

# Special considerations for adolescent athletic and asthmatic patients

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**Abstract:** Asthma is defined as a chronic inflammatory disorder of the airways with bronchial hyperresponsiveness and variable bronchoconstriction, and is one of the most common diseases in childhood and adolescence. Exercise-induced asthma-like symptoms and asthma are also frequently seen in highly trained athletes. Exercise-induced asthma (EIA) and exercise-induced bronchoconstriction (EIB) are found in 8%–10% of healthy school-aged children and in 35% of children with asthma. Highly increased ventilation, inhalation of cold, dry air and air pollutants (eg, chlorine) are thought to be important triggers for EIA and EIB. EIA is often experienced concurrently with vocal cord dysfunction, which needs to be considered during the differential diagnosis. The pharmacological treatment of EIA is similar to the treatment of asthma in nonexercising adolescents. The therapy is based on anti-inflammatory drugs (eg, inhaled glucocorticosteroids) and bronchodilators (eg,  $\beta_2$ -agonists). The treatment of EIB is comparable to the treatment of EIA and leukotriene modifiers offer a new and promising treatment option, particularly in EIB. Generally, athletes may not use  $\beta_2$ -agonists according to the prohibited list of the World Anti-Doping Agency (WADA). However, the WADA list contains specific  $\beta_2$ -agonistic substances that are permitted to be used by inhalation.

**Keywords:** exercise-induced asthma, exercise-induced bronchospasm, adolescents, asthma, athletes

## Introduction

Asthma is defined as a chronic inflammatory disorder of the airways with bronchial hyperresponsiveness and variable bronchoconstriction, and is one of the most common diseases in childhood and adolescence.<sup>1</sup>

Because children are generally physically active and take part in high-intensity exercise, and their physically active lifestyle is widely promoted, it can be deduced that many children will also suffer from asthma. Asthmatic athletes are at increased risk of ventilatory symptom injury through exercise than athletes without asthma. When physical exercise itself is the cause of asthmatic symptoms, the condition is referred to as exercise-induced bronchoconstriction (EIB).<sup>2</sup> Inherently, when children and adolescents participate in sports, they also have an increased risk of experiencing EIB. However, it is generally accepted that physical activity and sports are beneficial for young asthmatic patients, and given that asthmatic symptoms are well controlled with medication, most young asthmatic athletes are able to perform without restriction, even at elite level.

The focus of this review is to illustrate the different types of exercise-induced ventilatory symptoms, their mechanisms, treatment options, and differential

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diagnosis in adolescent athletes. Treatment side effects and antidoping aspects are also discussed.

To obtain the relevant scientific data, we searched PubMed and Medline for terms such as “exercise-induced asthma” (EIA), “exercise-induced bronchoconstriction”, “asthma and child and athlete”. Whenever relevant, further references and reviews were included.

In contrast to the fairly rigid medical treatment guidelines for asthmatic adults, it may be appropriate to manage the symptoms of asthma in children and adolescents with more flexibility, depending on their planned physical exercise. Currently, the pharmacological management of asthma and EIB in young athletes is in accordance with the guidelines for the treatment of asthma in nonexercising adolescents, and is primarily based on the administration (through inhalation) of anti-inflammatory drugs (eg, inhaled glucocorticosteroids [ICS]) and bronchodilators (eg,  $\beta_2$ -agonists). Short-acting inhaled  $\beta_2$ -agonists (SABAs) can be used prophylactically prior to exercise or reactively in case of acute bronchoconstriction occurring during exercise or other conditions. Long-acting  $\beta_2$ -agonists (LABAs) are often used in combination with ICS as a basic treatment for severe cases.<sup>3</sup>

Although the use of  $\beta_2$ -agonists by athletes is forbidden according to the prohibited list of the World Anti-Doping Agency (WADA),<sup>4</sup> EIB and asthma in athletes are common and often require the use of inhaled  $\beta_2$ -agonists. Therefore, the WADA list contains specific  $\beta_2$ -agonist substances which are permitted for use by inhalation only.<sup>5</sup>

Differential diagnosis in asthma-like symptoms should further be considered in young athletes with respiratory symptoms. Particularly upper airway obstructions such as vocal cord dysfunction (VCD) have more recently become suspected as triggers for exercise-induced shortness of breath.<sup>6,7</sup>

## Epidemiology of asthma and EIB in athletes and adolescent athletes

Exercised-induced bronchoconstriction and exercise-induced asthma-like symptoms are often diagnosed in highly trained athletes. The prevalence of asthma is higher in elite athletes than in the general population.<sup>8</sup> The highest reported prevalence for EIB is 45% in cyclists.<sup>9</sup> Up to 22% of Olympic athletes from the United States and Italy (Olympic Games 1996, 1998, and 2000) had asthma.<sup>9–12</sup> The prevalence of asthma in other highly trained athletes is reported to be between 10% and 23%<sup>13–15</sup> and in adolescent athletes between 12% and 38%.<sup>16,17</sup> The prevalence of EIB is high both in summer and winter sports, but is more common in winter-sport athletes.<sup>11,12,18–20</sup> Studies show a high prevalence of EIB in

cross-country skiers, and other so-called “cold-weather-athletes”.<sup>21–23</sup> Within the “warm-weather athletes”, endurance athletes<sup>15,24</sup> have the highest prevalence, with swimmers and cyclists having the highest proportion of clinically relevant EIB cases. Asthma also seems more common among female athletes,<sup>9,12,15</sup> but this has not been entirely confirmed.<sup>10</sup>

Exercise-induced asthma (EIA) is found in 8%–10% of healthy school-aged children and 35% in children with asthma.<sup>25</sup> Furthermore, the degree of EIA in children seems to depend on exercise intensity. A study of children who exercised at 85% of maximum oxygen uptake ( $VO_{2max}$ ) showed a fall in forced expiratory volume in one second ( $FEV_1$ ) of 8.8%, whereas exercising at 95%  $VO_{2max}$  led to a fall in  $FEV_1$  by 25.1%.<sup>26</sup> In addition, the type of training and the type of sport can influence the prevalence of asthma.<sup>9–13,15,18,19,24,27–30</sup>

The prevalence of EIB is reported to be up to 40% in patients with allergic rhinitis. Therefore, athletes with allergic rhinitis should be tested for EIB even if they only have minor clinical EIB symptoms.<sup>31</sup>

The differentiation of EIA and EIB in the international literature is inconsistent, and many papers do not even differentiate between the two. Carlsen describes two phenotypes of asthma in athletes; the first includes athletes who have had asthma from early childhood, often accompanied by allergic symptoms, the second describes those athletes expressing acute asthmatic symptoms triggered by the exercise stimulus itself.<sup>25</sup> Although in the second group, traditional asthmatic symptoms may not be obvious, but subjects experience coughing and the release of mucus only after exercise or over prolonged periods of time. These athletes are more likely to suffer from EIB.

## Mechanisms of exercised-induced bronchoconstriction

The mild hyperventilation during exercise and the inhalation of cold, dry air are thought to be important triggers for EIB.<sup>32</sup> These findings are leading to the development of different etiological theories. One theory concerns the cooling and the other the dehydration of airway epithelial cells, but both result in inflammation of the airway epithelium and airway narrowing. Higher concentrations of inflammatory cells in the sputum of subjects with EIB compared to subjects without EIB have been observed following exercise.<sup>33</sup> Another mechanism thought to contribute to EIB in elite athletes is minimal airway injury following plasma exudation and cell movement into the airway. Hyperventilation on an injured airway epithelium is believed to dehydrate the airway cells,

leading to degranulation and the release of inflammatory mediators.<sup>34–36</sup>

The risk of EIB seems to be higher in athletes training more than 20 hours per week compared with athletes training less than 10 hours per week.<sup>15</sup> Atopic disposition and exposure to pollutants are risk factors for marked exercise-related bronchoconstriction.<sup>13,30,37,38</sup> Finally, respiratory tract infections were found to increase the bronchial hyperresponsiveness in athletes compared with nonactive subjects during exercise.<sup>39</sup>

The relatively high occurrence of EIB in swimmers<sup>24,27,28</sup> is interesting and due to issues specific to the sport of swimming. Approximately 36% of the swimmers in the 2008 German Olympic team had asthmatic symptoms and applied for a therapeutic-use exemption (TUE) to use inhalable  $\beta_2$ -agonists.<sup>40</sup> One possible reason for the high prevalence of EIB in swimmers is the water in swimming pools, which has chlorine added for disinfection. Inhaling the air floating just above the water surface exposes the swimmers to high concentrations of chlorine.<sup>27</sup> In athletes with a pre-existing bronchial hyperreactivity, bronchoconstriction is the logical result of chloride gas inhalation. Furthermore, it has been suggested that the repeated exposure to chlorine gas may promote the development of asthma. On the basis of recent studies,<sup>41–44</sup> it has been suggested that products containing chlorine may provoke an increase in lung-epithelium

permeability in susceptible swimmers, increasing the risk of developing EIB.

As with chlorine exposure, other harmful agents in the environment can serve as triggers for airway epithelia injuries. In athletes, performing long bouts of regular exercise up to twice daily with high tidal volumes increases exposure to environmental air pollutants and chemicals compared to sedentary people. Different types of exercises will result in different levels of environmental exposure. For example, cross-country skiers are repeatedly exposed to cold air,<sup>45</sup> and athletes training and competing on ice (eg, speed skating, ice hockey) may be exposed to nitric oxide as well as to ultrafine particles from resurfacing machines. Athletes training and competing on streets such as cyclists and marathon runners are exposed to traffic air pollution. In addition, many outdoor athletes face exposure to aeroallergens (eg, pollens and moulds) and ozone. One study has shown that participation in sports in regions with high ozone levels led to an increased risk of asthma in children after a 5-year follow up compared to children who were active in areas with lower ozone levels.<sup>45</sup>

## Differential diagnosis

The diagnosis of EIA and EIB can be achieved by standard bronchial provocation or standardized exercise testing (Figure 1). Further differential diagnoses should always

<p><b>Bronchodilator test</b> After administering a "permitted" <math>\beta_2</math>-agonist (eg, salbutamol) by inhalation, a bronchial reversibility test is considered positive if the increase in FEV<sub>1</sub> is 12% or more of the baseline FEV<sub>1</sub>.</p> <p><b>Bronchial provocation tests</b></p> <p>1. <i>Eucapnic voluntary hyperpnea test</i> The eucapnic voluntary hyperpnea test is considered positive when a fall in FEV<sub>1</sub> of 10% or more from baseline is recorded after a 6-minute period of hyperpnea in dry air.</p> <p>2. <i>Exercise challenge in the laboratory or in the field</i> The response to the exercise challenge is considered positive when there is a fall in FEV<sub>1</sub> of 10% or more compared to baseline during the first 30 minutes postexercise.</p> <p>3. <i>Hyperosmolar aerosols</i> A fall in FEV<sub>1</sub> of 15% or more from baseline after inhaling 22.5 mL of 4.5 gm% saline (eg, 4.5 g NaCl/100 mL water) or a dose of 635 mg of dry powdered mannitol is a positive response and is consistent with a diagnosis of asthma or EIA/EIB. The response to 4.5% saline and the response to mannitol is usually reported as the dose required to provoke a 15% fall in FEV<sub>1</sub> (PD15) but should also be reported as the maximum fall after the final dose of aerosol.</p> <p>4. <i>Methacholine test</i> A test is considered positive if there is a fall in FEV<sub>1</sub> of 20% or more from baseline at a dose (PD20) less than or equal to 400 <math>\mu</math>g/2 <math>\mu</math>mol (cumulative dose) or 200 <math>\mu</math>g/1 <math>\mu</math>mol (noncumulative dose) or a concentration (PC20) less than or equal to 4.0 mg/mL when the subject is not taking inhaled corticosteroids or has taken them for less than 1 month.</p>
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**Figure 1** Diagnosis of EIB/EIA according to IOC Guidelines.<sup>81</sup>

**Abbreviations:** FEV<sub>1</sub>, forced expiratory volume in 1 second; EIB, exercise-induced bronchodilation; EIA, exercise-induced asthma; IOC, International Olympic Committee.

be considered. Recently it has been shown that EIB coexists and may be confounded by exercise-induced VCD. This observation was first described in adults by Refsum<sup>46</sup> and later in adolescents by Landwehr et al.<sup>47</sup> It may occur in 5%–27% of patients primarily diagnosed with EIB.<sup>48–51</sup> VCD is characterized by a paradoxical closure of the vocal cords during inspiration. It often occurs as noisy breathing, dyspnea, wheezing, coughing, and sensations of obstruction at the level of the upper chest. In a retrospective study of juvenile patients with VCD Powell et al found signs of gastroesophageal reflux disease. A relationship between VCD and psychological stress has also been shown.<sup>52</sup> Direct visualization of the vocal cords using endoscopy during exercise is the gold standard in diagnosis, but is difficult to obtain. VCD is suspected in the presence of an incomplete or truncated inspiratory loop in the flow–volume curve.<sup>53,54</sup>

The treatment is difficult and many different approaches have been undertaken in the past.<sup>53–57</sup> A consultation with a speech pathologist seems to be indicated, whereas reassurance of the athletes about the non-life-threatening condition by the physician should always be the first step. Further, therapeutic attempts have been described with hypnosis and biofeedback training. Other differential diagnoses, such as chronic respiratory or cardiac conditions, eosinophilic bronchitis, or environmental exposures to toxins are rare, but need to be excluded.

## Recommendations for the treatment of EIB in adolescent athletes

Currently, the treatment of adolescent athletes with EIB is similar to the treatment of adult athletes.<sup>3,58,59</sup> Baseline therapy is mostly anti-inflammatory, preferably with ICS. In athletes with only rare episodes of EIB, the prophylactical administration of inhaled SABAs may be sufficient. SABAs should be given prior to exercise to prevent attacks of EIB. If athletes use their SABAs more than twice a week, an ICS should be added. In athletes with severe symptoms, a combined therapy with inhaled corticosteroids and LABA is recommended.<sup>3,58,59</sup>

The efficiency of inhaled  $\beta_2$ -agonists has been demonstrated for several substances.<sup>60,61</sup> The positive effects for LABAs such as salmeterol and formoterol have also been shown.<sup>62,63</sup> Formoterol has a significant protective effect against EIB compared with placebo.

In a recent review from Ducharme et al it was reported that in asthmatic adults on low and high doses of inhalative corticosteroids as a monotherapy, the addition of a LABA

reduced the rate of exacerbations, improved lung function and symptoms, and modestly decreased the need for SABAs.<sup>64</sup> The effects of this treatment option in children are not known, mainly due to the absence of relevant studies.

Thus far, randomized and controlled studies concerning the effects of other substances such as cromoglycate and nedocromil sodium on EIB in elite athletes have not yet been conducted, although here is some evidence that leukotriene antagonists may help prevent EIB.<sup>65–69</sup> Due to the links between the development of exercise-induced bronchospasm and the release of inflammatory mediators such as histamine and leukotrienes, leukotriene receptor antagonists and leukotriene synthesis inhibitors have received some interest.<sup>70</sup> Of these potential treatments, montelukast is the most studied substance for the control of EIB in patients aged 15 years and older and is considered a useful treatment of EIB.<sup>65,70</sup>

However, in a later review from Ducharme et al for asthmatic adults and children for most asthma measures, inhalative corticosteroids (eg, of 400  $\mu\text{g}/\text{day}$  of beclomethasone-equivalent) were more effective than antileukotriene agents given in the recommended doses.<sup>64,71</sup> Still, leukotriene modifiers should remain a treatment option in athletes with EIB in whom therapy with SABA and ICS is insufficient and may be considered before starting therapy with ICS and LABA.

In athletes with an underlying allergic problem, the treatment of allergy symptoms with non-sedating antihistamines and, where appropriate, with nasal steroids should be considered. For athletes in whom allergic exposure plays an important role in their nasal and bronchial symptoms, immunotherapy (hypersensitization) against environmental allergens should be considered. In such cases where subcutaneous immunotherapy with regular injections might be a logistic problem for athletes who travel much, sublingual immunotherapy could be a feasible option.

The treatment of EIB should be followed by regular control visits. Early recognition of exacerbation with appropriate stepping up of medication is important to obtain sufficient disease control.

## Relevant side effects of inhaled $\beta_2$ -agonists

Athletes can have fatal asthmatic exacerbations during and immediately after participating in sport activities, especially high-intensity training sessions or competition.<sup>72</sup> Therefore, sufficient diagnosis, prevention, and therapy are necessary. There are however, important and relevant adverse effects of  $\beta_2$ -agonists. The most frequent adverse effects from inhalation of  $\beta_2$ -agonists are tachycardia and muscle fascillation/tremor,

which are more pronounced in short-acting agents.<sup>73</sup> Further known adverse effects are headaches and irritability and, at very high doses, hyperglycemia and hypokalemia.<sup>73</sup> Furthermore, regular administration of  $\beta_2$ -agonists may be associated with the development of tolerance to their effects and increased airway inflammation.<sup>63,74–76</sup> Tachyphylaxis may develop with both SABAs and LABAs, and the daily use of LABAs attenuates the bronchodilator effect of short-acting substances.<sup>74,75,77</sup> A combination with inhaled corticosteroids does not necessarily reduce tolerance, but is thought to inhibit this problem.

The development of tolerance to the bronchodilator effects of  $\beta_2$ -agonists could influence the success of rescue therapy in severe EIA/EIB.<sup>74–76</sup> The increased tolerance is associated with downregulation of peripheral  $\beta_2$ -receptors and desensitization of the receptors.<sup>75</sup> In addition, tachyphylaxis to  $\beta_2$ -agonists could be modulated by  $\beta_2$ -adrenoceptor gene polymorphisms.<sup>78</sup>

In a review of the problems of inhaled LABAs,<sup>79</sup> it was concluded that a minor tolerance to bronchodilator activity was seen with formoterol, but not with salmeterol. However, there is a partial loss of protection against EIB with regular use of either of these LABAs. Cardiac risks were not documented. In the same review, it was pointed out that the frequent administration of SABAs induces some loss of bronchodilatation and decrease in bronchoprotective action. Nonetheless, it is accepted that the regular use of ICS and inhaled  $\beta_2$ -agonists is the best current therapy for minimizing chronic damage to the bronchial system related to asthma.<sup>58,59</sup>

## Relevant side effects of ICS

ICS are the most effective medications available for patients with EIB. Nevertheless concerns about potential adverse systemic effects of ICS contribute to their underuse. In an American review the safety of ICS was investigated with respect to potential systemic side effects.<sup>80</sup> Negative side effects of ICS on the ocular system and on bone mineral density and adrenal function are minimal in patients receiving recommended ICS doses. One-year growth studies in children have shown decreased growth velocity with ICS, but long-term studies on inhaled budesonide and beclomethasone showed no effect on final adult height, suggesting that these effects are transient.

## World Anti-Doping Code and therapeutic use exemptions

The so-called prohibited list was first published in 1963 under the leadership of the International Olympic Committee (IOC). Since 2004, as mandated by the World Anti-Doping

Code, WADA is responsible for the preparation and publication of the prohibited list. In the current WADA list all  $\beta_2$ -agonists are prohibited, both in and out of competition. The following exceptions are permitted by inhalation for the prevention and/or treatment of asthma and EIB: formoterol, salbutamol, salmeterol, and terbutaline. A therapeutic use exemption is not needed to justify the use of either ICS or the three  $\beta_2$ -agonists permitted by inhalation. However, all athletes are required to report their  $\beta_2$ -agonist use in the antidoping control form when tested. Further and current information can be found on the WADA website (see <http://www.wada-ama.org>).<sup>4</sup>

## Summary and conclusion

Exercise-induced breathing disorders are common in exercising children and adolescents. The underlying mechanism of this disorder is a bronchoconstriction caused by inflammatory processes as a result of hyperventilation on irritated airways. When EIA/EIB is suspected in athletes, a spirometry should follow the extensive medical history and medical examination. Specific objective tests which may confirm the diagnosis, such as standardized exercise tests, metacholine bronchial challenge, or voluntary hyperpnea and mannitol test should follow to confirm the diagnosis. Correct documentation is advised and it is important to comply with the antidoping regulations. If a decision is made to treat with inhaled medications, the only substances should be used are those permitted by WADA.

Regular follow up should be a regular part of disease management to ensure proper and timely therapy adjustment if necessary. The treatment of adolescent EIA and EIB is similar to that of nonathletic asthmatics. Mild forms of EIA may be sufficiently treated with inhaled SABAs, whereas EIB is most likely to be controlled by ICS. The baseline therapy for more severe cases of EIA and EIB is anti-inflammatory with inhaled corticosteroids combined with LABA if necessary. Leukotriene antagonists such as montelukast may provide a feasible alternative or be used in combination, especially in EIB. Differential diagnosis of EIA (eg, VCD) should always be considered especially when treatment with inhalative antiasthmatic agents is ineffective.

In summary, the early diagnosis and anti-inflammatory treatment of EIB in adolescent athletes is necessary to prevent ongoing inflammatory processes in the airway epithelium. A sufficient relief and treatment of these exercise-induced breathing problems further helps to prevent aggravation of EIB and reduce the harmful effects of environmental triggers. Appropriately treated children and adolescents with

controlled asthma can exercise, train, and compete similarly to their nonasthmatic peers without any limitations.

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