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Exercise-induced Bronchospasm In Children

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Abstract This review will encompass definition, history, epidemiology, pathogenesis, diagnosis, and management of exercise –induced bronchospasm in the pediatric individual with and without known asthma. Exercise induced asthma is the conventional term for transient airway narrowing in a known asthma in association with strenuous exercise usually lasting 5-10 minutes with a decline in pulmonary function by at least 10%. Exercise induced asthma will be referred to as exercise induced bronchospasm in an asthmatic. Exercise–induced bronchospasm (EIB) is the same phenomenon in an individual without known asthma. EIB can be seen in healthy individuals including children as well as defense recruits and competitive or elite athletes. The diagnosis with objective exercise challenge methods in conjunction with history is delineated. Management is characterized with pharmacotherapy and non pharmacotherapeutic measures for underlying asthma as well as exercise induced bronchospasm and inhalant allergy. Children can successfully participate in all sports if asthma is properly managed.

Keywords Exercise · Asthma · Bronchospasm · Pulmonary function · Pharmacotherapy

Introduction

Exercise-induced asthma (EIA) is defined as a syndrome of cough and/or wheezing, or chest symptoms of tightness or pain associated with 6–8 min of continuous or strenuous exercise in individuals with known asthma. It has been recognized since the first century that exercise precipitates asthma. However, the term "exercise-induced asthma" came into vogue in the 1960s and 1970s, particularly in reference to the pediatric response to exercise and the impact of medication on EIA [1, 2]. Asthma symptoms with exercise (EIA) is generally regarded as a measure of control or manifestation of chronic asthma rather than a distinct entity, although this suggestion is controversial [3–5]. In contrast, exercise-induced bronchospasm (EIB) is defined as a syndrome of airway obstruction related to exercise in an individual without known asthma. EIA may be regarded as EIB with asthma symptoms. In this review, EIA will be referred to as EIB in asthmatics. The term "exercise-induced bronchospasm" (EIB) is now widely used in the literature, and provides greater latitude because it is the temporary airway narrowing after strenuous exercise without specification of asthma [6–8].

An estimated 12% of the pediatric population has EIB, and 30% of these patients may develop adult asthma emphasizing the importance of recognizing EIB early in life [9]. Up to 23% of school children have EIB with 40% never having been clinically diagnosed with asthma [5–10]. EIB is usually characterized by at least a 10% decline in FEV_1 from before exercise. EIB in asthmatics is usually related to atopy and is associated with sputum eosinophilia. Allergen exposure increases the response to exercise, and 90% have baseline responsiveness to methacholine. Inhaled steroids over several months, cromolyn, nedocromil, and leukotriene antagonist provide 50–60% protection against EIB in asthmatics [7]. EIB alone without known asthma is less predictably associated with atopy, or responsive to inhaled steroids or cromolyn [5–11].

EIB is conventionally defined as at least 10% of more decline in pulmonary function, using preferably FEV_1 or the more variable peak expiratory flow rate, from the value before exercise [2–8]. Exercise is the most frequent trigger of

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bronchospasm in 50–90% of known asthmatics, 40–50% of those with allergic rhinitis and at least 10% of an unselected population who have no known asthma or atopy [12, 13].

Exercise-induced bronchospasm is often the first indication of underlying asthma and the last symptom complex to resolve [10]. It is often underrecognized and therefore undertreated [5–8, 10, 12, 14] as athletes are often poor historians with denial or poor insight. Objective criteria defined as an exercise challenge are essential to establish a diagnosis, as often the history or questionnaire is no better than a "coin toss" [11, 15]. Becker et al. [16] documented 61 deaths over 7 years associated with asthma during a sporting activity. Eighty-one percent of the fatalities occurred in those less than 21 years of age, and 57% in elite or competitive athletes with poorly controlled asthma. Ten percent of deaths occurred in those with no known asthma or atopy [16].

Although fatalities are not always preventable, early recognition and intervention of EIB are essential so that the general physician, trainer, and coach who manage athletes are knowledgeable about the presentation, diagnosis, and management of the athlete. This review will discuss EIB in the exercising pediatric individual using the predominance of studies, which are drawn from older and more elite athletes for analysis.

History and Epidemiology

EIB has been known since biblical times: Aretaeus the Cappadocian [17] in 169 (Table 1). Sir John Floyer, an asthma sufferer himself, described in his Treatise on Asthma [18] the levels of asthma based on the degree of ventilation and exercise. In 1972, an Olympic swimmer was divested of his gold metal for the 400-m freestyle for taking theophyline/ephedrine for his asthma when ephedrine was noted in his urine [19]. This event stimulated the United States and Australia to develop a list of accepted and banned medications, and led to a more accurate diagnosis and management of asthma for sporting events. Diagnostic requirements including objective evidence of asthma were demanded by the International Olympic Committee in the face of increase in the utilization of beta agonists [8, 12, 14].

Table 1 History of exercise induced bronchospasm

Event and people
First Century Ad: Aretaeus
1698: Sir John Porter
1972: Olympics
1984: Olympic Program for Management
2002: Required Objective Testing

Table 2 Prevalence of EIB

Authors	Population	Percent with asthma	Method	Prevalence
Rupp et al. [26]	Adolescents	0%	Treadmill	28%
Weiler et al. [20]	College football players	12%	Methacholine	50%
	Basketball players	0%		
Mannix et al. [120]	High school	21%	EVH	38%
Holzer et al. [121]	Summer elite Athletes	54%	EVH	50%
Rundell et al. [12]	Winter Olympic	21%	EVH	45%
			Exercise	29%
Mannix et al. [54]	Fitness center	0%	EVH	19%
Seear et al. [28]	Children	100% "EIA"	Treadmill	15.9%

EVH = Eucapneic hyperventilation

The epidemiology of EIB is hampered by the inclusion of asthmatic individuals in the data without clear differentiation of the nonasthmatic athlete [8] (Table 2). One of the first athletic teams evaluated for bronchial responsiveness was a team of American football players. There is a 30% prevalence of EIA symptoms and 50% demonstrated bronchial hyperresponsiveness (BHR) by methacholine challenge. However, a control group of medical students had a 41% prevalence of hyperresponsiveness [20]. Wilber et al. documented that 18–26% of Olympic winter athletes

Table 3 High- and low-intensity (ventilation) sports

High-intensity (Ventilation)	Low-intensity (Ventilation)
Track	Baseball
Ice Hockey	Bowling
Swimming	Volleyball
Racquet sports	Golf
Cross country running	Weight lifting
Cross country skiing	Diving
Soccer	
Field Hockey	

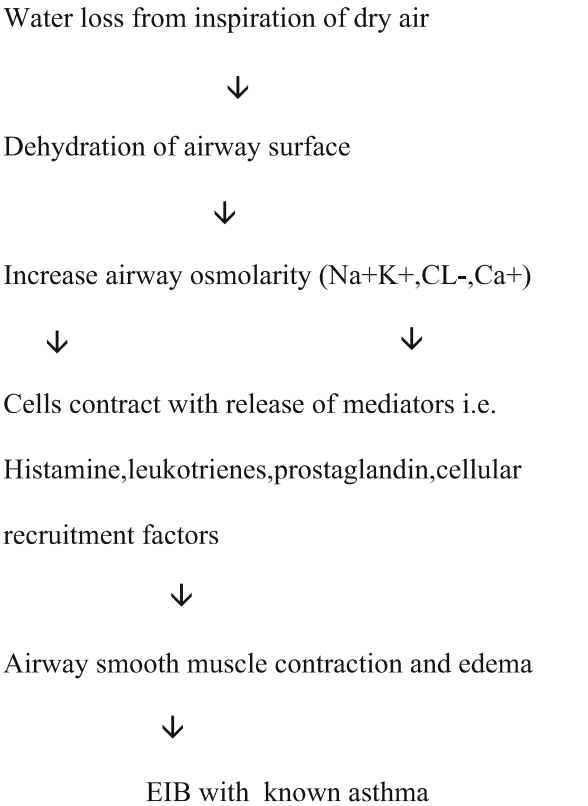

Fig. 1 Pathogenesis of EIB in asthmatics; EIB = Exercise-induced bronchoconstriction

and 50% of cross-country skiers had EIB [21]. Voy [22] documented 11% prevalence in the 1984 US Summer Olympic team. Weiler [23] documented 17% prevalence in the 1996 US Summer Olympic team. In the 1998 Winter Olympics [24], 28% of the athletes had EIB with asthma. Rundell [12] reported a 23% prevalence of EIB in Winter Olympic sports athletes, and 50% of cross-country skiers had EIB. A similar high prevalence is reported in high school athletes by Hammerman [25]. EIB is more common in more strenuous sports particularly in cold air such as ice hockey, cross-country skiing and less prevalent in less strenuous sports such as racquet sports or baseball [26–28] (Table 3).

In one of the only large studies in a pediatric population by Rupp et al. [29], 29% of 230 middle and high school athletes had EIB after excluding those with asthma. In studies from Thailand [30], France [31], and South Africa [32], EIB was less frequent in the rural areas and more frequent in urban areas. The impact of training and the competitive athletic environment with inhalation of allergens and irritants on EIB is essential to explain the increasing prevalence with recreational roadrunners [33] as well as elite athletes including swimmers [5], hockey players, runners, and skiers [33–38]. A discussion of the pathogenesis of EIB is essential to understand the multiple factors that influence EIB.

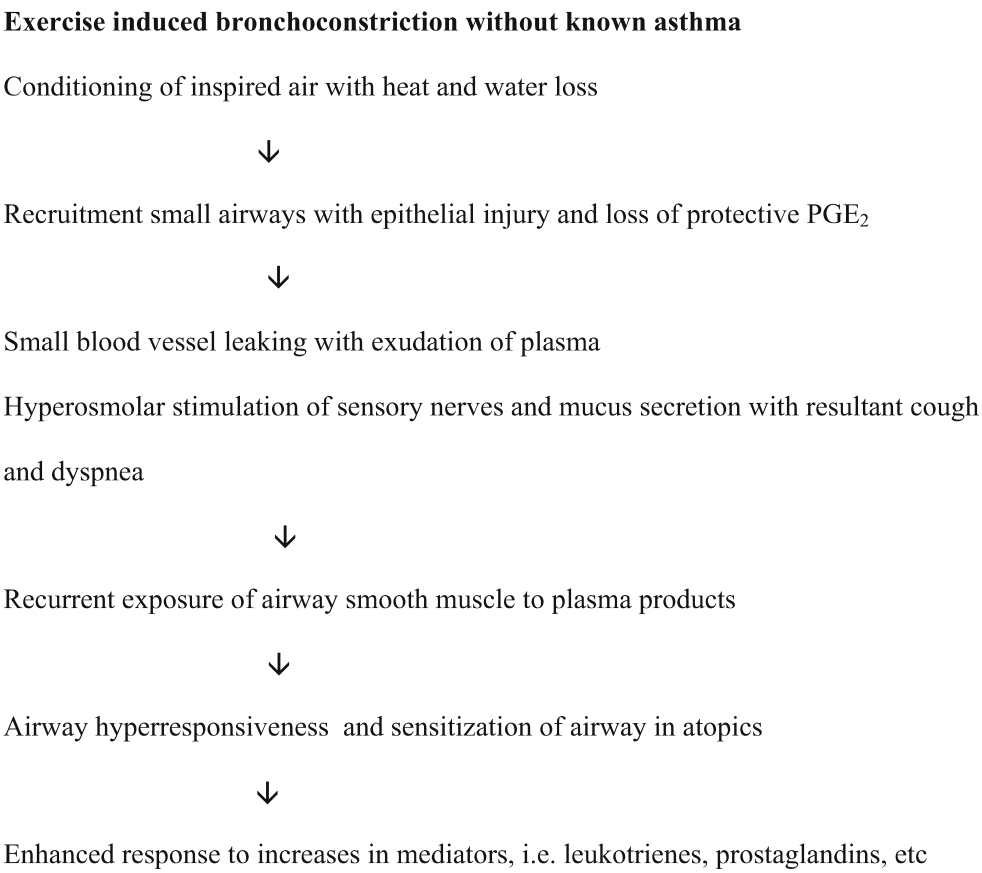

Fig. 2 Exercise-induced bronchospasm without known asthma (modified from [6]). FEV_1 = Forced expiratory volume in 1 s; PGE_2 = Prostaglandin E2

Pathogenesis

There are two competing theories of EIB: 1) one based on the vascular response to thermal change, and the other more widely accepted theory: 2) osmolar theory, which suggests that dehydration of the airway leads to a hyperosmolar release of mediators from airway mast cells and epithelial cells (Figs. 1 and 2). The inhalation of up to 200 l/min of air in highly competitive athletes reaches down to 10–12 generations of airways, but the additional factor of cold air or other irritants may invoke the smaller airway <1 mm leading to endothelial injury, leakage of plasma proteins, and over time sensitization of the airways to irritants leading to EIB [6, 7]. Daily use of beta agonists over days to weeks can desensitize mast cells with release of mediators aggravating bronchoconstriction and leading to loss of bronchoprotection [6, 7].

EIB in healthy subjects without a previous history of asthma develops by a mechanism related to dry air hyperventilated with exercise. Dry air with moderate ventilation (60 l/min) creates a hyperosmolar environment with dehydration of the airway. Thirty percent of the water in the airways is derived from below the pharynx to condition the inspired air. This leads to increased loss of heat and water from the respiratory mucosa, which promotes a hyperosmolar environment. This environment activates the mast cell and epithelial cell leading to the release of leukotrienes, prostaglandins, histamines, and chemokines recruiting eosinophils, neutrophils, and lymphocytes [6, 7]. Different investigators have reported enhanced levels of mediators and increased eosinophils [4, 5, 39], neutrophils [3, 13, 39], and/or columnar epithelial cells [15] precipitated by ongoing asthma and/or injury. These inflammatory cells are not consistently related to airway bronchial reactivity and are not impacted by inhaled steroids as is typical of asthma. They may represent nonspecific markers of inflammation secondary to exercise alone as they may resolve with discontinuation of exercise or training in highly competitive or elite athletes [5, 15, 39–41].

As the exercise becomes more intense as with elite athletes, and the air becomes drier and colder, a greater percentage of water is derived from below the pharynx, requiring more small airway recruitment with resulting bronchospasm or EIB without known asthma. Recruitment of the small airway serves as a conditioning process as the ventilation rate gets higher, duration of exercise longer, and the airways drier, necessitating the recruitment of smaller and smaller airways. This determines the severity of airway narrowing for an athlete whether asthmatic or not [6, 7]. Submucosal edema occurs in response to the dehydration process. This edema serves to enhance the airway narrowing secondary to bronchial smooth muscle contraction leading to EIB in elite athletes (Fig. 1). The ATP and adenosine are significant regulators of airway surface liquid, with adenosine release associated with bronchoconstriction.

The leukotriene pathway plays a major role in asthma with 1,000-fold greater potency than histamine. Leukotriene LTE4 is found in the urine in exercising individuals [6–8]; it counteracts the airway relaxant effect of prostaglandin PGE2 [6, 7]. Enhanced transcription of the genes for 5-lipoxygenase and its activating protein (5−lipoxygenase-activating protein) 2 and 6 h after exercise has been documented [42]. The severity of EIB in Korean children [43] was shown to be influenced by leukotriene C4 synthase promoter polymorphism.

Presentation

The typical presentation of EIB is lower respiratory tract symptoms of cough and/or wheezing and/or chest pain or tightness or vague symptoms of “locker room cough” or post-exercise cough [8, 12, 36]. Cough is the symptom most frequently reported in athletes with positive exercise challenge [34]. The symptoms seen in EIB are listed in Table 4. Unfortunately, athletes with negative exercise challenge reported symptoms as often as those with positive challenge. The diagnosis of EIB based on self-reported symptoms generates unacceptably increased rates of false-positive and false-negative diagnoses [29, 34, 44, 45]. Diagnosis of EIA requires objective exercise challenge [6–8, 14, 26, 29, 36, 37, 44]. More poorly defined symptoms include (Table 4) fatigue, impaired performance for level of conditioning and activity, avoidance, abdominal pain, headaches, muscle cramps, and dizziness [29, 36]. Children and adolescents may present with chest pain, which is seen

Table 4 Presentation of EIB (signs and symptoms)

Signs of symptoms
Most Common
Cough (post-race usually) or “locker room cough”
Wheezing
Chest pain
Chest tightness or congestion
Shortness of breath
Less Common
Stomachache (young children)
Sore throat (young children)
Fatigue with expected exercise for age
Abdominal pain
Prolonged respiratory illness
Exacerbation of allergens and asthma seasonally particularly with exertion
Muscle cramping
Side ache
Headache

in a majority of adolescents (70%) with negative cardiac evaluation [46]. Pediatric athletes may fail to recognize or underrepresent symptoms because of poor perception or denial [14, 36]. Other presenting symptoms may include prolonged upper respiratory illness, nocturnal cough, inability to keep up with peers, sensation of heaviness in the legs, seasonal variation in asthma and allergy symptoms with humidity, pollens, and pollutants, and sore throat in young children [25, 29, 36, 44, 45]. EIB with asthma may exacerbate with allergen exposure, tobacco smoke, or other pollutants. Dyspnea alone is rarely a symptom of asthma as indicated by a recent study, which indicates that dyspnea is usually an indicator of poor conditioning [47].

Exercise for 5–8 min at a workload of 80% maximal predicted heart rate or oxygen consumption is necessary to generate EIB in the majority of athletes [48]. There is typically bronchodilation during exercise related to catecholamine release, and shortly thereafter symptoms of EIB follow within 5 min of 5–8 min of exercise [6–8, 14, 36, 37]. Symptoms reach a peak 5–10 min after exercise. These symptoms persist for 30 min if no bronchodilator medication is used [49]. Spontaneous recovery occurs within 60 min [48]. Athletes experiencing prolonged symptoms may have impairment of their sports activities. However, treatment is available enabling any child or young athlete to participate in sports without limitation [36].

Diagnosis

The diagnosis of EIB requires objective exercise challenge as the history is often nonspecific (Table 5). The tremendous variability in prevalence in EIB across sports can be attributed in part to the variability or lack of consensus in diagnostic methods.

Table 5 Diagnosis of EIB

Diagnostic methods
History and physical
Objective testing with spirometry
Indirect: more specific
Treadmill
Cycloergometer or bike
Free running
Sports challenge in given sport
Hyperosmolar: sensitive and specific (lab-based)
Saline
Eucapneic hyperventilation (EVH)
Mannitol
Direct: sensitive not specific (lab-based)
Methacholine
Histamine
Amp (5 amp)

Objective testing commences with spirometry pre- and post-bronchodilator. This testing will discover the asthmatic athlete with an abnormal baseline with a response to bronchodilator. However, many athletes will have a normal testing baseline [14, 29, 36]. For athletes with a normal physical exam, spirometry bronchoprovocation testing is needed. A bronchoprovocation test that is positive mandates treatment for EIB. A decline in FEV_1 (>10%) or less reliable, a decline in peak expiratory flow rate between pre- and post-bronchoprovocation testing confirms the diagnosis of EIB [14, 29, 36, 49]. Alternative diagnoses need to be entertained if the history, physical, spirometry, and bronchoprovocation testing are all negative in an athlete with exercise-associated symptoms.

The various types of bronchoprovocation testing include direct pharmaceutical methods such as methacholine, histamine, cold air, saline, adenosine, or mannitol challenge, which are sensitive but not specific and indirect challenges including treadmill, cycle, and free running, which are specific but not sensitive. Newer hyperosmolar indirect challenges including eucapneic hyperventilation (EVH) approved by the International Olympic Committee and mannitol have a sensitivity of 96% and a specificity of 92% to confirm a positive response to EVH. Mannitol inhalation is a surrogate for exercise, and only one investigation documented EIB specifically in athletes [8, 50–56]. The most predictable method for documenting EIB is to perform an exercise challenge in the environment known to cause symptoms [49]. If symptoms of cough, wheezing, chest tightness can be reproduced with running on a treadmill for 8 min then this is confirmatory if there is a decline in FEV_1 of at least 10% [43, 56]. If symptoms cannot be reproduced then a challenge should be conducted in the environment and with the identical exercise intensity under which the individual reports symptoms, i.e., a sports challenge [57]. If testing is being conducted with a patient who has not complained of EIB in the past, the individual should be given a treadmill test with exercise for 8 min [29, 36]. The individual should be exercised to achieve a heart rate minimum of 80–90% of predicted maximum and in the 6 min remaining, exercise should be continued at this heart rate. Ventilation should be 40–60% of maximum [58]. A decline of at least 10% in FEV_1 is adequate to make the diagnosis particularly if symptoms accompany the decline in FEV_1 [58]. Pulmonary function should be monitored immediately after 2, 5,10, 15, 20, 25 min and then for at least 30 min after exercise to assure that delayed decline in FEV_1 is not overlooked [48]. Temperature and relative humidity should be controlled so that the air that is inspired is dry (from a dry tank if possible) and cool (15–20°C).

Eucapneic hyperventilation requires hyperventilation of a gas mixture of 5% CO2 and 21% O2 at 85% of maximum voluntary ventilation for 6 min and the evaluation of FEV_1

at specified intervals after the test. EVH has been demonstrated to have greater specificity for EIB [51]. However, unlike the other indirect methods except mannitol, it has a higher sensitivity to detect EIB than methacholine [14], field- or lab-based challenges [51, 52]. As it is portable, inexpensive, and standardized between labs and has high specificity and sensitivity [53], it is highly desirable as a screening test as approved by the Olympic Committee. EVH may provide increase detection of EIB higher than previously reported. Mannix et al. [54] found 38% prevalence rate among 79 high school students using EVH. Methacholine detected 21% (9/42) prevalence of EIB in 42 elite athletes with respiratory complaints, whereas EVH detected 60% in the study of Holzer et al. [14]. Mannitol may be the most practical surrogate for exercise challenge with more than 90% sensitivity and specificity [14, 55]. It is currently in trials in the United States, but approved in Australia [14]. Nitric oxide studies have indicated that this agent may be used at 12 ppb or 21 ppb in children as a cutoff surrogate for exercise challenge [59]. Recent studies utilizing the interrupter resistance measurements for evaluation of EIA in children have demonstrated the reliability of this technique in the diagnosis of EIA alone (EIB) in children [60]. However, a decline in FEVI of at least 7% or greater after treadmill challenge in the lab may be sufficient for elite athletes as opposed to at least 10% in sports-specific challenge to diagnose EIA [61]. Whereas indirect challenge tests such as Eucapneic hyperventilation or treadmill have better correlation with EIA than direct pharmaceutical challenges such as methacholine, they are not sensitive enough to diagnose asthma that is mild or clinically unapparent [62, 63].

Differential Diagnosis

The differential diagnosis of EIB encompasses cardiac or respiratory diseases that are associated with dyspnea on exertion, exercise-related laryngeal dysfunction (including vocal cord dysfunction and laryngeal prolapse), conditioning, gastroesophageal reflux disease (GERD) and exercise-induced hyperventilation and exercise-induced anaphylaxis with or without a food trigger [64]. These conditions can largely be ruled out with a comprehensive history, physical, spirometry, bronchial hypersensitivity evaluation, and cardiopulmonary monitoring of exercise challenge performed by a boarded allergy specialist.

Exercise-induced laryngeal dysfunction (EILD) is an aberrant laryngeal response to exercise encompassing closely related clinical phenomena: 1) exercise-induced or paradoxical vocal cord dysfunction (VCD) [65]; 2) exercise-induced laryngeal prolapse [66]; and/or 3) exercise-related laryngomalacia [67]. These conditions present with exercise-related stridor on inspiration with tightness in the throat during the height of intense exercise that resolves within 5 min of discontinuation. They are seen predominately in adolescent females [68, 69]. The inspiratory stridor during exercise with laryngeal dysfunction contrasts with the dyspnea of EIB occurring 5 to 20 min after discontinuation of exercise, and involving the expiratory rather than the inspiratory phase of respiration. Early diagnosis of EILD avoids unnecessary pharmacotherapy. Laryngeal dysfunction should be considered on initial presentation particularly if symptoms have failed to abate with typical bronchodilator and/or steroid therapy [68]. Vocal cord dysfunction is a common presentation of EILD seen in adolescents and young adults with competitive “type A” personality [69], which is associated with dyspnea and stridor on inspiration, which is often misdiagnosed for the wheeze of EIA. When the individual with VCD is symptomatic, direct visualization by laryngoscopy of vocal cord adduction and truncation of the inspiratory loop of the flow-volume curve represents the diagnostic standard for VCD. These findings can be intermittent with stress and can be missed. Evaluation of the athlete or child after exercise by auscultation of larynx and chest has also been recommended [69]. As noted, failure to respond to beta agonist with a normal exercise challenge should prompt consideration of the differential diagnosis including VCD. VCD may coexist in up to 33% of stressed adolescent patients with severe asthma [69]. Exercise-induced laryngeal prolapse occurs with intense exercise with a respiratory pattern that generates elevated inspiratory flows precipitating an increase in the negative pressure gradient over the hypopharynx with an aberrant pattern of arytenoid movement and upper airway collapse [70, 71]. Finally, laryngomalacia is a third presentation of EILD, which may present as congenital weakness and collapse of the larynx with recurrence during childhood particularly after strenuous sports activity [72]. It is often mistaken for EIA and is often defined as exercise-induced laryngeal prolapse on endoscopy [73].

Exercise may precipitate gastroesophageal reflux disease in conjunction with VCD. Cough and dyspnea promote a combination of low thoracic pressure during forced respiration and enhanced abdominal pressure during exercise [65]. Videolaryngoscopic or laryngoscopic assessment of individuals with VCD reveals that 63–89% have findings consistent with GERD [74]. The role of laryngopharyngeal reflux in EILD is controversial but likely [75]. Exercise-induced hyperventilation with hypocapnia and an aberrant ventilatory pattern may generate chest tightness and complaints of dyspnea easily mistaken for EIB [76]. This phenomenon can be ruled out by treadmill [47] and/or voluntary hyperventilation maneuver [77].

Exercise-induced anaphylaxis (EIAna) is characterized by pulmonary distress with exercise in conjunction with

pruritus, generalized urticaria, and angioedema with rapid progression to vascular deterioration. It is classified by the severity of presentation and onset initiated by vigorous exercise. Food-dependent exercise-induced anaphylaxis (FDEIAna) is a defined variation of exercise-induced anaphylaxis that encompasses both strenuous exercise and ingestion of specific foods or infrequently any food in the several hours before exercise. Epicutaneous skin testing may characterize food allergens that exacerbate FDEIAna such as celery, shellfish, and wheat [78]. The association of food and exercise is defined by history. FDEIAna is corroborated by an ingestion of the characterized food followed by an exercise challenge. However, the risk/benefit needs to be evaluated for diagnostic confirmation versus the inherent danger of precipitating anaphylaxis.

Further, rare differential diagnoses include idiopathic hypoxemia of exercise, cystic fibrosis, atrial septal defect, and mitochondrial aberrations [79].

Pharmacotherapy/Nonpharmacotherapy Treatment of EIB

There have been extensive investigations on the pharmacotherapy of EIB especially in treatment of EIB asthmatic athletes. It is essential to manage EIB in asthmatic children so that they can perform in sports activity [80]. Inhaled steroids may be helpful in managing the inflammation of EIB in children with asthma [81]. However, a rapid-acting beta agonist is recommended for those who still have EIB or whose only manifestation of asthma is EIB [82]. Formoterol has a rapid onset of action like albuterol, but can protect against EIB for up to 12 h [78, 79]. There are no guidelines for recreational vs. competitive or athletic children who have only EIB, nor is it known whether the therapy used for the asthmatic athlete applies to those with only EIB [8].

Nonpharmacologic intervention includes warm-up of 10–15 min with calisthenics with extension exercises with the goal of achieving 50–60% of maximum heart rate [83]. A prophylactic beta agonist should be utilized if asthma symptoms occur and exercise commenced again when symptoms resolve [84]. A refractory period may develop after exercise and can be present for 2–3 h during which EIB is blocked particularly in children and individuals with mild asthma. A variable amount of exercise is necessary to produce a refractory period depending on the athlete and the time period. This maneuver may be used to prevent EIB, but is usually only partially successful in competitive athletes who need pharmacotherapy. As EIB may reflect less than optimal control of underlying asthma, it is critical to optimize therapy for overall asthma control. In contrast, in the child who presents with EIB alone, it is critical to evaluate for underlying asthma and treat accordingly. The most widely used therapy for EIB is the preventative use of short-acting beta agonist bronchodilators, e.g., albuterol usually administered 15–30 min before exercise [8, 29, 36, 37, 85]. This is regarded as the most effective intervention for prophylaxis of symptoms of EIB in individuals with known asthma [86]. Therapy with beta 2 agonists (β_2 receptor agents) 15 min before exercise results in a peak bronchodilator effect in 15–60 min and bronchoprotection from EIB for a minimum of 3 h in most individuals [48, 87]. However, continuous use of β2 agonists has been demonstrated to lead to tachyphylaxis with loss of bronchoprotection, desensitization of the mast cell, and paradoxical bronchoconstriction exacerbating existing EIB and asthma [6–8, 36, 37]. Long-acting beta agonists (LABA) such as formoterol or salmeterol are also effective. Formoterol can be taken shortly, i.e., 5 min before exercise, whereas salmeterol has an onset that is delayed up to 90 min for complete protection from exercise [88–90].

If beta agonists are administered daily, there is likelihood of tachyphylaxis or at least partial loss of efficacy [91, 92]. A decline in efficacy may be seen as a lessened bronchodilator response with beta agonist, or a shorter duration of effect. The duration of action may decline from about 12 h to no more than 3–4 h after 4 weeks of therapy [93]. Fifteen to twenty percent of the population with certain $beta_2$ agonist receptor genotypes such as Arg/Arg may have detrimental effects from both long- and short-acting beta agonist therapy [94].

Inhaled corticosteroids are recommended as the primary antiinflammatory controller agents for athletes with asthma and EIA [78]. However, at least one study showed that the efficacy of budesonide was questionable in nonasthmatics with EIB [41]. Thio et al. [95] demonstrated that a single high dose of inhaled fluticasone propionate had a protective outcome on the acute bronchial response to exercise in the majority of asthmatic subjects in the study. Jonasson [81] demonstrated that 3 months of low-dose budesonides administered once or twice daily relieved exercise intolerance and symptoms in subjects with mild asthma with EIA. Studies by Peterson et al. [96] with HFA beclomethasone and Subbarro et al. [97] using the prodrug ciclesonide demonstrated efficacy over 4 weeks in dose response fashion.

Leukotriene modifiers, e.g., montelukast, demonstrate effectiveness in control of EIB in a number of studies [12, 80, 98, 99]. Montelukast is a once-a-day regimen, has no significant side effects, approved for very young children, and can also be administered continuously without tachyphylaxis. Leff et al. [98] demonstrated significant protection of montelukast over placebo, and improvement in maximal decline in FEVI after exercise. There was no tolerance to medication or rebound in pulmonary function after discontinuation. The protective effect of montelukast begins after12 h and lasts up to 24 h after its discontinuation [100, 101]. Rundell et al. [102] demonstrated

that a single dose of montelukast delivered protection against bronchoconstriction from exercise. Only one study [103] has compared inhaled steroids with montelukast for EIB; 84% of subjects with mild asthma were protected by budesonide compared to 61% by montelukast over 4 weeks of the study period. When low dose fluticasone (100–200 μg) or budesonide (200–400 μg) does not prove sufficient for EIB then the addition of montelukast is recommended http://www.ginasthma.com) A favorable response to montelukast was associated with a younger age and a less prolonged duration of disease in mild to moderate persistent asthma [99, 104]. It is particularly useful in children with EIB and concomitant allergic rhinitis and dermatitis because of its systemic effect on these other atopic conditions [104, 105]. Zileuton [106] and zafirlukast [107] may also be used as EIB therapy without tachyphylaxis.

Mast cell stabilizers such as cromolyn and nedocromil have been used widely for the prevention of EIA. They function by blocking mast cell degranulation and subsequent histamine release [108]. Both agents administered 15–30 min before exercise in athletes are equally efficacious [108, 109]. In a metaanalysis [110], nedrocromil was demonstrated to enhance FEV_1 by an average of 16% and to decrease the duration of EIB symptoms to less than 10 min. These agents are generally second line because of the duration of effect and the efficacy is less than beta agonists. However, use of these agents and isomeric beta agonist agents such as levalbuterol may be preferred in pediatric populations over generic beta agonists for their relative lack of side effects, e.g., tachycardia and tremor [8, 36, 79]. Combination of agents (Table 6) may provide greater convenience and efficacy. Weiler et al. [111] reported that combination fluticasone and salmeterol provided long-term protection against EIB in individuals with persistent asthma, and had a more prolonged duration of effect compared to a combination of short-acting beta agonist and cromolyn or from either medication alone [111].

Table 6 Pharmacological treatment of EIB

Treatment
Beta agonists
Short acting , i.e., albuterol/terbutaline/maxair
Long acting: Formoterol/Salmeterol
Nonsteroidals: Cromolyn/Nedocromil/Theophylline
Leukotriene modifiers: Montelukast/ Zafirlukast/ Zileuton
Anti IgE (Xolair)
Steroids inhaled
Budesonide
Fluticasone
Triamcinolone
Beclomethasone
Flunisolide
Momethasone
Ciclesonide (in trials not approved for market)
Combination
Fluticasone and salmeterol
Budesonide and formoterol
Atrovent

Table 7 Nonpharmacological treatment of EIB

Treatment
Warm-up 10–15 min to 60% maximum heart rate
Warm-down 10–15 min
Facemask
Breathe through the nose
Environmental avoidance

Theophylline and anticholinergics are third line therapy and are infrequently needed or recommended [8, 112] except when other controller therapy combinations fail [113]. Allergen evaluation and avoidance, pharmacotherapy with appropriate nasal steroids and nonsedating antihistamines, and immunotherapy with allergen and/or antiIgE therapy is also important especially in an atopic individual [5]. Pharmacogenetics plays a role in the response to LABA in 16% of Caucasians and 25% of African Americans. Failure to respond to LABA may be related to these genetic factors [8, 37].

Nonpharmacologic therapy encompasses warm-up for 10–15 min and warm-down for 10–15 min [114]. Avoidance of allergen or irritant triggers, overtraining [38], and immunotherapy for relevant allergic triggers where indicated [5] are recommended. Athletes discover empirically that warm-ups are helpful in attenuating the EIB. This phenomenon is known as the refractory period and constitutes a 2-h period after exercise during which the athlete with asthma is “refractory” to further asthma. It is only noted in athletes with asthma, but may not be observed in those with EIB alone [115, 116]. The refractory period is postulated to be secondary to catecholamine release including norepinephrine and epinephrine, which are bronchodilators, and simultaneous depletion of mast cell mediators including histamine and leukotrienes, which are bronchoconstrictors.

Other nonpharmacologic interventions include wearing a facemask (Table 7) to warm and condition the humidity of inspired air particularly in recreational and elite athletes in winter sports [117]. Inhalation through the nose and avoiding breathing through the mouth, where possible, will improve EIB [118] by enhancing the warmth, humidity, and filtration of cool and dehydrated inspired air. Avoidance of allergen triggers is effective by timing exercise to minimize allergen exposure or exercising indoors if outdoor allergens are the problem. Evaluation of the pediatric athlete with EIB by a boarded allergist with skin testing and spirometry pre- and post-bronchodilator with bronchoprovocation testing as relevant is essential for identifying underlying inhalant allergies and asthma. The allergist can develop a

program for environmental control of allergens, appropriate pharmacotherapy such as nasal steroids and nonsedating antihistamines, and, if needed, allergen immunotherapy [5, 14, 119]. The allergist must be informed by these elite athletes about their allergy and asthma medications. Therapeutic use exemption applications need to be completed for elite athletes with supporting documentation. Doping or illegal use of medication to enhance performance is never acceptable and should be actively opposed by the healthcare provider.

Both pharmacologic and nonpharmacologic therapies are necessary to optimize the management of EIB and avoid adverse effects. Management of EIB in the asthmatic pediatric athlete should consist of a short-acting bronchodilator before exercise, appropriate instructions for warm-up and warm-downs, and avoidance of proven triggers. This approach will control EIB in asthmatics in greater than 80% of affected athletes [50]. If symptoms progress or persist, then inhaled corticosteroids as maintenance therapy and/or montelukast can be used [8, 36, 79, 81, 95]. Alternatively, nonsteroidals including cromolyn or nedocromil can be utilized if beta 2 agonists fail to provide sufficient control or are poorly tolerated. Return to school and work after an asthma exacerbation may be possible within the week with appropriate therapy, but the return to sports may take longer as EIB is the first symptom to signal an exacerbation and the last to return [10].

Conclusion

EIB and asthma can be well controlled in pediatric athletes, allowing full participation in the majority of cases in any chosen sport. Attention to medication and warm-up and warm down with breathing through the nose and treatment of inhalant allergy will result in the ability to play sports and enjoy activity. Further research is needed on EIB therapy in the nonasthmatic.

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