

Pharmacologic Strategies for Exercise-Induced Bronchospasm with a Focus on Athletes



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KEYWORDS

• Exercise • Asthma • Treatment • EIB • Doping

KEY POINTS

- Short-acting beta agonists are effective first-line agents for exercise-induced bronchospasm (EIB). Tolerance can develop with frequent use.
- Multiple other medication classes are effective in the treatment of EIB, and selection of these agents can be stratified by the presence or absence of underlying asthma and the frequency of short-acting beta-agonist use.
- In the future, therapy may be guided by the identification of one or more specific EIB endotypes.
- Lack of specific data regarding EIB in elite athletes results in recommendations for treatment strategies that are similar to EIB in nonathletes.
- Athletes and providers must be cognizant of the World Anti-Doping Agency's regulations with regard to EIB therapy in elite athletes.

INTRODUCTION

Exercise-induced bronchoconstriction (EIB) is the transient narrowing of the airways during and after exercise that occurs in response to increased ventilation in susceptible individuals.¹ EIB is a common phenomenon affecting as many as 20% of the general population and most of the estimated 300 million patients with asthma worldwide.^{2,3} Among athletes, as reviewed by Matteo Bonini and William Silvers (See Matteo Bonini

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and William Silvers's article, "[Exercise-Induced Bronchoconstriction: Background, Prevalence, and Sport Considerations](#)," in this issue.) and others, the prevalence can be much higher depending on specific sport requirements; dry ambient conditions are known to contribute.⁴⁻⁸ The impact of the condition manifests in several very important ways, including the potential for EIB to do the following:

1. To theoretically cause changes in airway function⁹⁻¹¹
2. To act as a deterrent to exercise in an age when exercise is promoted as a therapy for many health conditions¹²⁻¹⁵
3. To negatively affect sport performance in competitive athletes¹⁶

For all of these reasons, bronchospasm that occurs in isolation with exercise or as a manifestation of chronic asthma is important to treat.

This review of EIB therapeutics relates pharmacologic interventions to known elements of disease mechanism and includes a discussion of EIB in patients with and without underlying asthma (EIBa and EIBwa, respectively) with an assumption that other causes of exertional cough and dyspnea, including exercise-induced laryngeal obstruction, have been excluded. As with most diseases, our knowledge of the mechanism exceeds the availability of pharmacologic agents that can effectively target important molecular or cellular intermediaries of the disease. Pascale Kippelen and colleagues (See Pascale Kippelen and colleagues' article, "[Mechanisms and Biomarkers of Exercise-Induced Bronchoconstriction](#)," in this issue.) thoroughly review the current knowledge regarding the disease mechanism, calling attention to the isolation of EIBwa as a distinct endo-type of asthma.¹⁷⁻¹⁹ Extending this line of thinking, it is possible that multiple endo-types of EIBwa exist with varying inflammatory profiles and may be supported by decades of observations of differential responses to medication across subjects.^{20,21} Kenneth W. Rundell and colleagues (see Kenneth W. Rundell and colleagues' article, "[Exercise-Induced Bronchoconstriction and the Air We Breathe](#)," in this issue.) thoroughly review environmental factors that could also modulate the molecular and cellular responses to increased ventilation during exercise acutely and chronically.²²

In this review, the authors summarize all of the medication classes that are commonly used in the treatment of EIB. The authors highlight specific benefits, drawbacks, and situational considerations of the medications as supported in the medical literature. In this process, the authors refer to consensus recommendations that have been recently published by the American Thoracic Society and the Joint Task Force on Practice Parameters representing the American Academy of Allergy, Asthma & Immunology, the American College of Allergy, Asthma & Immunology, and the Joint Council of Allergy, Asthma & Immunology.^{23,24} The authors highlight important considerations with regard to the World Anti-Doping Agency's (WADA) current regulations.²⁵

OVERVIEW OF PHARMACOLOGIC THERAPY FOR EXERCISE-INDUCED BRONCHCONSTRUCTION

Although molecular and clinical asthma literature increasingly discusses the use of asthma endo-types to guide therapy, at the current time, there is not literature that strongly recommends stratification of therapy across groups with potentially distinct inflammatory signatures with isolated EIBwa or across the larger groups of EIBa and EIBwa. For this reason, many of the observations and recommendations that follow can be considered for all patients who experience EIB. This approach is in line with recommendations from the recently published practice parameter and the International Olympic Committee's consensus conference on asthma and the elite athlete.^{24,26} However, a personalized approach can guide EIB therapy for reasons

unrelated to inflammatory signatures. As per current guidelines, such an approach should include concurrent evaluation and treatment of conditions extrinsic to isolated EIB that affect EIB, including nonallergic sino-nasal disease (See Brecht Steelant and colleagues' article, "[Exercise and Sino-Nasal Disease](#)," in this issue.), allergic disease, underlying asthma, exercise frequency, medication nonadherence, and poor medication delivery (the details of which are beyond the scope of this review).^{27,28} This approach may also extend to considerations relevant to specific sports, including cold-weather endurance sports and swimming, that present unique challenges and daily training regimens, which could potentially induce bronchodilator tolerance.²⁹

Beyond personalized recommendations, the authors discuss incremental therapy for patients who continue to experience symptoms despite appropriate monotherapy followed by a framework for approaching patients with difficult-to-manage symptoms. Although there are little experimental data to support individual steps in an incremental approach to EIB therapy, the stepwise approach outlined in the "Expert Panel Report 3"²⁷ for asthma management provides a useful therapy model.

Short-Acting Beta₂ Agonists: First-Line Therapy for Exercise-Induced Bronchoconstriction

Short-acting beta agonists (SABAs) should be considered the first-line agents for broncho-protection against EIB and acute bronchodilation in the treatment of EIB based on consistent results across multiple meta-analyses of head-to-head trials against all other classes of medications commonly used in the condition and consensus guidelines.^{23,24,27,28,30,31} Typically, SABAs are administered 15 to 20 minutes before exercise in a dose of albuterol (salbutamol) 0.2 to 0.4 mg inhaled or terbutaline 0.5 to 1.0 mg inhaled. They have a rapid onset and duration of action of 2 to 4 hours.³²

Although effective in most patients, multiple studies in both children and adults, using a variety of exercise challenges, indicate SABAs may not protect against EIB in roughly 15% to 20% of patients.^{32–34} Chronic SABA administration may lead to tolerance, defined as a lack of broncho-protection or shortened duration of broncho-protection that occurs after repeated medication use, a phenomenon that affects treatment guidelines.^{23,31} Hancox and colleagues,³⁵ in 2002, demonstrated that daily use of salbutamol for 6 to 10 days resulted in decreased broncho-protection to exercise challenge and delayed the response to salbutamol given after exercise as a rescue in 8 participants. Inman and O'Byrne³⁶ demonstrated a similar decrease in broncho-protection in 10 participants after 7 days of regular use of albuterol, although albuterol was effective after exercise in their trial. The mechanism for development of tolerance is suspected to be downregulation of beta₂ receptors on mast cells and airway smooth muscle.³⁷ The clinical significance of SABA tolerance in athletes is unknown. Furthermore, the prevalence of tolerance among elite athletes and threshold dosing to induce tolerance are also unknown. Thus, the current guidelines suggest if SABAs are needed daily for EIB, an additional agent should be added to decrease the frequency of SABA use.²³ With respect to treatment of elite athletes, it is important to know that regulations change over time. The WADA's current regulations require therapeutic use exemptions (TUEs) for all selective and nonselective SABAs except inhaled albuterol (salbutamol, with a maximum dosage of 1600 µg over 24 hours or 800 µg over 12 hours).²⁵

Alternative First-Line Therapies and Additions to Short-Acting Beta-Agonist Therapy

Inhaled corticosteroids

Inhaled corticosteroid (ICS) can be used as specific therapy for EIBa and EIBwa, with effectiveness associated with the duration of therapy and dosage. Although a single

dose of ICS improves EIB airflow physiology,^{38,39} the measured benefit of low-dose ICS increases incrementally to a plateau that may occur weeks after initiating therapy.^{40,41} Increased broncho-protection has been measured with high-dose ciclesonide regimens when compared with low-dose regimens in a trial evaluating incremental doses.⁴¹ With regard to the treatment of elite athletes, current (WADA) regulations permit the use of ICSs and require TUEs for oral, intravenous, intramuscular, and rectal administration of glucocorticoids.²⁵

Long-acting beta₂ agonists

As SABAs did not resolve all symptoms in all patients, there is a need to understand alternative therapies for patients who are nonresponders to SABAs and adjunctive therapies for patients who are partially responsive. Long-acting beta₂ agonists (LABAs) have also been demonstrated to be protective for EIB with an expected longer duration of protection than SABAs,³² but they are not to be used without an undelining inflammatory controller with inhaled steroid.^{42–44} This tolerance is not diminished by adding ICS (**Fig. 1**).⁴⁵ As with chronic SABA use, the prevalence and impact of SABA tolerance in elite athletes using chronic LABAs are unknown. Concerns regarding serious adverse events associated with LABA use, specifically the increased risk of severe exacerbations and death, have led to recommendations that LABAs never be used as monotherapy for underlying asthma.^{27,28} Given the nature of these potential events, the recommendation against LABA monotherapy is reflected in guidelines in the management of EIB.^{23,24} With respect to the treatment of elite athletes, current (WADA) regulations require TUEs for all selective and nonselective LABAs except inhaled formoterol (with a maximum dosage of 54 µg over 24 hours) and inhaled salmeterol (with a maximum dosage of 200 µg over 24 hours).²⁵

Leukotriene receptor antagonists and 5-lipoxygenase inhibitors

As the cysteinyl leukotriene pathway has been demonstrated to be involved in the pathophysiology of EIB,^{46,47} LTRAs have been studied for decades as monotherapy and adjunct therapy for EIB.

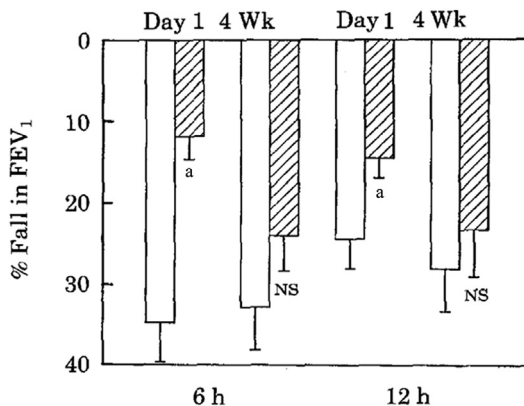


Fig. 1. Percentage decrease in forced expiratory volume in 1 second (FEV₁) after exercise challenge. NS, non significant. ^a Significant difference ($P < .05$) between salmeterol (▨), placebo (□). (From Ramage L, Lipworth BJ, Ingram CG, et al. Reduced protection against exercise induced bronchoconstriction after chronic dosing with salmeterol. *Respir Med* 1994;88(5):363–8; with permission.)

Several trials have demonstrated efficacy after a single dose of montelukast given 1 to 2 hours before exercise with protection documented at 12 and 24 hours after dosing.^{48,49} In a trial (of 10 subjects) evaluating multiple medications in these classes, single doses of montelukast, zafirlukast, and the 5-lipoxygenase inhibitor zileuton were all effective in preventing EIB.⁵⁰ Montelukast has been demonstrated to be effective in preventing EIB when used chronically without the development of tolerance, which is observed in patients chronically using SABAs and LABAs.^{51,52} There are few studies of LTRAs in isolated populations of athletes. Montelukast protected against EIB in collegiate hockey players in low- and high-particulate-matter environments (Fig. 2).^{53,54} With respect to the treatment of elite athletes, LTRAs and zileuton are both currently permitted under the WADA's regulations.²⁵

MAST CELL STABILIZING AGENTS

Mast cell stabilizing agents (MCSAs), such as cromolyn or nedocromil, have been used for decades in the treatment of EIB because the mast cell is known to play an important role in the pathophysiology of EIB.⁵⁵ The investigators of a Cochrane review concluded that MCSAs are effective in the treatment of EIB when compared with placebo but less effective than SABAs when trialed head-to-head and ineffective when used as a therapy in addition to SABAs.³⁰ Although it is theoretically possible that specific subgroups of patients preferentially respond to MCSAs, the use of these agents is somewhat limited, as these medications are not available in all countries. With respect to the treatment of elite athletes, MCSAs are currently permitted under the WADA's regulations.²⁵

ANTICHOLINERGIC AGENTS

Short-acting muscarinic antagonists (SAMAs), including ipratropium, which target muscarinic receptors on bronchial smooth muscle leading to relaxation and bronchodilation, are effective single agents when used for broncho-protection or bronchodilation in patients with EIB.^{21,56,57} Ipratropium is not as effective as SABAs in terms of

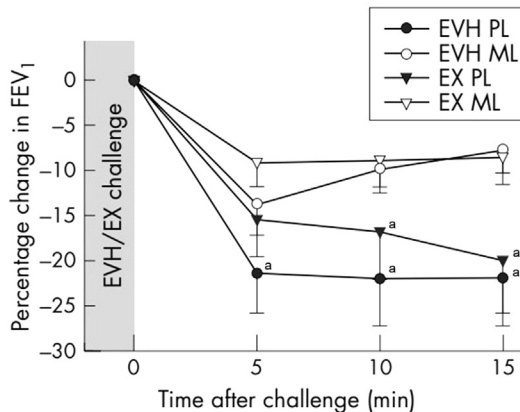


Fig. 2. Percentage change from baseline in forced expiratory volume in 1 second (FEV_1) 5, 10, and 15 minutes after the completion of eucapnic voluntary hyperventilation (EVH) and high-intensity 6-minute cycle ergometer challenge in cold-temperature-conditions (EX) trials on placebo (PL) and montelukast (ML) treatments. ^a Significant differences between placebo and montelukast for respective challenges at each time point. (From Rundell K, Spiering B, Baumann J, et al. Effects of montelukast on airway narrowing from eucapnic voluntary hyperventilation and cold air exercise. *Br J Sports Med* 2005;39(4):234; with permission.)

broncho-protective or bronchodilator activity; but it fills a clinical niche, as it maintains its effectiveness in patients with SABA tolerance given its alternative mechanism of action.^{57,58} There are also data demonstrating an additive benefit of ipratropium to albuterol in terms of acute asthma symptom control outside of exercise.⁵⁹ There are not data evaluating the efficacy of long-acting muscarinic antagonists (LAMAs), including tiotropium, for broncho-protection in EIB, although the medication has been evaluated (with and without LABA) with respect to its effect on exercise tolerance in patients with chronic obstructive pulmonary disease.^{60,61} With respect to treatment of elite athletes, SAMAs and LAMAs are currently permitted under the WADA's regulations.²⁵

SCIENTIFIC EXPERIENCE WITH MULTIDRUG THERAPY FOR EXERCISE-INDUCED BRONCHOCONSTRICTION

Clinical experience and experimental evidence suggests that there is a need to develop treatment strategies for patients who continue to struggle with symptoms of EIB despite the use of albuterol as a broncho-protective agent in EIBa and EIBwa.³² However, definitive evidence favoring specific agents for add-on therapy to SABA is scant because there are notable challenges to implementation of clinical trials designed to identify the relative effectiveness of SABA therapy adjuncts in EIB, including variability in measured bronchoconstriction across time within subjects, stratification of subjects based on the presence of EIBa versus EIBwa, and the effectiveness of SABAs. Given the lack of direct evidence, practice patterns may be driven by indirect evidence, including the effectiveness of controller therapy regimens in patients with baseline asthma against bronchoconstriction caused as a result of exercise or surrogate challenge (performed without SABA broncho-protection).^{62–64}

APPROACH TO PATIENTS WITH DIFFICULT-TO-MANAGE EXERCISE-INDUCED BRONCHOCONSTRICTION

As experimental evidence is lacking regarding selection of the best add-on therapy to SABAs for the treatment of confirmed EIB, clinicians must interpret and prioritize related information.

The authors recommend 2 initial assessments. First, it is important to characterize patients who require add-on therapy as having EIBa or EIBwa. This decision is important because current guidelines suggest that clinicians view persistent exercise symptoms in patients with EIBa as a reflection of poorly controlled underlying asthma.²⁷ Secondly, it is important to characterize exercise frequency as daily versus less frequent. The reasoning behind this stratification is related to the development of SABA tolerance and guideline recommendations to institute add-on therapy in patients requiring daily SABAs.²³

In patients with EIBwa, it is especially important to determine exercise frequency and SABA use frequency with an eye toward avoiding tolerance. In patients who exercise daily and use SABAs daily (or more), recent consensus panels have strongly supported the addition of ICSs.²³ LTRAs are an option as well based on these guidelines in this circumstance.²³ In patients who do not exercise or use SABAs daily, recent guidelines suggest that add-on therapy for EIB may focus primarily on broncho-protection before exercise. In this case, the addition of SAMAs or MCSAs is a reasonable option.²³

In patients with EIBa and frequent EIB symptoms, the current guidelines strongly recommend the initiation of inhaled steroids as an initial daily therapy.^{27,28} With respect to underlying asthma, ICSs reduce mortality, exacerbation frequency, exacerbation severity, symptoms, and airway inflammation and improve lung function and

quality of life.^{65–68} Although a detailed review of baseline asthma management is beyond the scope of this review, step-up therapy options from low-dose ICSs include the addition of LABAs, LTRAs, or transition to medium-dose ICSs.^{27,69} Tiotropium has also been studied in adults as an add-on therapy in moderate asthma management.^{70,71} When clinicians are treating patients with EIBa who perform daily exercise in whom step-up from low-dose ICSs is indicated, it is rational to consider moderate-dose ICSs preferentially over ICS/LABA combinations in order to avoid SABA tolerance.⁴¹ This theoretic benefit must be weighed against the documented decrements in linear growth velocity and adult height that accompany incremental increases in inhaled steroid usage in children and adolescents.⁷² It is important to note that there is not experimental evidence that confirms the effectiveness of this approach. A decision tree graphically representing this logic is reproduced (Fig. 3).

EXERCISE-INDUCED BRONCHOCONSTRICTION THERAPY STRATIFIED BY ENDO-TYPE

As our ability to characterize the biology of patients improves, it is possible to envision EIB therapy decision trees based on inflammatory profiles or other biological parameters that can be linked to a distinct mechanism. A pilot trial for this type of decision-making has been completed in patients with mild intermittent asthma (which is not synonymous with EIBwa).²⁰ In this trial, subjects demonstrated a differential EIB response to incremental doses of ICS, with the response associated with steroid-

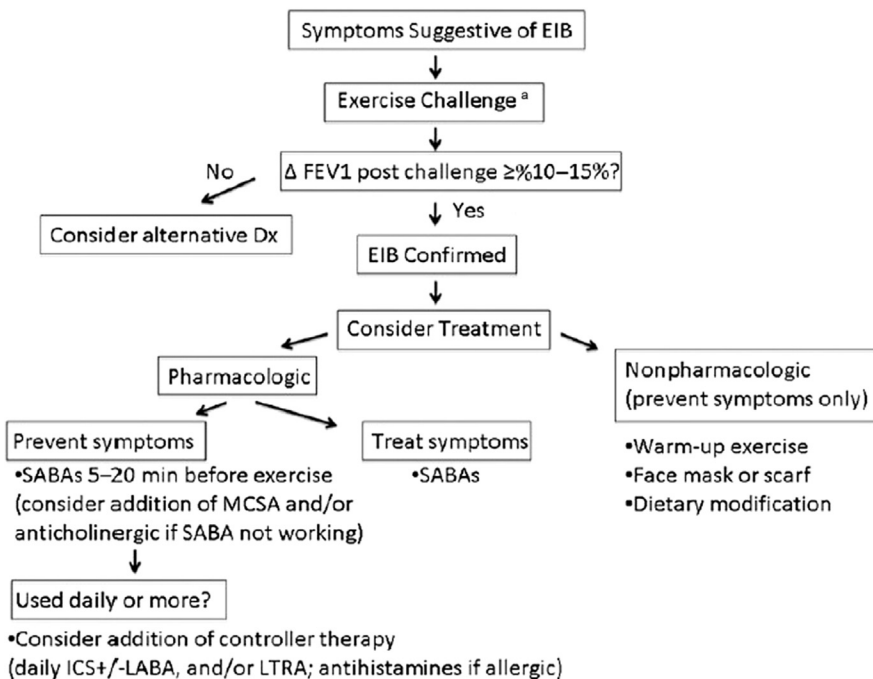


Fig. 3. Diagnostic and treatment algorithm for EIB. Dx, diagnosis. ^a Or surrogate challenge, for example, hyperpnea or mannitol. (From Parsons JP, Hallstrand TS, Mastroradarde JG, et al. An Official American Thoracic Society Clinical Practice Guideline: Exercise-induced Bronchoconstriction. *Am J Respir Crit Care Med* 2013;187(9):1018; Reprinted with permission of the American Thoracic Society. Copyright © 2018 American Thoracic Society. The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society.)

naïve sputum eosinophil counts. Subjects with sputum eosinophil counts greater than 5% responded to the low-dose ICS (defined as an experiencing a decrease in postexercise decrement in forced expiratory volume in 1 second [FEV₁]), with an enhanced response to a high-dose ICS. Subjects with sputum eosinophil counts less than 5% also responded to a low-dose ICS but did not show an enhanced response to a high-dose ICS.

Elite Nordic skiers may have a different inflammatory phenotype than other patients with EIBa or EIBwa, with a notably low eosinophil count.^{18,73} Currently, there are no specific data that favor a specific medication strategy in this group of patients. Future clinical trials of SAMAs and LAMAs may be warranted in Nordic skiers with EIB based on the experimental observation that elite athletes in general have increased vagal tone compared with population controls.⁷⁴

TREATMENT OF ACUTE EXACERBATION IN ELITE ATHLETES AND THE DOPING PERSPECTIVE

Athletes with asthma and the providers who are responsible for medication prescription must be cognizant of the WADA's regulations that are relevant to asthma exacerbations, defined by symptomatic or physiologic criteria.⁷⁵ As with all patients, there are strong recommendations to treat asthma exacerbations with oral steroids and increases in bronchodilators.²⁷ However, it is important to note that the use of oral, intramuscular, intravenous, and rectal corticosteroids requires a TUE under the WADA's current regulations.²⁵ With respect to bronchodilators, inhaled SABAs and inhaled LABAs are permitted, subject to the dosing restrictions noted earlier, under the WADA's current regulations.²⁵ Urinary measures of SABAs and LABAs that exceed threshold levels thought to correlate with maximal inhaled dosing are considered adverse analytical findings.²⁵ SAMAs and LAMAs are currently permitted per the WADA's regulations.²⁵ Further specific information is available online at the following address: www.globaldro.org.

SUMMARY

Several pharmacologic agents are available and effective in the treatment of EIBa and EIBwa, with SABAs demonstrating head-to-head advantages over all other medication classes. An estimated 15% of patients suboptimally respond to SABAs and require a second agent to manage the disease. In these situations, and the authors recommend, stratifying treatment based on the presence or absence of underlying asthma and the frequency of exercise and SABA use, a strategy promoted in recent guidelines. In the future, stratification may be driven by endo-typic characterization of patients. Athletes with EIB and their health care providers must be cognizant of the WADA's regulations, which can change over time and currently mandate TUEs for multiple classes of medications used in the treatment of EIB and asthma exacerbations.

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