

## Work Group Report: Perspectives in Diagnosis and Management of Exercise-Induced Bronchoconstriction in Athletes



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For reference only.

Exercise-induced bronchoconstriction, otherwise known as exercise-induced bronchoconstriction with asthma or without asthma, is an acute airway narrowing that occurs as a result of exercise and can occur in patients with asthma. A panel of members from the American Academy of Allergy, Asthma & Immunology Sports, Exercise, & Fitness Committee reviewed the diagnosis and management of exercise-induced bronchoconstriction in athletes of all skill levels including recreational athletes, high school and college athletes, and

professional athletes. A special emphasis was placed on the recommendations and regulations set forth by professional athletic organizations after a detailed review of their collective bargaining agreements, substance abuse policies, antidoping program manuals, and the World Anti-Doping Agency antidoping code. The recommendations in this review are based on currently available evidence in addition to providing guidance for athletes of all skill levels as well as their treating physicians to better understand which pharmaceutical and

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*Abbreviations used*

*EIB- Exercise-induced bronchoconstriction*  
*EIBa- Exercise-induced bronchoconstriction with asthma*  
*EVH- Eucapnic voluntary hyperpnea*  
*GERD- Gastroesophageal reflux disease*  
*ICS- Inhaled corticosteroid*  
*PD- Provoking dose*  
*PVFM- Paradoxical vocal fold movement*  
*SABA- Short-acting  $\beta_2$ -adrenergic receptor agonist*  
*TUE- Therapeutic use exemption*  
*WADA- World Anti-Doping Agency*

**nonpharmaceutical management options are appropriate as well as which medications are permitted or prohibited, and the proper documentation required to remain compliant.** © 2020 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;8:2542-55)

**Key words:** Asthma; Exercise-induced bronchoconstriction; Airway hyperresponsiveness; Bronchial provocation; Athlete; Sports; Environment; Diagnosis; Differential diagnosis; Therapy; Nonpharmacologic; Pharmacologic

## INTRODUCTION

In the first century AD, Aeraetus the Cappadocian made one of the first attempts at characterizing exercise-induced bronchoconstriction: "If from running, gymnastics, or any other work, breathing becomes difficult, it is called asthma."<sup>1</sup> An article in the *British Journal of Diseases of the Chest* in the 1960s defined the airway obstruction following free running exercise challenge in children as "exercise induced asthma."<sup>2</sup> The term exercise-induced bronchoconstriction (EIB) describes transient airway narrowing that occurs during or after vigorous exercise because of large volumes of unconditioned air entering the lower airways to meet increased ventilatory demands.<sup>3</sup> Acute episodes of bronchospasm that occur during exercise can result in significant morbidity in athletes and may affect athletic performance. The prevalence of EIB has been shown to be higher in competitive athletes than in the general population, with ranges up to 50% depending on the type of sport, environmental conditions, and maximum exercise level.<sup>4</sup> EIB may be observed in individuals with and without clinically diagnosed asthma based on spirometry.<sup>5</sup> The term exercise-induced asthma is no longer a preferred term because it might imply incorrectly that exercise causes rather than exacerbates or triggers an asthma attack.<sup>5</sup> Instead, exercise-induced asthma is now referred to as exercise-induced bronchoconstriction with asthma (EIBa). For the purposes of this article, exercise-induced bronchoconstriction without asthma will be referred to as EIB.

Both EIBa and EIB commonly share airway hyperactivity. Distinguishing between them is important for accurate diagnosis and management. Patients with EIBa have a history of asthma that is exacerbated by exercise, whereas patients with EIB do not have a history of asthma, but experience symptoms of asthma with exercise only.<sup>6</sup> Respiratory specialists are frequently consulted by athletes for accurate diagnosis and management of EIBa and EIB. Sound knowledge of the medications used in the management of these conditions by physicians and athletes is

essential to maximize athletic performance and health. This article reviews the diagnosis and management of EIBa and EIB in athletes at every skill level including recreational athletes, high school and college athletes, and professional athletes, with special emphasis on the regulations set forth by professional athletic organizations in managing these disease states. Noncompliance with these regulations can affect a professional athlete's ability to compete and even jeopardize his or her career. Although elite athletes must abide by certain rules defined by governing bodies for permission to use pharmaceutical agents, both recreational and professional athletes with EIBa and EIB can be treated in a similar manner.

## PATHOGENESIS

The exact mechanisms of EIB have not been established with certainty, but proposed mechanisms include both airway cooling and postexercise rewarming of the airways. Vigorous exercise requires increased ventilation, leading to respiratory water loss and subsequent airway cooling and drying. In susceptible individuals, dehydration of airway surface liquid leads to an inflammatory response with the release of mast cell mediators including prostaglandins, leukotrienes, and histamine that can stimulate smooth muscle.<sup>7</sup> This inflammatory response causes bronchoconstriction and a change in vascular permeability.<sup>7</sup> Leukotrienes released from eosinophils and neuropeptides released from sensory nerves may also be involved in EIB, while inspired cold air further increases dehydration of the surface area and causes changes in bronchial blood flow.<sup>7,8</sup> Anderson and Daviskas<sup>9</sup> demonstrated that evaporative water loss leads to an increase in the osmolality of the airway surface liquid and the consequent release of mediators represents the major stimulus and mechanism for EIB.<sup>9</sup> Epithelial damage in and throughout the bronchial tree to the peripheral airways represents the predominant pathogenic mechanism in individuals with EIB, with or without clinically diagnosed asthma.<sup>7</sup>

## PREVALENCE

The relative risk of EIB increases with the more prolonged strenuous sports associated with cold (dry) air such as winter sports, soccer, long-distance running, basketball, or swimming with chloramine as opposed to racket sports where exercise is intermittent. Atopy and air pollutants also contribute. The relative risk of EIB increases by the following: 25-fold in atopic speed and power athletes, 42-fold in atopic long-distance runners, and 97-fold in atopic swimmers when compared with nonatopic control subjects.<sup>10</sup>

### Prevalence of EIB in children

The prevalence of EIB has been reported to be 10% in schoolchildren<sup>11</sup>; however, estimates of up to 20% have been reported.<sup>12</sup> Overall, there is a paucity of data from cohort studies in children that examine changes in the prevalence of EIB over time. Researchers exercised 15,241 children using a 6-minute run and a decrease of 15% for peak flow as an indicator of EIB.<sup>13</sup> In this cohort, girls (8.5%) were more likely than boys (6.4%), and those from urban settings (8.9%) were more likely than those from rural environments (7%) to have a positive challenge result. As expected in all populations, symptoms were a poor predictor of positive challenge results.<sup>13</sup>

**TABLE I.** Examples of sports and their potential risk of EIBa and EIB

Low-risk sports	Medium-risk sports	High-risk sports
All sports in which the athlete performs a <5-8-min effort	Team sports in general, in which the continuous effort rarely lasts more than 5-8 min	All sports in which the athlete performs a >5-8-min effort in a dry/cold air environment
Track and field:	Soccer Rugby	Track and field:
• Sprint (100, 200, and 400 m)	American football Basketball Volleyball Handball	• Long distance (5,000 and 10,000 m)
• Middle distance (800 and 1,500 m)	Baseball Cricket	• 3,000 m steeplechase
• Hurdles (100, 110, and 400 m)	Field hockey	• Pentathlon (mixed)
• Jumps		• Walks (20 and 50 km)
• Throws		• Marathon
• Decathlon		• High-altitude sports
• Heptathlon		Cycling
Tennis		Cross-country skiing
Fencing Gymnastics		Ice hockey
Downhill skiing		Ice skating Biathlon
Boxing		
Golf		
Body building		
Weightlifting		
Martial arts		
Diving		
Swimming, water polo		

Del Giacco et al.<sup>1</sup>

### Prevalence of EIB in everyday athletes

The everyday adult beginner or amateur athlete presents with potentially different EIB issues than high school, college, or professional athletes. Patients with a family history of asthma and atopic history are more likely to have EIB.<sup>14-16</sup> Prevalence of EIB in adults is estimated to be around 19%; however, this can be affected by ethnic background, age, sex, and environment.<sup>5</sup> There is variability in the prevalence of asthma and EIB in adult athletes, ranging from 8% to 61%, depending on sport and environment.<sup>5</sup> One study among adults at an urban fitness gym revealed a prevalence of EIB of 19%.<sup>17</sup> Two studies of adult elite athletes showed a higher prevalence of asthma symptoms among women.<sup>18</sup>

### Prevalence of EIB in high school and college athletes

In 107 collegiate athletes, Parsons et al<sup>19</sup> found that the prevalence of EIB was 35% and 36% in athletes with and without symptoms of EIB, respectively. Athletes in high-ventilation sports were significantly more symptomatic (48%) than athletes in low-ventilation sports (25%), with no difference in EIB prevalence between groups.<sup>19</sup>

### Prevalence of EIB in professional athletes

Several studies have shown that the prevalence of EIB in professional athletes surpasses that in the general population.<sup>20-23</sup> Anderson and Daviskas<sup>24</sup> found that the prevalence of airway hyperactivity in this subgroup ranged from 11% to 50%, whereas the prevalence among the general population ranged from 4% to 20%. Other data suggest that the prevalence of asthma and EIB among professional athletes is even higher, with estimates between 30% and 70%, depending on the type of sports performed.<sup>25</sup>

### DIAGNOSIS AND TESTING

EIB usually develops within 15 minutes after 5 to 8 minutes of intensive aerobic training and usually resolves within 60 minutes.<sup>18</sup> Athletes may not always be aware of their EIB symptoms.<sup>3</sup> Athletes in high-ventilation sports, such as track, cross-country, soccer, ice hockey, field hockey, swimming, and cross-country skiing, are more likely to have EIB symptoms compared with those in low-ventilation sports (golf, baseball, bowling, diving, weightlifting, volleyball, football).<sup>3</sup> Competitive swimmers in particular show an increase in asthma prevalence, with a mixed eosinophilic-neutrophilic airway inflammation phenotype leading to epithelial damage and bronchial hyper-responsiveness.<sup>1</sup> In general, low-risk sports, such as golf and diving, are ones in which exercise lasts less than 5 to 8 minutes (Table I).<sup>1,18</sup> There appears to be an increased frequency of EIB in winter sports athletes, possibly due to cooling of the airways and resulting hyperemia in pulmonary vessels.<sup>3</sup>

The diagnosis of EIBa or EIB can be made only when characteristic symptoms are accompanied by objective findings of variable airway obstruction through either spirometry with bronchodilator reversibility testing or bronchoprovocation tests. Athletes presenting with characteristic symptoms of EIBa or EIB should initially undergo spirometry with bronchodilator reversibility testing. Bronchodilator administration is important to perform because athletes commonly have higher baseline FEV<sub>1</sub> than nonathletes, and spirometry without testing for bronchodilator reversibility may appear normal. Reversibility is determined by an increase in FEV<sub>1</sub> of more than 200 mL and more than or equal to 12% from baseline measure after inhalation of a short-acting  $\beta$ 2-adrenergic receptor agonist (SABA).<sup>26</sup> Although the National Asthma Education and Prevention Program's Expert Panel Report 3 uses the 12% cutoff as evidence of airway reversibility in establishing the diagnosis of asthma, the validity of

**TABLE II.** Bronchial provocation tests approved by the WADA for the diagnosis of exercise-induced bronchospasm

Bronchial provocation test	Decrease in FEV1 for positive test result
EVH	≥10% fall in FEV1
Methacholine aerosol challenge	≥20% fall in FEV1—PC20 <4 mg/mL (steroid-naive)
Mannitol inhalation	≥15% fall in FEV1 after challenge
Hypertonic saline aerosol challenge	≥15% fall in FEV1
Exercise challenge (field or laboratory)	≥10% fall in FEV1
Histamine challenge	≥20% fall in FEV1 at a histamine concentration of 8 mg/mL or less during a graded test of 2 min

- A positive response to any 1 of the above provocation tests confirms airway hyperresponsiveness, if not already confirmed by spirometry and bronchodilatation test.
- Sometimes, the athlete may have positive response to one test and negative response to another.
- Some athletes may be free of symptoms and have a negative provocation test response during periods of rest, whereas a test result can be positive during intense periods of competition.

**TABLE III.** Diagnosis methods and positivity criteria set by the International Olympic Committee to document EIB in athletes

Method	Protocol	Positivity criteria
Bronchodilation test	FEV1 before and 15 min after inhalation of a standard β2-agonist	FEV1 increase from baseline ≥200 mL and ≥12% of predicted
Bronchial provocation challenge		
Methacholine test	PD20 or provoking concentration (PC20) of inhaled methacholine inducing an FEV1 decrease ≥20% from baseline	PC20 ≤4 mg/mL or PD20 ≤400 μg (cumulative dose), or ≤200 μg (noncumulative dose) in those not taking ICS PC <sub>20</sub> ≤16 mg/mL or PD <sub>20</sub> ≤1600 μg (cumulative dose) or ≤800 μg (noncumulative dose) in those taking ICS for at least 1 mo
EVH	FEV1 before and within 30 min of 6-min dry (or dry and cool) air inhalation at 85% of predicted maximum voluntary ventilation	≥10% decrease in FEV1 from baseline
Hypertonic saline inhalation	FEV1 before and after inhaling 22.5 mL of 4.5% NaCl	≥15% decrease in FEV1 from baseline
Exercise challenge (field or laboratory)	FEV1 before and within 30 min after exercise challenge achieving a heart rate >85% for at least 4 min	≥10% decrease in FEV1 from baseline

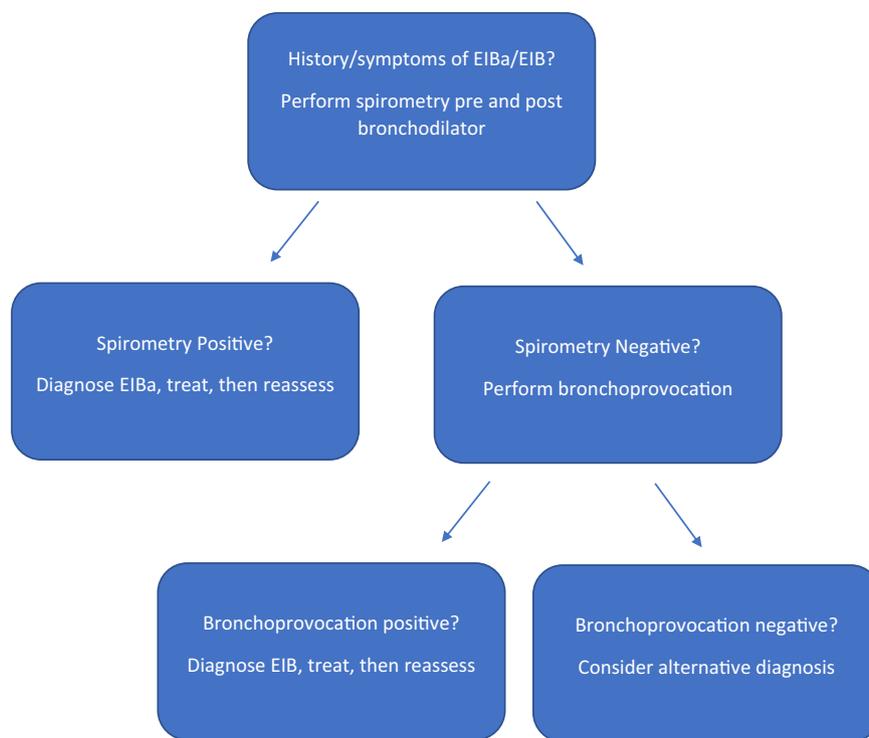
this cutoff has been questioned in the pediatric population.<sup>26,27</sup> Data from Tse et al<sup>28</sup> suggest that a threshold of less than 8% performs better than 12% in younger populations. Given the variability in spirometric testing in children, it might not be appropriate to choose a specific bronchodilator reversibility cutoff as a criterion for the diagnosis of asthma in younger children.<sup>28</sup>

Response to therapy can be assessed subjectively in terms of symptom control and exercise tolerance. Patients should be encouraged to monitor progress closely to see whether pretreatment improves exercise tolerance. If this is not possible, peak expiratory flow measurement before and after exercise may be helpful. If spirometry is equivocal or normal and EIB is suspected, the patient should undergo bronchoprovocation testing.<sup>5,6,29</sup> Bronchoprovocation testing can be through direct or indirect provocation. Sport-specific exercise field testing, attempting to replicate the environment in which the athlete experiences his or her symptoms, is not the preferred first-line investigation due to its poor sensitivity and difficulty in performing reliably.<sup>30</sup> Exercise challenge testing can be performed with treadmill and cycle ergometer, which can be standardized.<sup>6</sup> During an exercise challenge, a target heart rate of 85% (95% for children) of maximum should be reached within 2 to 3 minutes, and exercise should last for a maximum of 8 minutes.<sup>5</sup> Standardized protocols should be used (such as from the American Thoracic Society).<sup>5</sup> Spirometry should be

performed at baseline and at time intervals after exercise (such as 5, 10, 15, 30, 45 minutes).<sup>5</sup> However, if there is a high degree of suspicion for EIB during exercise, spirometry can be measured at 1 and 3 minutes after exercise.<sup>6</sup> A 10% or greater decrease in FEV<sub>1</sub> compared with preexercise baseline at any 2 consecutive time points is diagnostic of EIB.<sup>5</sup>

The International Olympic Committee recommends indirect provocation with eucapnic voluntary hyperpnea (EVH) as the criterion standard provocation test.<sup>31</sup> EVH requires the athlete to ventilate 22 to 30 times per minute for 6 minutes while breathing dry, cold air containing 5% carbon dioxide. The length of time, ventilation level, and temperature can be adjusted to mimic a specific sport. A 10% decrease in FEV<sub>1</sub> is suggestive of EIB during EVH testing. Unfortunately, EVH is not often readily available to most clinicians. Alternative provocation tests include direct testing with histamine or methacholine or indirect testing with exercise or hyperosmolar aerosols (mannitol or hyperosmolar saline).<sup>32</sup>

In a mannitol challenge, mannitol is given in increasing inhaled doses (graded challenge) to produce a specified decrease in FEV1.<sup>6</sup> Then, a dose-response curve can be produced to determine the provoking dose (PD) to cause the specified drop (PD15 or PD10) of 15% or 10% in FEV1.<sup>6</sup> A PD of less than 35 mg of mannitol is classified with severe airway



**FIGURE 1.** Approach to athlete with suspected EIBa or EIB.

hyperresponsiveness, a value between 35 and 155 mg with moderate airway hyperresponsiveness, and a value between 155 and 635 mg with mild airway hyperresponsiveness.<sup>6</sup> Before any testing for EIB, most allergy and asthma medications need to be held for about 8 to 24 hours, depending on specific class of medication.<sup>5</sup> Other tests that have been evaluated include fractional exhaled nitric oxide measurement, but it is not currently standard of care in diagnosing EIB in children or adults.<sup>17</sup> Reproducibility is problematic, and there can be variation between airway response to exercise compared with EVH and mannitol and even with the same test in the same subject.<sup>33-36</sup> The response on initial challenge has a 62% sensitivity of predicting EIB on subsequent challenge.<sup>34,35</sup> Comparative studies of treadmill versus EVH by Filho et al<sup>37,38</sup> with Brazilian children found that these diagnostic techniques were not interchangeable. Ideally, the original technique used for diagnosis should be reproduced always during the time of intense exercise or training or reproduced with a different technique.<sup>37-39</sup>

There are various agencies that provide recommendations for diagnostic testing. The World Anti-Doping Agency (WADA), for example, has a list of approved tests and diagnostic criteria detailed in Table II.<sup>40</sup> The International Olympic Committee has a similar set of diagnostic tests outlined in Table III.<sup>25,31,41</sup> Ultimately, indirect testing is more sensitive than direct testing in detecting EIB and is the preferred method of bronchoprovocation.<sup>3</sup> Negative bronchoprovocation testing should prompt consideration of other conditions. A synopsis of this process is included in Figure 1.

It is important to remember that personnel working closely with athletes on a regular basis (ie, athletic trainers) play a vital role in management and are often the first to recognize and treat deteriorating symptoms of EIBa or EIB. Health care

**TABLE IV.** Details that must be provided in the medical file to support an application for a TUE in athletes with EIBa or EIB

- Complete medical history as described and clinical examination with specific focus on the respiratory system
- Spirometry report with flow-volume curve
- If airway obstruction is present, the spirometry will be repeated after inhalation of a SABA to demonstrate the reversibility of bronchoconstriction

providers and the asthma care team can work in partnership to instruct athletic trainers with guideline-based, systematic evaluation and management tools for achieving and maintaining symptom control, improve athletic performance, and reduce the frequency of exacerbations. Athletic trainers should incorporate prescribed written asthma action plans for each athlete with EIBa and EIB.

Once the diagnosis has been confirmed, documentation of the correct diagnosis is very important, especially when dealing with professional athletes. There are requirements for the official medical record that are mandated by WADA to support an application for a therapeutic use exemption (TUE) in a case of an athlete with asthma or any of its clinical variants (Table IV).<sup>40</sup>

## DIFFERENTIAL DIAGNOSIS AND COMORBID CONDITIONS

The athlete who presents with EIBa or EIB commonly experiences symptoms of cough, chest tightness, shortness of breath, and wheezing during or after exercise.<sup>5,42</sup> However, patient-reported symptoms alone are unreliable in diagnosing

**TABLE V.** Differential diagnosis of EIBa or EIB

1. Exercise-induced laryngeal dysfunction
<ul style="list-style-type: none"> <li>• PVFM (vocal cord dysfunction)</li> <li>• Exercise-induced laryngeal prolapse</li> <li>• Exercise-induced laryngomalacia</li> <li>• Variants, including arytenoid collapse while the vocal cords move normally</li> </ul>
2. Obstruction/restrictive lung disease
3. Obesity, skeletal defects, diaphragmatic paralysis, interstitial fibrosis
4. Exercise-induced anaphylaxis
5. Breathlessness with exercise due to possible cardiovascular, pulmonary, or gastrointestinal mechanisms
6. Exercise-induced dyspnea (poor physical fitness) or overtraining syndrome
7. Exertional gastroesophageal reflux disease
8. Mitochondrial enzyme deficiency
9. Psychological (anxiety, conversion disorder)

**TABLE VI.** Treatment goals and effectiveness of EIB therapy

Main goals of EIB treatment <sup>5,25,53</sup> :
- Prevent or minimize symptoms induced by exercise
- Be able to participate fully in any activities
- Achieve and maintain control with as few side effects as possible
- Prevent and control risk factors for acute events (eg, exacerbations)
- Maximize lung function to allow optimal performance
- In high-level athletes, ensure compliance with sports-authorities' regulations
Effectiveness of EIB therapy can vary over time because of <sup>5,25,53</sup> :
- Changes in airway responsiveness over time
- Environmental conditions
- Intensity of exercise
- Differences in baseline airway responsiveness
- Susceptibility to tachyphylaxis
- Patient compliance
- Genetic factors

EIBa or EIB because various masquerading diseases mimic both conditions.<sup>32,42</sup> The differential diagnosis of EIBa or EIB is extensive and requires a comprehensive clinical history and appropriate testing. Exercise-induced laryngeal dysfunction can often mimic EIB symptoms and encompasses a constellation of disorders including vocal cord dysfunction or paradoxical vocal fold movement (PVFM), exercise-induced laryngeal prolapse, exercise-induced laryngomalacia, and other variations.<sup>5</sup> Exercise-induced laryngeal dysfunction can occur alone or coexist with EIB; however, there are a number of unique features that can distinguish between them.<sup>43</sup> Breathing difficulties (classically inspiratory stridor) occur and peak during exercise in exercise-induced laryngeal dysfunction as opposed to after exercise with EIB. ELID is also more common in young adult female athletes, and patients often fail to respond to typical asthma treatment. PVFM presents with intermittent narrowing of vocal folds during the respiratory cycle and is often triggered by breathing in lung irritants such as strong scents/odors or exercising. Unlike asthma, PVFM causes more difficulty breathing in than breathing out. Flattening of inspiratory flow-volume loops on

pulmonary function/spirometry can occur with PVFM, and direct laryngoscopy evaluation during exercise is used to confirm the diagnosis.<sup>5</sup> A therapeutic management program promoting controlled breathing exercises, diaphragmatic breathing, and avoidance of triggers may allow the athlete to gain control during episodes of dyspnea. Exercise-induced laryngeal prolapse is associated with partial occlusion of larynx, and can occur with laryngochalasia, a condition in which aryepiglottic folds move into the endolarynx.<sup>5</sup> Laryngomalacia usually occurs in pediatric patients, with symptoms developing under extreme exertion, but resolving quickly as the degree of exercise is decreased.<sup>5</sup> Exertional gastroesophageal reflux disease (GERD) and laryngopharyngeal reflux can worsen with exercise and is often associated with the length and intensity of the physical activity undertaken, especially high-impact, high-intensity workouts such as running, cycling, or rowing.<sup>5</sup> Cardiopulmonary exercise testing can be used to differentiate dyspnea on exertion in obese patients from EIB, because it can reveal increased oxygen consumption rather than bronchoconstriction.<sup>5</sup> In addition, patients with dyspnea on exercise with systemic allergic symptoms such as pruritis, urticaria, and hypotension may have exercise-induced anaphylaxis, and food ingestion may be associated.<sup>5</sup> Cardiac pathologies in adults may be associated with palpitations, dizziness, or syncope.<sup>43</sup> Workup includes electrocardiography, transthoracic echocardiography, and troponin measurement.<sup>31</sup> The clinician should be aware of other uncommon causes of dyspnea in an adult athlete including pulmonary embolus and pneumomediastinum.<sup>43</sup> Personal and family history of blood clots and oral contraceptive use can be assessed in the history.<sup>43</sup> Psychological factors and diagnoses can also be considered, especially if objective testing does not reveal a diagnosis.<sup>5</sup> A summary of the differential diagnosis of EIB is provided in Table V.<sup>5,31</sup>

Certain comorbid disorders are shown to be associated with difficult-to-control asthma and are predominantly higher in severe asthma.<sup>44</sup> The most frequently reported asthma comorbid conditions include rhinitis, sinusitis, GERD, obstructive sleep apnea, hormonal disorders, anxiety, depression, and stress. These conditions may, first: share a common pathophysiological mechanism with asthma; second: influence asthma control, its phenotype, and response to treatment; and third: be more prevalent in patients with asthma but without obvious influence on this disease.<sup>45</sup> Guidelines emphasize the need to identify and address comorbid factors before increasing medication doses or using novel and expensive therapies.

Asthma symptoms may increase complications of GERD through changes in intrathoracic pressure or medications acting on the gastroesophageal sphincter.<sup>46</sup> Implementing GERD management lifestyle provisions, including avoiding certain foods, avoiding eating 2 to 3 hours before sleep, and elevating the head of the bed 6 inches, can significantly reduce complications of GERD. Acid-suppressive medications should be considered for treatment of symptomatic GERD. For patients suspected of having GERD-induced asthma and no warning symptoms, an initial empiric therapy with a proton pump inhibitor for 1 to 2 months should be considered.<sup>47</sup> Adverse outcomes associated with proton pump inhibitors most often occur among patients who receive long-term therapy. Minimizing the duration of treatment by periodically assessing the patient's need for acid-suppressive therapy could eliminate or substantially reduce the risk of adverse outcomes.<sup>48</sup>

**TABLE VII.** Summary of pharmacologic and nonpharmacologic treatment options for EIB

Pharmacologic	Nonpharmacologic
Intermittent prophylaxis	Preexercise warm-up
- Short- and long-acting $\beta$ 2-agonists	Attempting to control the environment
- LTRA	- Mechanical barriers such as face masks
- Chromones	- Train indoors during cold weather, high pollen count days, and poor air quality days
Maintenance prophylaxis	- Avoid running next to busy roads
- Inhaled corticosteroid	- Reduce chloramine formation by improving ventilation and showering before entering pool
- LTRA	
Inconsistent results/investigative therapies	Dietary changes
- Anticholinergic	- Low-salt diet
- Methylxanthines	- Fish oils
- Antihistamines	- Ascorbic acid (vitamin C)
- Ca channel blockers	
- $\alpha$ -Adrenergic receptor antagonists	
- Inhaled furosemide	
- Inhaled heparin	
- Caffeine	
- Hyaluronic acid	
<ul style="list-style-type: none"> <li>• Daily use of either SABA or LABA, even in combination with ICS, usually will lead to tolerance (reduced duration of protection and prolongation of recovery).</li> <li>• Monotherapy with LABAs on a daily basis is not recommended.</li> <li>• Do not prescribe daily LABA/ICS therapy to treat EIB unless being used to treat moderate-to-severe persistent asthma.</li> </ul>	

LABA, Long-acting  $\beta$ 2-agonist; LTRA, Leukotriene receptor antagonist.

Among patients with atopic asthma with sensitization to inhalant allergens, EIBa may be more likely to occur when the exercise includes exposure to the relevant allergen. Athletes with allergic rhinitis should be tested for EIB even if they have minor clinical EIB symptoms.<sup>49</sup> Runners are more likely to report exercise-related asthma symptoms during their pollen or mold season. Appropriately managing the treatment of allergic rhinitis can impact asthma control.<sup>49</sup> Failure to implement the appropriate treatment regimen and management of allergic rhinitis results in deteriorating asthma and EIB.

## MANAGEMENT

There is a high prevalence of asthma and EIB in athletes that are underdiagnosed and undertreated with suboptimal use of asthma medications.<sup>50</sup> Managing athletes with EIBa or EIB is similar to the management of nonathlete patients with asthma. Initial management should focus on both the pharmacologic aspect and the nonpharmacologic aspect of patient care. The nonpharmacologic aspect of EIBa and EIB management stresses patient education, reducing both allergic and irritant environmental exposures as well as treating comorbid conditions, such as rhinitis and GERD.<sup>5</sup> The pharmacologic aspect of managing these conditions focuses on using appropriate medication for prophylaxis, control of symptoms, and rescue.<sup>5</sup> EIBa can often be a manifestation of inadequately controlled asthma, especially in nonelite athletes. Underlying chronic asthma should be controlled adequately as specified by current guidelines.<sup>5</sup>

Once appropriate testing has been performed and diagnosis has been made, both pharmacologic and nonpharmacologic measures can be implemented to offer better control. Medications used to control persistent asthma can also be used to treat

bronchial hyperresponsiveness in EIB. Poor response to therapy, both subjectively and objectively, should prompt reevaluation of the diagnosis (see differential diagnosis). Ultimately, none of the available medications completely eliminates EIB; rather, pharmacotherapy shifts the dose-response relationship to a more favorable position after exercise.<sup>5,51,52</sup> It is important for athletes and physicians to develop a comprehensive Asthma Action Plan outlining how to manage EIB symptoms on a daily basis as well as how to recognize worsening symptoms.

Patients should be provided education on proper inhaler-use technique, environmental control measures, and the importance of medication adherence. Regular follow-up is important to determine effectiveness of medications and confirm compliance. Treatment plans should be reviewed not only with the patient but with coaches and trainers as well. Ultimately, EIB should not limit either participation or success in vigorous activities and all athletes should be able to participate in any activity they choose without experiencing asthma symptoms. Although there should not be any limitations in sport selection for patients with EIBa, selecting a sport on the basis of its low asthmogenic potential may decrease symptoms.<sup>25</sup> Treatment goals and effectiveness are outlined in Table VI.

## NONPHARMACOLOGIC THERAPIES AND MINIMIZING TRIGGERS

Evidence suggests that supplementing traditional EIB therapy with nonpharmacologic strategies can lead to improved control.<sup>8,54,55</sup> Preexercise warm-up routines are frequently used to elicit a refractory period to reduce or prevent EIB in up to 50% of athletes.<sup>8,56</sup> This refractory period is induced by the release of protective prostaglandins and by airway smooth-muscle tachyphylaxis to mediators of bronchoconstriction.<sup>54</sup> During this time

(~2 hours), airways are less likely to constrict after exercise. The most consistent and effective attenuation of EIB was observed with high-intensity interval and variable intensity preexercise warm-ups, but data are conflicting.<sup>55,57</sup> Common recommendations encourage a warm-up of 10 to 15 minutes that includes calisthenics with stretching exercises in an attempt to reach 50% to 60% of maximum heart rate.<sup>57</sup>

Manipulating the environment is another strategy that attempts to reduce symptoms of EIB. Cold and dry environments are thought to promote bronchoconstriction by dehydration of airway surface liquid, epithelial cell damage, and airway remodeling.<sup>7,58</sup> Mechanical barriers, such as face masks that feature a heat and moisture exchanger, are not always well tolerated but they promote humidification and prevent water loss during cold weather endurance exercise and reduce inhalation of particulate air pollution.<sup>55,59,60</sup> Training indoors during cold weather is ideal, but if athletes must train outdoors then they should make every effort to nose breathe when exercising in cold, dry conditions. Breathing through a loosely fitted scarf or mask has a similar effect of warming and humidifying the air before it reaches the lungs, which has been shown to reduce the incidence of bronchoconstriction when exercising.<sup>61,62</sup>

Urban athletes should avoid running next to busy roads or should schedule outdoor training around low-traffic hours. Smog and air quality are at their worst later in the day; therefore, early morning workouts are advisable. These recommendations may be difficult to comply with, particularly for athletes residing in large metropolitan areas. If an athlete has outdoor pollen sensitivity, running outside early in the morning and early in the evening is more likely to trigger symptoms because pollen counts are usually higher at these times of day. Showering immediately after outdoor workouts will help to ensure pollen is removed from hair and clothes. Exposure to chlorine, especially in indoor pool environments, has been shown to adversely affect airway health. Pool smell is due not to chlorine but to chloramines that result from the combination of 2 ingredients: (1) chlorine disinfectants and (2) perspiration, oils, and urine that enter pools on the bodies of swimmers.<sup>63</sup> Measures to reduce chloramine formation (pool smell) in chlorinated pools include improved ventilation and showering before entering the pool. Swimming in water treated with nonchlorine disinfection methods such as ozone, copper, or silver may be advised.<sup>17,18,55</sup>

Although many studies have examined the effects of dietary modification on EIB, the evidence supporting these changes is weak.<sup>64-69</sup> The American Thoracic Society and AAAAI practice parameter EIB update both discuss the implementation of a low-salt diet and dietary supplementation with fish oils (omega-3 polyunsaturated fatty acids) and ascorbic acid (vitamin C).<sup>3,5</sup> These dietary adjustments and supplements were found to have some effect in reducing the severity of EIB.<sup>3,5</sup> The studies on which the recommendations were based had important limitations, so their findings should be considered preliminary until confirmed in larger trials. Even less well studied are the effects of caffeine (1,3,7-trimethylxanthine), which is a nonselective competitive antagonist of the adenosine receptor that can have a bronchodilator effect on adults with EIB.<sup>55</sup> Common amounts of caffeine having a bronchodilator effect include 5 to 10 mg/kg of body weight per day (~2-4 cups of coffee).<sup>55</sup>

Physicians should stress the importance of cardiovascular fitness for beginner athletes with symptoms of EIB, because continued improvements in cardiovascular fitness will reduce the

minute ventilation required for a given level of exercise and decrease the stimulus for bronchoconstriction.<sup>70</sup> Breathing exercises, including yoga and inspiratory muscle training, can also be used as a supplement to pharmacologic measures in the treatment of EIB.<sup>55</sup>

## PHARMACOLOGIC THERAPIES

Both recreational and elite athletes with EIB and EIBa can be treated in a similar fashion with treatments focusing on alleviating airway inflammation and hyperresponsiveness. Although multiple pharmacologic therapies are available, no single or combination therapy completely resolves EIB.<sup>5</sup> SABAs are usually considered first-line therapy for EIB and should be given 15 to 20 minutes before exercise.<sup>71</sup> SABAs have a rapid onset within 5 to 7 minutes and duration of 2 to 4 hours.<sup>71</sup> This treatment is supported by consensus guidelines and has consistent results based on meta-analyses against other classes of medications.<sup>32,71-73</sup> Unfortunately, chronic or recurrent use may lead to tachyphylaxis, which results in a loss of efficacy and duration of effect in as little as 10 days.<sup>74,75</sup> Tolerance develops with repeated and/or prolonged use of  $\beta_2$ -agonists due to downregulation of  $\beta_2$  receptors on smooth muscle in airway and on mast cells.<sup>71</sup> SABAs are not protective against EIB in around 15% to 20% of patients.<sup>76-78</sup> Conversely, long-acting  $\beta_2$ -agonists have a longer duration of action but are not recommended to be prescribed as monotherapy.<sup>71</sup> As with SABAs, tolerance can also develop with long-acting  $\beta_2$ -agonists.<sup>5</sup> Leukotriene receptor antagonists (montelukast) can be administered daily for prophylaxis, as an add-on therapy to inhaled steroids, or given 1 to 2 hours before exercise, which has shown efficacy in preventing EIB for up to 12 to 24 hours.<sup>79-83</sup> Other leukotriene receptor antagonists including zafirlukast and zileuton, a 5-lipoxygenase inhibitor, have also been shown to be effective in EIB. Leukotriene inhibitors cannot reverse existing airway obstruction but have not been shown to induce tolerance.<sup>71</sup>

Inhaled corticosteroids (ICSs) are the treatment of choice in patients with EIB/EIBa and symptomatic asthma.<sup>5</sup> However, ICSs do not eliminate the need for additional acute treatment with  $\beta_2$ -agonists.<sup>5</sup> There is both a dose- and time-dependent effect of ICSs. Even 1 dose can have a bronchoprotective effect on EIB; however, the efficacy tends to plateau after a few weeks of therapy.<sup>5,71</sup> For children, prolonged ICS use can lead to a decrease in linear growth velocity and adult height, and this must be weighed against tachyphylaxis with combination therapy.<sup>84</sup> In athletes, especially at the professional level, controller pharmacotherapy with a daily ICS is recommended over a combination ICS/long-acting bronchodilator (ICS/long-acting  $\beta_2$ -agonist) inhaler because of the potential for  $\beta_2$ -agonist tolerance to develop with daily  $\beta_2$ -agonist use.<sup>3,5,85,86</sup> This tolerance decreases the duration of bronchoprotection during exercise and competition and prolongs recovery time. SABAs should be reserved for breakthrough or emergency symptoms and preexercise prophylaxis.

Another class of agents used to treat EIB is mast cell stabilizers, such as cromolyn and nedocromil. Unfortunately, these medications are not currently available in the United States.<sup>87</sup> These agents attenuate EIB when given before exercise, but have a relatively brief duration of action.<sup>5,87</sup> Short-acting muscarinic receptor antagonists (anticholinergics) such as

**TABLE VIII.** Permitted medications in the management of EIBa or EIB

Medication category	Examples
Corticosteroids (inhaled)	Fluticasone, blemecethasone
Muscarinic receptor antagonists	Ipratropium, tiotropium
Xanthines	Theophylline
Cysteine-leukotriene receptor antagonists	Montelukast, zafirlukast
Anti-IgE and anti-IL-5 inhibitors	Omalizumab, mepolizumab
Antihistamines	Loratadine, cetirizine
Mast cell stabilizers (cromones)	Nedocromil sodium, cromolyn sodium

ipratropium bromide act on receptors on smooth muscle, which leads to muscle relaxation and bronchodilation, but there is inconsistent data on its effect on EIB.<sup>72</sup> Methylxanthines and antihistamines should be used cautiously or selectively because they have inconsistent results.<sup>5</sup> Other medication classes that have been studied in EIB include calcium channel blockers,  $\alpha$ -adrenergic receptor antagonists, inhaled furosemide, inhaled heparin, caffeine, and hyaluronic acid, but these also have inconsistent results.<sup>87</sup> Immunotherapy has limited efficacy in EIB treatment, and has not been formally studied in athletes. A summary of available treatment options is provided in Table VII.

Individualized EIBa or EIB management plans should take into consideration the severity of disease, type of environment the athlete competes in (swimmers exposed to chloroform; ice skaters exposed to cold, dry air), and any medication regulations set forth by the governing body overseeing the sport the athlete trains and competes in. In the case of professional athletes, prohibited medications can be prescribed and used in certain cases if approved by the governing body after going through an application process, such as a WADA TUE.

### HIGH SCHOOL AND COLLEGE-LEVEL ATHLETES

Student-athletes in high school and college undertake immense responsibility working toward achieving an academic degree and pursuing athletic success. Athletes with EIB face many challenges including pressure of performance, keeping up with academics, maintaining their physical health, attending all workouts and practices, as well as navigating relationships with coaches, fans, and in some cases the media. These challenges are more apparent in the high-pressure environment of division I collegiate athletics where bowl-game revenues, television deals, and future multimillion-dollar contracts can be at stake. The increased demands placed on young athletes lead to both physical and mental fatigue.

Consequently, psychosocial, socioeconomic, behavioral, and lifestyle risk factors are associated with an increase in asthma exacerbations and morbidity.<sup>55,88</sup> Studies show that the prevalence of anxiety and depressive disorders is often elevated among patients with asthma than in the general population.

Incorporating psychosocial and coping strategies with each clinical encounter is therefore of the utmost importance. Athletes with asthma who have effective coping skills will experience less psychological morbidity and will have the tools to achieve better long-term control of their disease.

### SPORT-SPECIFIC MEDICATION REGULATIONS FOR HIGH SCHOOL AND COLLEGE-LEVEL ATHLETES

Participation in high school sports continues to increase in the United States along with the number of athletes experiencing sports-related injury.<sup>89</sup> High schools are required to have policies for heat modification, concussion, and orthopedic injuries, but reference to EIB is limited. High school and college athletes are permitted to possess and self-administer approved medications at any time while on school property or at a school-sponsored event generally with approved documentation from their health care provider.<sup>90</sup> School personnel, coaches, and athletic trainers must understand implementation of the appropriate treatment regimen and identify symptoms and complications of EIB for athletes. An Asthma Management Plan or Written Asthma Action Plan is imperative to have at the school for each athlete with asthma and EIB. The plan should identify worsening asthma symptoms and appropriate interventions, including when to seek urgent medical attention. Asthma education programs with emphasis on asthma and EIB should be provided for all coaches, athletic trainers, athletes, and other appropriate personnel.

According to the National Collegiate Athletic Association (NCAA), all NCAA member institutions are subject to NCAA drug testing. The drug-testing program involves urine collection and laboratory analyses for substances on a list of banned drug classes approved by the NCAA Board of Governors.<sup>90</sup> The NCAA upholds the rule that all student-athletes are ultimately responsible for anything they ingest. The NCAA list of banned drug classes (NCAA Bylaw 31.2.3) is composed of substances that are generally purported to be performance enhancing and/or potentially harmful to the health and safety of the student-athlete.<sup>90</sup> The NCAA distinguishes that some medications banned are used for legitimate medical purposes.<sup>90</sup> Accordingly, the NCAA allows exception to be made for those student-athletes with a documented medical history demonstrating the need for treatment with a banned medication.<sup>90</sup> Exceptions may be granted for substances included in the following classes of banned drugs:  $\beta$ 2-agonist and stimulants, diuretics, beta-blockers. Collegiate institutions must maintain documentation in the student-athlete's medical record on campus. Documentation should contain information as to the diagnosis including appropriate verification of the diagnosis, medical history, and dosage information including route of administration.

Student-athletes who test positive for a banned substance, or who breach NCAA protocol, are subject to loss of eligibility and may be future tested for all NCAA banned substances by the NCAA at any time. Student-athletes who are ineligible as a result of an NCAA positive drug test or a breach of protocol may be future tested for all banned substances by the NCAA at any time during their period of ineligibility.<sup>90</sup>

### PROFESSIONAL ATHLETES

Clinicians and professional athletes with EIBa or EIB must be aware that governing bodies overseeing the athlete's sport may have regulations on certain medications used to treat EIBa or EIB. Noncompliance with these regulations could jeopardize the athletes' ability to train and compete, and in some cases their career. Major sports organizations operating within the United

**TABLE IX.** WADA prohibited medications in the management of EIBa or EIB

Medication category	Examples	Exceptions
β2-Agonists (inhaled, oral, injectable)	Albuterol, terbutaline	Formoterol, salbutamol,* salmeterol, TUE
Corticosteroids (systemic)	Prednisone, methylprednisolone	TUE

\*Oral salbutamol is prohibited, but inhaled salbutamol is permitted.

States include Major League Baseball, Major League Soccer, National Association of Stock Car Racing, National Basketball Association, National Football League, National Hockey League, the Olympics, United States Tennis Association, United States Golf Association, and Women’s National Basketball Association. Many of these organizations use the WADA Code of medication regulations, but some have their own medication regulation policies.

**SPORT-SPECIFIC MEDICATION REGULATIONS FOR PROFESSIONAL ATHLETES**

The WADA was established in 1999 as an international independent agency to provide scientific research and education, develop antidoping capacities, and monitor the WADA Code—the document harmonizing antidoping policies in all sports and countries.<sup>91</sup> Medications may be prohibited if they are seen as enhancing performance, hazardous to health, or against the spirit of the sport.<sup>92</sup> The World Anti-Doping Code (Article 4.5) states that “WADA, in consultation with Signatories and governments, shall establish a monitoring program regarding substances which are not on the Prohibited List, but which WADA wishes to monitor in order to detect patterns of misuse in sport.”<sup>93</sup>

The WADA Prohibited list is the comprehensive document serving as the international standard for identifying substances and methods prohibited in sports.<sup>93</sup> WADA allows competing athletes to use ICSs and β2-agonists but requires athletes to provide documentation that the medication is prescribed for therapeutic use. Combination of β2- agonists, including all optical isomers, is prohibited, with the exception of inhaled salbutamol (maximum 1600 μg over 24 hours in divided doses not to exceed 800 μg over 12 hours starting from any dose), inhaled formoterol (maximum delivered dose of 54 μg over 24 hours), and inhaled salmeterol (maximum 200 μg over 24 hours).<sup>93</sup> Athletes should initially review United States Anti-Doping Agency for current status of their medication.

Asthma medications permitted by the WADA and the above major US sports organizations for use without restriction are listed in Table VIII. Most inhaled β2-agonists and all oral and injectable β2-agonists, with the exception of oral formoterol, are prohibited by the WADA (Table IX). The only inhaled β2-agonists that are permitted by the WADA are inhaled rapid-acting salbutamol and long-acting formoterol and salmeterol. Of note, the WADA Code states that “the presence in urine of salbutamol in excess of 1000 ng/mL is presumed not to be an intended therapeutic use of the substance and will be considered as an adverse analytical finding” subject to possible repercussions;<sup>93</sup> although 24-hour use of inhaled salbutamol resulting in a maximum dose of 1600 μg (not to exceed 800 μg every 12 hours) should, in most professional athletes, not result in the urinary threshold being exceeded.<sup>92</sup> Formoterol is the only oral β2-agonist permitted, but is permitted only up to a maximum dose of 54 μg over a 24-hour period. The WADA has established a urinary excretion threshold of 40 ng/mL.

**TABLE X.** Athletic organizations using the WADA Code vs inter-national organization policy

Sport	Uses the WADA Code	Uses organization policy
MLB		•
MLS	•	
NASCAR		•
NBA		
NFL		•
NHL		•
The Olympics	•	
USGA		•
USTA	•	
WNBA		•

MLB, Major League Baseball; MLS, Major League Soccer; NASCAR, National Association of Stock Car Racing; NBA, National Basketball Association; NFL, National Football League; NHL, National Hockey League; USGA, United States Golf Association; USTA, United States Tennis Association; WNBA, Women’s National Basketball Association. • in the absence of reversible airway obstruction, a bronchial provocation test is required to establish the presence of airway hyper responsiveness • exact name, specialty and contact details of examining physician • if the athlete reappplies for a TUE that has expired, the application should include the documents that confirm the initial diagnosis as well as the reports and pulmonary function tests from regular asthma follow-up visit.

Salmeterol appears in urine in low concentrations and has never been demonstrated to enhance exercise performance.<sup>94</sup> Although salmeterol urine levels are not monitored, the inhaled dose is advised to not exceed a maximum dose of 200 μg over a 24-hour period. Inhaled glucocorticoids are always permitted, but systemic glucocorticoids are prohibited (Table IV).

**Major League Baseball**

Major League Baseball’s Joint Drug Prevention and Treatment Program does not follow the WADA Code, but instead has its own governing policies. All medications from Table VIII are permitted. In addition, all β2-agonists are permitted except for clenbuterol and zilpaterol, due to their anabolic effects.<sup>92,95</sup> All forms of corticosteroids are also permitted.

**Major League Soccer**

The Major League Soccer Substance Abuse and Behavioral Health policy incorporates the WADA Code, which prohibits all β2-agonists with the exceptions of formoterol, salbutamol, and salmeterol, as well as systemic corticosteroids during competition (Table IX). Major League Soccer players who play for their national team are also subject to Fédération Internationale de Football Association regulations on medication use. Unlike the WADA Code, Fédération Internationale de Football Association prohibits all inhalational β2-agonist and glucocorticoid use unless a TUE is obtained.<sup>96</sup> Fédération Internationale de Football Association also prohibits the use of systemic corticosteroids.<sup>96</sup>

### National Association of Stock Car Racing

The National Association of Stock Car Racing does not follow the WADA Code. To date, the program administrator and medical review officer is Dr Doug Aukerman, the director of sports medicine for Samaritan Health Services and senior associate athletic director/sports medicine at Oregon State University.<sup>97</sup> It is up to Aukerman to determine whether any use of drugs is in a manner inconsistent with the instructions provided by the manufacturer, the pharmacist, or the prescribing physician and whether the medication causes a competitive advantage or impairs abilities. Prohibited drugs include stimulants, narcotic analgesics, ephedrine class, benzodiazepines, barbiturates, performance-enhancing drugs, beta-blockers, sleep aids, and alcohol.<sup>97</sup> Information was difficult to obtain, but the National Association of Stock Car Racing's drug policy does not specifically state any asthma medications are prohibited.

### National Basketball Association

A comprehensive list of prohibited drugs is listed under exhibit I-2 in the National Basketball Association collective bargaining agreement and include the following: drugs of abuse, marijuana, steroids and performance-enhancing drugs, and diuretics.<sup>98</sup> There is no mention of specific asthma medications on this list, but under article 33.17 (Prescriptions Under the Anti-Drug Program), before any player is prescribed a drug or substance (whether or not it is a Prohibited Substance) the Medical Director or Steroids and Performance-Enhancing Drugs Medical Director (as applicable) will notify the designated physician of the player's team of the name of the drug or substance, the medical justification for the prescription of the proposed substance, and the name of the prescribing physician.<sup>98</sup>

### National Football League

The National Football League's Policy and Program on Substances of Abuse does not follow the WADA Code, but instead has its own governing policies. All medications from Table VIII are permitted. In addition, all  $\beta_2$ -agonists are permitted except for clenbuterol and zilpaterol, due to their anabolic effects.<sup>93,99</sup> All forms of corticosteroids are also permitted.

### National Hockey League

The National Hockey League requires a TUE for all asthma medications, including inhalational  $\beta_2$ -agonists and corticosteroids.

### The Olympics

The Olympics follows the WADA Code, which prohibits all  $\beta_2$ -agonists with the exceptions of formoterol, salbutamol, and salmeterol, as well as systemic corticosteroids during competition (Table IX).

### United States Golf Association

The United States Golf Association under the Professional Golf Association and Ladies Professional Golf Association Anti-Doping Program prohibits all  $\beta_2$ -agonists with the exceptions of inhaled formoterol (maximum delivered dose of 54  $\mu\text{g}$  over 24 hours), salbutamol (1600  $\mu\text{g}$  over 24 hours, not to exceed 800  $\mu\text{g}$  every 12 hours), and salmeterol (maximum 200  $\mu\text{g}$  over 24 hours).<sup>100</sup> The Program states that "the presence in urine of salbutamol in excess of 1000 ng/mL or formoterol in excess of 40 ng/mL is presumed not to be an intended therapeutic use of the

substance and will be considered as an Adverse Analytical Finding unless the Athlete proves, through a controlled pharmacokinetic study, that the abnormal result was the consequence of the use of the therapeutic dose (by inhalation)."<sup>100</sup> Systemic glucocorticoids are prohibited at all times.<sup>100</sup>

### United States Tennis Association

The United States Tennis Association follows the WADA Code, which prohibits all  $\beta_2$ -agonists with the exceptions of formoterol, salbutamol, and salmeterol, as well as systemic corticosteroids during competition (Table IX).

### Women's National Basketball Association

Women's National Basketball Association medication policy does not follow the WADA Code, but instead has its own governing policies. All medications from Table VIII are permitted. In addition, all  $\beta_2$ -agonists are permitted except for clenbuterol and zilpaterol, due to their anabolic effects.<sup>101</sup> All forms of corticosteroids are also permitted.

A summative table (Table X) is provided comparing the use of the WADA Code versus internal organization policy for each athletic organization.

## MEDICATION MONITORING AND REGULATION NONCOMPLIANCE

Drug policy monitoring for EIBa and EIB medications is through urine sampling for the detection of  $\beta_2$ -agonists or glucocorticoids. The timing and frequency of testing varies by athletic organization and is often random and multiple times throughout the year, especially when competing. Consequences of medication regulation noncompliance vary between sports and whether the professional athlete has any history of noncompliance. As an example, Toronto Maple Leafs forward Carter Ashton was suspended 20 games without pay, amounting to \$169,185, for violating the National Hockey League's drug policy after using a friend's inhaler during an asthma attack. Ashton released a statement saying he inadvertently ingested inhaled clenbuterol after incorrectly assuming there were no problems with the device.<sup>102</sup> Typically, first-time offenders receive a suspension from training and/or competition and/or a monetary fine. Further offenses can result in indefinite suspension from the professional sport organization.

## EXEMPTIONS FOR PROHIBITIVE MEDICATION USE

An exacerbation of EIBa or EIB requiring treatment with prohibited medications should be objectively documented, for example, by spirometry and peak expiratory flow recordings. In acute emergency situations, the athlete's health is the priority, but the effect of the treatment and follow-up after an emergency should be well documented. Professional athletes with acute symptoms of EIBa or EIB requiring immediate treatment with a prohibited medication should have their diagnosis and symptoms objectively documented in a clinical report and seek a TUE or similar exemption from their governing body in a timely manner. As an example, the WADA requests that a clinical report and application for TUE include the following<sup>91</sup>:

- Complete medical history and clinical examination with specific focus on the respiratory system.

- Spirometry with flow-volume curve. If airway obstruction is present, spirometry is repeated after inhalation of a SABA to demonstrate reversibility of bronchoconstriction.
- In the absence of reversible airway obstruction, a bronchial provocation test is needed to establish the presence of airway hyperresponsiveness.
- Exact name, specialty, and contact information of the examining physician.

Where circumstances are deemed to be exceptional, that is, medical emergencies and treatment must be initiated before a TUE can be approved, references should be made to the governing body's policies concerning retroactive/emergency TUEs. Full and clear documentation of the medical incident is required, and the (retroactive) TUE application process must be initiated at the first opportunity. Often, exemptions are filed retroactively given the acute nature of respiratory exacerbations and prompt need for treatment. An athlete's health should never be jeopardized by withholding medication in an emergency.

### ATHLETE AND CLINICIAN RESPONSIBILITY

Adherence to professional sport medication regulations creates an additional level of complexity in the management of professional athletes with EIBa or EIB not experienced in nonprofessional athletes. This complexity requires a strong patient-clinician relationship built on trust, attentiveness, and communication to ensure appropriate control while maintaining compliance with regulations. Failure to establish this relationship and comply with regulations could result in inappropriate management of EIBa or EIB in addition to jeopardizing the professional career of the athlete.

Professional athletes with EIBa or EIB and clinicians managing these patients must understand the medication regulations set forth by the athlete's professional sports organization. Unfortunately, although WADA regulations are easily accessible on the agency's Web site, other US professional sport medication regulations are not as readily available, with some guarded to the point of seeming proprietary. This can delay the management and compliance of professional athletes with EIBa or EIB and can be frustrating for both the athlete and the clinician. Nonetheless, both the professional athlete and the clinician must understand which medications are permitted and which are prohibited, including proper formulations and dosing. If use of a prohibited medication is sought, proper documentation with a clinical report and a TUE or similar application is required. Professional athletes and clinicians should frequently review regulations to ensure their understanding is up to date because regulations may change from year to year. In long-term management, the recommended validity of a TUE for an athlete with asthma is 4 years, with an annual review by a physician experienced in treating athletes. In some cases, an antidoping organization may impose conditions such as a review by a specialist within a certain time frame.

### CONCLUSIONS

Patients with different levels of athletic ability and training may present seeking diagnosis and/or management of EIBa or EIB. Prevalence rates of EIBa and EIB in athletes, especially professional athletes, continue to affect a large percentage of this population; however, little is known about the reasons for this or how to reduce risks. The differential diagnosis of EIB is extensive and requires a

comprehensive clinical history and appropriate testing. A patient with symptoms of cough, shortness of breath, chest tightness, and wheezing should undergo spirometry with or without bronchoprovocation testing if EIBa or EIB is suspected. The management of EIBa and EIB in athletes is like that of nonathletic patients with asthma with several pharmacologic limitations for professional athletes depending on the sport they train and compete in. To reduce the risk of exacerbating these conditions, athletes should be encouraged to avoid certain environmental and ambient triggers and address the frequency and intensity of their training if required. Development of tolerance/tachyphylaxis to  $\beta_2$ -agonists with regular use should also be addressed to prevent refractory disease. For the professional athlete, both the patient and the respiratory clinician must be aware of the antidoping regulations placed on asthma drugs so that the athlete is properly managed and is not penalized for noncompliance.

Ultimately, asthma is a heterogeneous syndrome ranging from mild to severe, with various genetic and environmental factors contributing to clinical disease. EIB represents an asthma phenotype that can be characterized clinically and is associated with an increasingly well-defined biological endotype.<sup>4</sup> As clinicians become better at characterizing asthma phenotypes and endotypes, management for the athlete will become more individualized, leading to more targeted and specific therapy.

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