:1198-207.
114. Becker JM, Rogers J, Rossini G, Mirchandani H, D'Alonzo GE Jr. Asthma deaths during sports: report of a 7-year experience. *J Allergy Clin Immunol* 2004;113:264-7.