Practice parameter

Exercise-induced bronchoconstriction update—2016

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The first practice parameter on exercise-induced bronchoconstriction (EIB) was published in 2010. This updated practice parameter was prepared 5 years later. In the ensuing years, there has been increased understanding of the pathogenesis of EIB and improved diagnosis of this disorder by using objective testing. At the time of this publication, observations included the following: dry powder mannitol for inhalation as a bronchial provocation test is FDA approved however not currently available in the United States; if baseline pulmonary function test results are normal to near normal (before and after bronchodilator) in a person with suspected EIB, then further testing should be performed by using standardized exercise challenge or eucapnic voluntary hyperpnea (EVH); and the efficacy of nonpharmaceutical interventions (omega-3 fatty acids) has been challenged. The workgroup preparing this practice parameter updated contemporary practice guidelines based on a current systematic literature review. The group obtained supplementary literature and consensus expert opinions when the published literature was insufficient. A search of the medical literature on PubMed was conducted, and search terms included pathogenesis, diagnosis, differential diagnosis, and therapy (both pharmaceutical and nonpharmaceutical) of exercise-induced bronchoconstriction or exercise-induced asthma (which is no longer a preferred term); asthma; and exercise and asthma. References assessed as relevant to the topic were evaluated to search for additional relevant references. Published clinical studies were appraised by category of evidence and used to document the strength of the recommendation. The parameter was then evaluated by Joint Task Force reviewers and then by reviewers assigned by the parent organizations, as well as the general membership. Based on this process, the parameter can be characterized as an evidence- and consensus-based document. (J Allergy Clin Immunol 2016;■■■:■■■-■■■.)

Key words: *Exercise-induced bronchoconstriction, exercise-induced bronchospasm, exercise-induced asthma, exercise-induced bronchoconstriction pathogenesis, diagnosis, differential diagnosis and therapy, nonpharmacologic, pharmacologic*

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Received for publication February 24, 2016; revised May 13, 2016; accepted for publication May 25, 2016.
0091-6749/$36.00
© 2016 American Academy of Allergy, Asthma & Immunology
http://dx.doi.org/10.1016/j.jaci.2016.05.029

These parameters were developed by the Joint Task Force on Practice Parameters (JTFPP), representing the American Academy of Allergy, Asthma & Immunology (AAAAI); the American College of Allergy, Asthma & Immunology (ACAAI); and the Joint Council of Allergy, Asthma & Immunology.

The AAAAI and ACAAI have jointly accepted responsibility for establishing "Exercise-induced bronchoconstriction update—2016." This is a complete and comprehensive document at the current time. The medical environment is a changing environment, and not all recommendations will be appropriate for all patients. Because this document incorporated the efforts of many participants, no single individual, including those who served on the JTFPP, is authorized to provide an official AAAAI or ACAAI interpretation of these practice parameters. Any request for information about or an interpretation of these practice parameters by the AAAAI or ACAAI should be directed to the Executive Offices of the AAAAI or the ACAAI.

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EIB EXECUTIVE SUMMARY

The first practice parameter on exercise-induced bronchoconstriction (EIB) was published in 2010. This update is required by the National Clearinghouse and JTF consistent with the requirement of an update every 5 years.

In the ensuing years, since the first publication of the EIB practice parameter, there has been increased understanding of the pathogenesis of EIB and improved diagnosis of this disorder by using objective pulmonary function tests. At the time of this publication, dry powder mannitol for inhalation is no longer available in the United States but is available in many other countries.

If baseline pulmonary function test results are normal to near normal (before and after bronchodilator) in a person with suspected EIB, then further testing should be performed by using a standardized exercise challenge or eucapnic voluntary hyperpnea (EVH).

Since 2010, the efficacy of nonpharmaceutical interventions, such as omega-3 fatty acids, has been challenged and needs validation.

This updated 2016 practice parameter was commissioned by the JTF to capture recent advances in the field of EIB, as elucidated in the most recent literature.

The chair of this workgroup, Dr John Weiler, convened workgroup members who are recognized as experts in the field of EIB. The members have been reviewed for conflicts of interest by the JTF, and conflicts of interest have been listed by the JTF on the JTF Web site at http://www.allergyparameters.org.

During the development of this practice parameter, at the request of the JTF, the workgroup also recruited a patient advocate to provide a dimension from the patient's perspective.

The workgroup was asked to update contemporary practice guidelines based on a current systematic literature review. The workgroup obtained supplementary literature, and consensus expert opinions were used when published literature was insufficient.

A search of the medical literature on PubMed was conducted, and all reference categories were included. Search terms included pathogenesis, diagnosis, differential diagnosis, and therapy (both pharmaceutical and nonpharmaceutical) of exercise-induced bronchoconstriction, or exercise-induced asthma (which is no longer a preferred term); asthma; and exercise and asthma.

References assessed as relevant to the topic were evaluated to search for other relevant references. Published clinical studies were appraised by category of evidence and used to document the strength of the recommendation (see category of evidence and strength of recommendation ratings). The parameter was then evaluated by JTF reviewers and then by reviewers assigned by the AAAAI and ACAAI, as well as the general memberships of the AAAAI and ACAAI. Based on this process, the parameter can be characterized as an evidence- and consensus-based document.

The pathophysiology of EIB has been elucidated in the last 2 decades. Strenuous exercise is known to create a hyperosmolar environment by introducing dry air in the airway with compensatory water loss, leading to transient osmotic change on the airway surface. The hyperosmolar environment leads to mast cell degranulation with release of mediators, predominately leukotrienes, but also including histamine, tryptase, and prostaglandins. In addition, eosinophils can also be activated, producing further mediators, including leukotrienes. In turn, this might lead to bronchoconstriction and inflammation of the airway, as well as stimulation of sensory nerves, with neurokinin release stimulating release of the gel-forming mucin MUC5AC. The water content of the inspired air, the level of ventilation achieved and maintained during exercise, or both are the major determinants of EIB. The major trigger for bronchoconstriction in

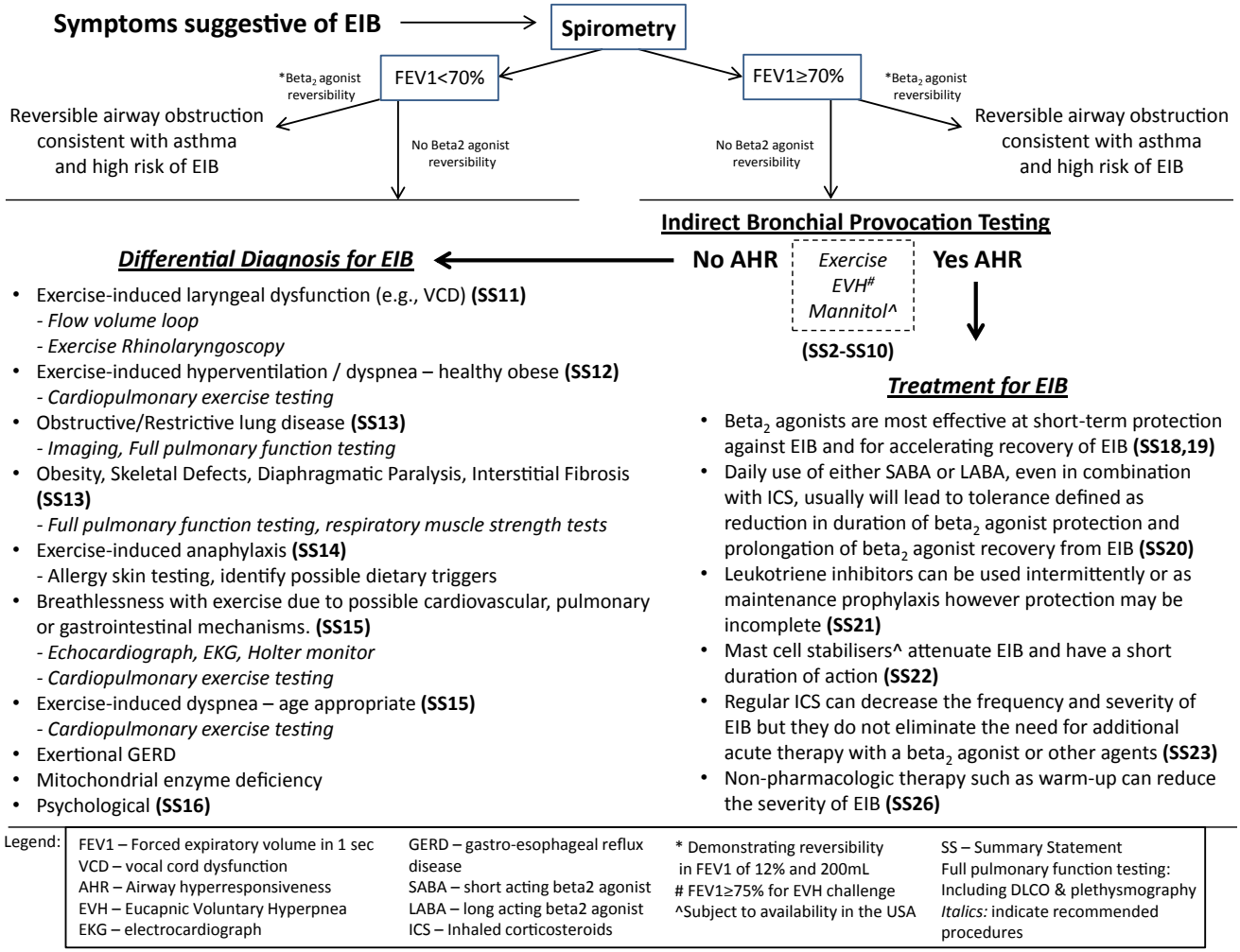

FIG 1. Algorithm for the diagnosis, treatment, and differential diagnosis of EIB.

a vulnerable subject is either the loss of water during periods of high ventilation or the addition of an osmotically active agent. Alterations in airway temperature develop during exercise, but thermal factors are thought to have only a minor effect on the amount of bronchoconstriction that occurs.

Exercise itself is not needed to cause bronchoconstriction, just the creation of a hyperosmolar environment. Diagnosis of EIB is made by using exercise or hyperosmolar surrogate challenges, such as EVH or mannitol. If pulmonary function test (PFT) results are normal, then exercise challenge or surrogate hyperosmolar challenge, such as with mannitol or EVH, should be performed.

Management of EIB is based on the understanding that EIB susceptibility varies widely among asthmatic patients, as well as those who do not have other features of asthma. Therefore EIB can occur in the presence or absence of asthma. Vulnerable subjects have characteristics of both airway inflammation with infiltration of the airways by mast cells and eosinophils and airway smooth muscle with hyperresponsiveness. These observations indicate that treatment should be based on the awareness that exercise causes release of mediators, including predominantly leukotrienes but also tryptase, prostaglandins, and histamine, to act on smooth muscle, leading to bronchoconstriction after exercise.

Therefore therapeutic interventions include short-acting β_2-agonists to provide bronchodilation and bronchoprotection. Additionally, anti-inflammatory medications, including inhaled steroids and leukotriene receptor antagonists (LTRAs) or combination therapy (with inhaled corticosteroids and long-acting β_2-agonists [LABAs]), are recommended for inflammation. Combination therapy that includes a LABA should not be used in persons with normal or near-normal baseline lung function (ie, FEV_1 >80% of predicted value) because regular use of short-acting β_2-agonists and LABAs can cause tolerance, limiting their ability to provide bronchoprotection and bronchodilation.

Use of face masks might promote humidification and prevent water loss, attenuating EIB.

The prevalence (Summary Statements 1-4) of EIB is poorly defined because there is no gold standard for diagnosis. EIB is frequently documented with asthma and reflects insufficient control of underlying asthma. Elite athletes have a higher prevalence of EIB than seen in the general population, varying with the intensity of exercise and the environment. EIB should be diagnosed by means of objective testing, preferably by using standardized bronchoprovocation challenge, because the prevalence of EIB varies with the type of challenge and climatic

conditions of relative humidity and temperature. It is important to reiterate that there is no firm consensus for a positive response or the conditions under which exercise should be performed.

Diagnosis (Summary Statements 5-10) of EIB relies on performing a standardized bronchoprovocation challenge in a subject who has been shown to have normal to near-normal PFT results both before and after bronchodilator (Fig 1). Self-reported symptoms and therapeutic trials without a diagnosis are not diagnostic. In a subject who has no history of current clinical asthma, normal PFT results, and no response to bronchodilator, an exercise challenge with a treadmill or cycle or in the sport venue or a surrogate challenge, such as EVH, can be indicated. With exercise challenge, the patient should achieve a heart rate at least 85% of maximum value (95% in children) for 6 minutes after 2 to 4 minutes of ramping up.

If EIB is to be investigated in a patient with known asthma, a graded challenge with inhaled mannitol, if available, might be preferable for reasons of safety to diagnose EIB. If there is no response to a graded challenge and EIB is still suspected, then consider an ungraded challenge.

Differential diagnosis (Summary Statements 11-16) of EIB requires distinguishing inspiratory stridor alone from inspiratory stridor with or without expiratory wheezing. This is essential to differentiate EIB from exercise-induced laryngeal dysfunction. Diagnosis requires performance of an appropriate exercise challenge, direct or indirect surrogate challenge, and flexible laryngoscopy. Providers should determine whether exercise-induced dyspnea and hyperventilation are masquerading as asthma. Furthermore, it is essential to perform spirometry and a focused detailed physical examination if shortness of breath with exercise is associated with underlying conditions, such as chronic obstructive pulmonary disease (COPD) or restrictive lung conditions. Providers should differentiate between exercise-induced anaphylaxis and EIB based on history of shortness of breath accompanied by pruritus, urticaria, and low blood pressure. Appropriate cardiopulmonary testing and referral to an appropriate specialist might be required when breathlessness with exercise with or without chest pain is caused by these mechanisms in the absence of EIB. A psychological evaluation can also be performed when history is suggestive of a psychiatric disorder (Fig 1).

Therapy (Summary Statements 17-28) for EIB requires re-evaluation of patients with frequent EIB, which suggests poor asthma control, and those who do not have appropriate management. Providers should recognize that there is intrapatient and interpatient variability in the effectiveness of pharmacotherapeutic agents on an individual basis. Patients should be scheduled to have regular follow-up of their therapy to determine the effectiveness of the medication. Medications can differ in effectiveness over time because of the variability of asthma, environmental conditions, intensity of exercise, and tolerance to β_2-agonists, as well as patient compliance (Fig 1).

Inhaled β_2-agonist monotherapy should be used only for short-term prophylaxis against EIB. Providers should only use a single dose of short-acting β_2-agonist (SABA) and/or LABA on an intermittent basis because this might protect against or attenuate EIB. SABAs are effective for 2 to 4 hours and LABAS for up to 12 hours. Caution is recommended in daily use of β_2-agonists alone or in combination with inhaled corticosteroids (ICSs) because this can lead to tolerance. Tolerance can manifest as a reduction in duration and magnitude of protection against EIB and a prolongation of recovery in response to SABAs after exercise.

Leukotriene modifiers can be used daily or intermittently to prevent EIB and do not lead to tolerance. However, they can provide incomplete protection and cannot reverse existing airway obstruction. Mast cell stabilizers, such as cromolyn and nedocromil, can be given shortly before exercise to attenuate EIB but have a short duration of action either alone or as added therapy with other drugs for EIB. These agents are not currently available in the United States.

ICSs taken alone or in combination with other therapies can decrease the frequency and severity of EIB. However, ICSs do not eliminate EIB in all subjects, and ICS therapy might not prevent occurrence of tolerance from daily LABA therapy.

Anticholinergic agents provide inconsistent results in attenuating EIB. Methylxanthines and antihistamines should be used cautiously or selectively because they have inconsistent results.

Nonpharmacologic therapy is recommended by using pre-exercise warm-up to prevent EIB and partially reduce the severity of EIB. Dietary supplementation with fish oil (ie, omega-3 fatty acids) and ascorbic acid and measures to reduce sodium intake are inconclusive in reducing the severity of EIB.

Competitive and elite athletes can have EIB alone, which might have different characteristics to those seen in patients with EIB with asthma in relation to pathogenesis, presentation, diagnosis, management, and requirements by governing bodies for permission to use pharmaceutical agents. However, recent studies indicate that both recreational and elite athletes with EIB with asthma can be treated in a similar manner. EIB alone, without underlying asthma, although not extensively studied in athletes, responds to similar treatment as with asthma. The presence of EIB reflects active asthma. Good control of EIB can be attained with the management discussed above, leading to a healthy lifestyle, including regular exercise and pursuit of the chosen sport.

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0091-6749/$36.00
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SUMMARY OF CONFLICT OF INTEREST DISCLOSURES

The following is a summary of interests disclosed on workgroup members' conflict of interest disclosure statements (not including information concerning family member interests). Completed conflict of interest disclosure statements are available on request.

Workgroup member	Disclosures
John Weiler, MD	*Employment and stockholder*: CompleWare Corporation *Stockholder*: Iowa Clinical Research Corporation
Christopher Randolph, MD	*Consultant*: GlaxoSmithKline, Astra, TEVA, and Sanofi *Advisory boards*: Astra, TEVA, and Sanofi *Speaker*: GlaxoSmithKline, Astra, TEVA, Sanofi, and Shire *Grants*: GlaxoSmithKline, Astra, Amgen, Genentech, and Merck
John D. Brannan, PhD	Receives a 10% share of royalties for Aridol/Osmohale given to Royal Prince Alfred Hospital, Sydney, Australia provided by Pharmaxis, Australia *Stockholder*: Pharmaxis At the time of writing, Aridol was not available in the United States but is US Food and Drug Administration approved
Teal Hallstrand, MD	No conflicts
Jonathan Parsons, MD	No conflicts
William Silvers, MD	No conflicts
William Storms, MD	*Grants*: Amgen, Genentech/Novartis, GlaxoSmithKline, Circassia, Meda, Mylan, Sanofi, Sunovion, and TEVA *Consultant*: Amgen, Astra, Bosch & Lomb, Merck, Sunovion, and TEVA *Speaker*: Astra, Genentech, Merck, Sanofi, and TEVA
Joanna Zeiger	No conflicts

Resolution of potential conflicts of interest

The JTF recognizes that experts in a field are likely to have interests that could come into conflict with development of a completely unbiased and objective practice parameter. A process

has been developed to prevent potential conflicts from influencing the final document in a negative way to take advantage of that expertise.

At the workgroup level, members who have a potential conflict of interest either do not participate in discussions concerning topics related to the potential conflict, or if they do write a section on that topic, the workgroup completely rewrites it without their involvement to remove potential bias. In addition, the entire document is reviewed by the JTF, and any apparent bias is removed at that level. Finally, the practice parameter is sent for review both by invited reviewers and by anyone with an interest in the topic by posting the document on the Web sites of the ACAAI and the AAAAI.

Statement	Definition	Implication
Strong recommendation (StrRec)	A strong recommendation means the benefits of the recommended approach clearly exceed the harms (or that the harms clearly exceed the benefits in the case of a strong negative recommendation) and that the quality of the supporting evidence is excellent (Grade A or B).* In some clearly identified circumstances, strong recommendations might be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits strongly outweigh the harms.	Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
Moderate (Mod)	A recommendation means the benefits exceed the harms (or that the harms exceed the benefits in the case of a negative recommendation), but the quality of evidence is not as strong (grade B or C).* In some clearly identified circumstances, recommendations might be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits outweigh the harms.	Clinicians should also generally follow a recommendation but should remain alert to new information and sensitive to patient preferences.
Weak (Weak)	An option means that either the quality of evidence that exists is suspect (grade D)* or that well-done studies (grade A, B, or C)* show little clear advantage to one approach versus another.	Clinicians should be flexible in their decision making regarding appropriate practice, although they might set bounds on alternatives; patient preference should have a substantial influencing role.
No recommendation (NoRec)	No recommendation means there is both a lack of pertinent evidence (grade D)* and an unclear balance between benefits and harms.	Clinicians should feel little constraint in their decision making and be alert to new published evidence that clarifies the balance of benefit versus harm; patient preference should have a substantial influencing role.

I. CLASSIFICATION OF RECOMMENDATIONS AND EVIDENCE

Recommendation rating scale

Category of evidence

- Ia Evidence from meta-analysis of randomized controlled trials
- Ib Evidence from at least 1 randomized controlled trial
- IIa Evidence from at least 1 controlled study without randomization
- IIb Evidence from at least 1 other type of quasiexperimental study
- III Evidence from nonexperimental descriptive studies, such as comparative studies
- IV Evidence from expert committee reports or opinions, clinical experience of respected authorities, or both

Strength of recommendation*

- A Directly based on category I evidence
- B Directly based on category II evidence or extrapolated recommendation from category I evidence
- C Directly based on category III evidence or extrapolated recommendation from category I or II evidence
- D Directly based on category IV evidence or extrapolated recommendation from category I, II, or III evidence
- LB Laboratory based
- NR Not rated

HOW THIS PRACTICE PARAMETER WAS DEVELOPED

The Joint Taskforce on Practice Parameters

The JTFPP is a 12-member task force consisting of representatives assigned by the AAAAI and the ACAAI. This task force oversees the development of practice parameters; selects the workgroup chair or chairs; and reviews drafts of the parameters for accuracy, practicality, clarity, and broad utility of the recommendations for clinical practice.

The Exercise-induced Bronchoconstriction Workgroup

The Exercise-induced Bronchoconstriction Practice Parameter Workgroup was commissioned by the JTF to develop and update a practice parameters that address the pathogenesis, diagnosis and differential diagnosis, epidemiology, management, and treatment, both pharmaceutical and nonpharmaceutical, of EIB.

The chair (John Weiler, MD) invited workgroup members who are considered experts in the field of EIB to participate in the parameter update development. Workgroup members have been vetted for financial conflicts of interest by the JTF, and their conflicts of interest have been listed in this document and are posted on the JTF Web site at http://www.allergyparameters.org. Where a potential conflict of interest is present, the potentially conflicted workgroup member was excluded from discussing relevant issues.

The charge to the workgroup was to use a systematic literature review in conjunction with consensus expert opinion and workgroup-identified supplementary documents to develop practice parameters that provide a comprehensive approach for understanding the pathogenesis, diagnosis and differential diagnosis, epidemiology, management, and treatment, both pharmaceutical and nonpharmaceutical, of EIB.

The authors note that this document contains an update of the earlier practice parameter[E1] and other documents published by various entities (the American Thoracic Society [ATS], AAAAI, GALEN, National Athletic Trainers Association, and Agency for Healthcare Research & Quality).

Protocol for finding evidence

Search terms and programs encompassed PubMed review or meta-analysis (2010-2014) for exercise-induced asthma (60 references), exercise-induced bronchospasm (93 references), exercised-induced bronchoconstriction (55 references), clinical or randomized controlled trial exercise-induced asthma (114 references), exercise-induced bronchospasm (174 references), and exercise-induced bronchoconstriction (99 references) in the last 5 years; National Institute for Health and Care Excellence (NICE) evidence search for exercise-induced asthma systematic review in the last 3 years (76 references), exercise-induced bronchoconstriction (36 references), and exercise induced-bronchospasm (26 references) in the last 3 years; NICE primary research for exercise-induced bronchoconstriction (3 references) and exercise-induced asthma (10 references); the Trip Database for exercise from 2010 systematic review for exercise-induced asthma (7 references), exercise-induced bronchoconstriction (13 references), exercise-induced bronchospasm (20 references), controlled clinical trial exercise-induced bronchospasm (11 references), exercise-induced bronchoconstriction (56 references), and exercise-induced asthma (77 references); the Health Services/Technology Assement Texts (HSTAT) collection for exercise-induced asthma (59 references); clinicaltrials.gov for exercise-induced asthma (78 references), exercise-induced bronchoconstriction (35 references), and exercise-induced bronchospasm (19 references); Cumulative Index of Nursing and Allied Health Literature (CINAHL) meta-analysis systematic review (2010) for exercise-induced bronchoconstriction and exercise bronchospasm (21 references), randomized control or clinical trial (77 references); Exerpta Medica database (EMBASE) for exercise bronchospasm (107 references), exercise-induced bronchoconstriction (232 references), exercise or exercise and induced asthma 2010-2014 (813 references), same search terms without year limit 4543 references, clinical or randomized control trial (38 references), clinical trial and controlled study (190 references); Sport Discus for exercise-induced asthma, exercise-induced asthma, bronchospasm, exercise-induced bronchoconstriction 2010 on (76 references); and ahrq.gov for exercise-induced bronchoconstriction, exercise-induced asthma, and exercise-induced bronchospasm (1 reference).

References identified as being relevant were evaluated and searched for additional references, which were searched also for citable references. In addition, members of the workgroup were asked to identify references of which they were aware that were missed by this initial search.

II. GLOSSARY

Exercise-induced bronchoconstriction (EIB) is defined as a transient narrowing of the lower airway after exercise in the presence or absence of clinically recognized asthma. The term *exercise-induced asthma* (EIA) is not used in this document because it might imply incorrectly that exercise causes rather than exacerbates or triggers an asthma attack.

Bronchial hyperresponsiveness (BHR) or *airway hyperresponsiveness* is an increase in sensitivity to an agent and is expressed as the dose or concentration of a substance that produces a specific decrease in FEV_1 (eg, PD_{20} or PC_{20}, respectively).

Bronchial reactivity is the rate of change in FEV_1 in relation to the dose or stimulus (eg, response/dose ratio with mannitol is the percentage decrease divided by the dose that achieves that decrease or the percentage decrease in exercise in response to the optimal stimulus).

Competitive athletes are persons who engage in strenuous aerobic activity at any level from grade school age and older.

Conditioning is defined as preparing the body for physical exercise and, in particular, sports performance. It is also a term used in relation to the heat and humidity conditions of the inspired air whereby water and heat are transferred to the air so that they match lower airway conditions.

Direct challenges are those in which a single pharmacologic agent, such as methacholine or histamine, is the provoking substance administered exogenously that acts directly through receptors on airway smooth muscle to cause contraction.

Elite athletes are highly competitive persons who train and compete consistently at higher levels (eg, Olympics or professional aerobic sports).

Eucapnic voluntary hyperpnea (EVH) describes a type of indirect challenge in which a subject inhales a eucapnic gas mixture (5% CO_2, 21% O_2, and balance N_2) for about 6 minutes and then performs spirometry.

Graded challenge is a challenge test in which an agent is administered by means of inhalation at increasing doses or concentration to cause a decrease in FEV_1. This permits the construction of a dose-response curve to determine the degree of airway sensitivity and is expressed as a provoking dose or provoking concentration.

Indirect challenges are those in which exercise or a surrogate, such as EVH; inhaled osmotic agents, such as mannitol or hypertonic saline; or inhalation of AMP is the provoking agent that in turn triggers endogenous mediator release that acts to cause airway smooth muscle contraction.

Tolerance is a decrease in the degree, duration, or both of response to an agent when used continuously instead of intermittently. Tolerance ordinarily refers to inhibition of bronchoconstriction and in some cases bronchodilation to β_2-adrenergic agents.

Ungraded challenges are challenges in which a single episode of hyperpnea (dose) is administered to cause a specific decrease in

FEV_1. FEV_1 is measured regularly over more than 1 time point at the conclusion of the challenge. No dose-response curve can be constructed, but the severity of the response is based on the decrease in FEV_1 (eg, laboratory or field exercise and EVH).

Exercise challenge in the assessment of asthma requires effort that is ramped up rapidly so that maximum heart rate should be achieved within 2 to 3 minutes. This should be considered for both laboratory-based exercise challenge tests with a treadmill or cycle ergometer and when performing field-based exercise challenge. This exercise protocol is more intensive in the initial stages of exercise than a cardiopulmonary exercise test, and it is for this reason that cardiopulmonary exercise testing is not recommended for investigating EIB.

III. PREFACE

The first practice parameter on EIB was published in 2010. This update is required by the National Clearinghouse and JTF consistent with the requirement of an update every 5 years.

In the ensuing years since the first publication of the EIB practice parameter, there has been increased understanding of the pathogenesis of EIB and improved diagnosis of this disorder by means of objective pulmonary function testing. At the time of this publication, dry powder mannitol for inhalation is not currently available in the United States but is available in many other countries.

If baseline pulmonary function test results are normal to near normal (before and after bronchodilator) in a person with suspected EIB, then further testing should be performed by using a standardized exercise challenge or EVH.

Since 2010, the efficacy of nonpharmaceutical interventions, such as omega-3 fatty acids, has been challenged and needs validation.

This updated 2016 practice parameter was commissioned by the JTF to capture recent advances in the field of EIB, as elucidated in the most recent literature.

The chair of this workgroup, Dr John Weiler, convened workgroup members who are recognized as experts in the field of EIB. The members have been reviewed for conflicts of interest by the JTF, and conflicts of interest have been listed by the JTF on the JTF Web site at http://www.allergyparameters.org.

During the development of this practice parameter, at the request of the JTF, the workgroup also recruited a patient advocate to provide a dimension from the patient's perspective.

The workgroup was asked to update contemporary practice guidelines based on a current systematic literature review. The workgroup obtained supplementary literature, and consensus expert opinions were used when published literature was insufficient.

A search of the medical literature on PubMed was conducted, and all reference categories were included. Search terms included pathogenesis, diagnosis, differential diagnosis, and therapy (both pharmaceutical and nonpharmaceutical) of exercise-induced bronchoconstriction or exercise-induced asthma (which is no longer a preferred term); asthma; and exercise and asthma.

References assessed as relevant to the topic were evaluated to search for other relevant references. Published clinical studies were appraised by category of evidence and used to document the strength of the recommendation (see the Category of evidence and Strength of recommendation ratings sections). The parameter was then evaluated by JTF reviewers and then by reviewers assigned by the AAAAI and ACAAI, as well as the general memberships of the AAAAI and ACAAI. Based on this process, the parameter can be characterized as an evidence- and consensus-based document.

IV. EXECUTIVE SUMMARY

The pathophysiology of EIB has been elucidated in the last 2 decades. Strenuous exercise is known to create a hyperosmolar environment by introducing dry air into the airway with compensatory water loss, leading to transient osmotic change on the airway surface. The hyperosmolar environment leads to mast cell degranulation with release of mediators, predominately leukotrienes, but also including histamine, tryptase, and prostaglandins. In addition, eosinophils can also be activated, producing further mediators, including leukotrienes. In turn, this can lead to bronchoconstriction and inflammation of the airway, as well as stimulation of sensory nerves with neurokinin release, stimulating the release of the gel-forming mucin MUC5AC. The water content of the inspired air, the level achieved and maintained during exercise, or both are the major determinants of EIB in subjects. The major trigger for bronchoconstriction in a vulnerable subject is either water loss during periods of high ventilation or the addition of an osmotically active agent. Alterations in airway temperature develop during exercise, but thermal factors are thought to have only a minor effect on the amount of bronchoconstriction that occurs.

Exercise itself is not needed to cause bronchoconstriction, just the creation of a hyperosmolar environment. Diagnosis of EIB is made by using exercise or hyperosmolar surrogate challenges, such as EVH or mannitol. If pulmonary function test (PFT) results are normal, then exercise challenge or surrogate hyperosmolar challenge, such as with mannitol or EVH, should be performed.

Management of EIB is based on the understanding that EIB susceptibility varies widely among asthmatic patients, as well as those who do not have other features of asthma. Therefore EIB can occur in the presence or absence of asthma. Vulnerable subjects have characteristics of both airway inflammation with infiltration of the airways by mast cells and eosinophils and airway smooth muscle with hyperresponsiveness. These observations indicate that treatment should be based on the awareness that exercise causes release of mediators, including predominantly leukotrienes, but also tryptase, prostaglandins, and histamine, to act on smooth muscle, leading to bronchoconstriction after exercise.

Therefore therapeutic interventions include short-acting β_2-agonists (SABAs) to provide bronchodilation and bronchoprotection. Additionally, anti-inflammatory medications, including inhaled corticosteroids (ICSs) and leukotriene receptor antagonists (LTRAs), or combination therapy (with ICSs and long-acting β_2-agonists [LABAs]) are recommended for inflammation. Combination therapy that includes a LABA should not be used in persons with normal or near-normal baseline lung function (ie, FEV_1 >80% of predicted value) because regular use of SABAs and LABAs can cause tolerance, limiting their ability to provide bronchoprotection and bronchodilation.

Use of face masks can promote humidification and prevent water loss, attenuating EIB.

The prevalence (Summary Statements 1-4) of EIB is poorly defined because there is no gold standard for diagnosis. EIB is frequently documented with asthma and reflects insufficient control of underlying asthma. Elite athletes have a higher prevalence of EIB than seen in the general population, varying

with the intensity of exercise and the environment. EIB should be diagnosed by means of objective testing, preferably standardized bronchoprovocation challenge, because the prevalence of EIB varies with type of challenge and climatic conditions of relative humidity and temperature. It is important to reiterate that there is no firm consensus for a positive response or the conditions under which exercise should be performed.

Diagnosis (Summary Statements 5-10) of EIB relies on performing a standardized bronchoprovocation challenge in a subject who has been shown to have normal to near-normal PFT results both before and after bronchodilator (Fig E1). Self-reported symptoms and therapeutic trials without a diagnosis are not diagnostic. In a subject who has no history of current clinical asthma, normal PFT results, and no response to bronchodilator, exercise challenge with a treadmill or cycle or in the sport venue or a surrogate challenge, such as EVH, might be indicated. With exercise challenge, the patient should achieve a heart rate at least 85% of maximum (95% in children) for 6 minutes after 2 to 4 minutes of ramping up.

If EIB is to be investigated in a patient with known asthma, a graded challenge with inhaled mannitol, if available, might be preferable for reasons of safety to diagnose EIB. If there is no response to a graded challenge and EIB is still suspected, then consider an ungraded challenge.

Differential diagnosis (Summary Statements 11-16) of EIB requires distinguishing inspiratory stridor alone from inspiratory stridor with or without expiratory wheezing. This is essential to differentiate EIB from exercise-induced laryngeal dysfunction. Diagnosis requires performance of appropriate exercise challenge, direct or indirect surrogate challenge, and flexible laryngoscopy. Providers should determine whether exercise-induced dyspnea and hyperventilation are masquerading as asthma. Furthermore, it is essential to perform spirometry and a focused detailed physical examination if shortness of breath with exercise is associated with underlying conditions, such as chronic obstructive pulmonary disease (COPD) or a restrictive lung condition. Providers should differentiate between exercise-induced anaphylaxis and EIB based on a history of shortness of breath accompanied by pruritus, urticaria, and low blood pressure. Appropriate cardiopulmonary exercise testing and referral to an appropriate specialist might be required when breathlessness with exercise with or without chest pain is caused by these mechanisms in the absence of EIB. A psychological evaluation can also be performed when history is suggestive of psychiatric disorder (Fig E1).

Therapy (Summary Statements 17-28) for EIB requires re-evaluation of patients with frequent EIB, which suggests poor asthma control, and those in whom appropriate management fails. Providers should recognize that there is intrapatient and interpatient variability in the effectiveness of pharmacotherapeutic agents on an individual basis. Patients should be scheduled to have regular follow-up of their therapy to determine the effectiveness of the medication. Medications can differ in effectiveness over time because of variability of asthma, environmental conditions, intensity of exercise, and tolerance to β_2-agonists, as well as patient compliance (Fig E1).

Inhaled β_2-agonist monotherapy should be used only for short-term prophylaxis against EIB. Providers should only use a single dose of SABA, LABA, or both on an intermittent basis because this can protect against or attenuate EIB. SABAs are effective for 2 to 4 hours and LABAS for up to 12 hours. Caution is recommended in daily use of β_2-agonists alone or in combination with ICSs because this can lead to tolerance. Tolerance can be manifested as a reduction in the duration and magnitude of protection against EIB and a prolongation of recovery in response to SABAs after exercise.

Leukotriene modifiers can be used daily or intermittently to prevent EIB and do not lead to tolerance. However, they can provide incomplete protection and cannot reverse existing airway obstruction. Mast cell stabilizers, such as cromolyn and nedocromil, can be administered shortly before exercise to attenuate EIB but have a short duration of action either alone or as added therapy with other drugs for EIB. These agents are not currently available in the United States.

ICSs taken alone or in combination with other therapies can decrease the frequency and severity of EIB. However, ICSs do not eliminate EIB in all subjects, and ICS therapy might not prevent occurrence of tolerance from daily LABA therapy.

Anticholinergic agents provide inconsistent results in attenuating EIB. Methylxanthines and antihistamines should be used cautiously or selectively because they have inconsistent results.

Nonpharmacologic therapy is recommended by using pre-exercise warm-up to prevent EIB and partially reduce the severity of EIB. Dietary supplementation with fish oil (ie, omega-3 fatty acids) and ascorbic acid and measures to reduce sodium intake are inconclusive in reducing the severity of EIB.

Competitive and elite athletes might have EIB alone, which can have different characteristics than are seen in patients with EIB with asthma in relation to pathogenesis, presentation, diagnosis, management, and requirements by governing bodies for permission to use pharmaceutical agents. However, recent studies indicate that both recreational and elite athletes with EIB with asthma can be treated in a similar manner. EIB alone, without underlying asthma, although not extensively studied in athletes, responds to similar treatment as with asthma. The presence of EIB reflects active asthma. Good control of EIB can be attained with the management discussed above, leading to a healthy lifestyle, including regular exercise and pursuit of the chosen sport.

V. SUMMARY STATEMENTS

Summary Statement 1: In asthmatic patients EIB can indicate lack of control of the underlying asthma. Therefore treat the uncontrolled asthma to get control of EIB. [Strength of Recommendation: Strong; Evidence: D]

Summary Statement 2: A diagnosis of EIB should be confirmed by demonstration of airways reversibility or challenge in association with a history consistent with EIB because self-reported symptoms are not adequate. [Strength of Recommendation: Strong; Evidence: B]

Summary Statement 3: Evaluate EIB in elite athletes by using objective testing. [Strength of Recommendation: Strong; Evidence: B]

Summary Statement 4: Perform a standardized bronchoprovocation (exercise or a surrogate) challenge to diagnose EIB because the prevalence of EIB will vary with the type of challenge and the conditions under which the challenge is performed. [Strength of Recommendation: Strong; Evidence: A]

Summary Statement 5: In subjects with no current clinical history of asthma, use an indirect ungraded challenge (eg, exercise challenge or surrogate testing, such as with EVH) for assessing EIB in the recreational or elite athlete who has normal lung function. [Strength of Recommendation: Strong; Evidence: D]

Summary Statement 6: Use an indirect graded challenge (eg, mannitol, if available) for assessing EIB in recreational or elite athletes who have normal to near-normal lung function and who might currently require treatment for the prevention of EIB or asthma. [Strength of Recommendation: Strong; Evidence: D]

Summary Statement 7: Perform an indirect challenge (eg, exercise challenge or surrogate testing, such as with EVH or mannitol, where available) instead of a direct challenge (eg, methacholine) for assessing EIB, recognizing that an indirect challenge is more sensitive for detection of EIB than a direct (eg, methacholine) challenge. [Strength of Recommendation: Strong; Evidence: B]

Summary Statement 8: Ensure the ventilation reached and sustained during exercise challenge testing is at least 60% of the maximum voluntary ventilation by using dry medical grade air to achieve an adequate challenge. If ventilation cannot be measured, ensure the heart rate as a percentage of maximum heart rate (HRmax) that is reached and sustained is at least 85% in adults and 95% in children and elite athletes. [Strength of Recommendation: Strong; Evidence: B]

Summary Statement 9: Perform EVH as the preferred surrogate challenge for the athlete without a current history of asthma participating in competitive sports in whom the diagnosis of EIB is suspected. [Strength of Recommendation: Strong; Evidence: D]

Summary Statement 10: If an indirect graded challenge (eg, mannitol) result is negative and EIB is still suspected, an ungraded challenge should be considered. [Strength of Recommendation: Weak; Evidence: B]

Summary Statement 11: To differentiate between EIB and exercise-induced laryngeal dysfunction (EILD), perform appropriate challenge tests (eg, exercise, EVH, and mannitol for EIB) and potentially flexible laryngoscopy during exercise for diagnosis of EILD. [Strength of Recommendation: Strong; Evidence: B]

Summary Statement 12: To determine whether exercise-induced dyspnea and hyperventilation are masquerading as asthma, especially in children and adolescents, perform cardiopulmonary exercise testing. [Strength of Recommendation: Moderate; Evidence: C]

Summary Statement 13: Perform spirometry, as well as detailed pulmonary examination, to determine whether shortness of breath with exercise is associated with underlying conditions, such as COPD, or restrictive lung conditions, such as obesity, skeletal defects (eg, pectus excavatum), diaphragmatic paralysis, or interstitial fibrosis, rather than EIB. [Strength of Recommendation; Moderate; Evidence: C]

Summary Statement 14: Consider a diagnosis of exercise-induced anaphylaxis (EIAna) instead of EIB based on a history of shortness of breath or other respiratory tract symptoms accompanied by systemic symptoms (eg, pruritis, urticaria, and hypotension). [Strength of Recommendation: Moderate; Evidence: C]

Summary Statement 15: Refer to appropriate specialists (eg, cardiologist or pulmonologist) to perform cardiopulmonary testing when breathlessness with exercise, with or without chest pain, might be caused by heart disease or other conditions in the absence of EIB. [Strength of Recommendation: Moderate; Evidence: C]

Summary Statement 16: Refer patients for psychological evaluation when the symptoms (eg, hyperventilation and anxiety disorders) are in the differential diagnosis of EIB. [Strength of Recommendation: Weak; Evidence: D]

Summary Statement 17: Schedule regular office visits with patients because medications can differ in effectiveness over time because of variability of asthma, environmental conditions, intensity of the exercise stimulus, and tachyphylaxis. [Strength of Recommendation: Strong; Evidence: A]

β_2-Adrenergic receptor agonists

Summary Statement 18: Prescribe inhaled short-acting β_2-adrenergic receptor agonists for protection against EIB and for accelerating recovery of pulmonary function when given after a decrease in pulmonary function after exercise. [Strength of Recommendation: Strong; Evidence: A][E2]

Summary Statement 19: Prescribe a single dose of SABA, LABA, or both on an intermittent basis (ie, <4 times per week) before exercise because this might protect against or attenuate EIB. [Strength of Recommendation: Strong; Evidence: A]

Summary Statement 20: Be cautious in daily use of β_2-adrenergic agents alone or in combination with ICSs because this can lead to tolerance manifested as a reduction in duration, magnitude, or both of protection against EIB and a prolongation of recovery in response to SABAs after exercise. [Strength of Recommendation: Strong; Evidence: A][E2]

Leukotriene inhibitors

Summary Statement 21: Consider prescribing daily therapy with leukotriene inhibitors because this does not lead to tolerance and has been shown to attenuate EIB in 50% of patients. It can also be used for intermittent or maintenance prophylaxis; however, it provides incomplete protection and is not effective for reversing airway obstruction. [Strength of Recommendation: Strong; Evidence: A][E2]

Mast cell stabilizers

Summary Statement 22: Consider prescribing inhaled cromolyn sodium and nedocromil sodium (currently not available in the United States as a metered-dose inhaler or dry powder inhaler) shortly before exercise; this attenuates EIB but can have a short duration of action. There is no bronchodilator activity. They might be effective alone or as added therapy with other drugs for EIB. [Strength of Recommendation: Strong; Evidence: A][E2]

ICSs

Summary Statement 23: Consider prescribing ICSs in combination with other therapies because ICSs can decrease the frequency and severity of EIB but not necessarily eliminate it. [Strength of Recommendation: Strong; Evidence: A][E2]

Summary Statement 24: Do not prescribe daily LABAs with ICS therapy to treat EIB unless needed to treat moderate-to-severe persistent asthma. The ICS might not prevent the occurrence of tolerance from daily β_2-agonist use. [Strength of Recommendation: Strong; Evidence: A]

Anticholinergic agents

Summary Statement 25: Consider prescribing inhaled ipratropium bromide for patients who have not responded to other agents; however, its ability to attenuate EIB is inconsistent. [Strength of Recommendation: Weak; Evidence: A][E2]

Nonpharmacologic therapy

Summary Statement 26: Prescribe pre-exercise warm-up for EIB because it can be helpful in reducing the severity of EIB. [Strength of Recommendation: Strong; Evidence: A][E2]

Summary Statement 27: Consider with caution the recommendation of reduction of sodium intake and ingestion of fish oil and ascorbic acid supplementation; results are questionable in reducing the severity of EIB. [Strength of Recommendation: Weak; Evidence: B][E2]

Competitive and elite athletes

Summary Statement 28: Treat athletes with EIB alone in a similar manner to those with EIB and asthma by using the recommended general treatments for asthma. This might require additional consideration in athletes in whom some governing bodies might have requirements for obtaining permission to receive pharmaceutical agents for competition. [Strength of Recommendation Strong; Evidence: A]

VI. PATHOPHYSIOLOGY

Definition and overview

A period of high ventilation causes respiratory water loss with cooling of the airways and a temporary increase in the osmolarity of the airway surface liquid (ASL) because of a loss of ASL volume. Changes in osmolarity occur only transiently and are rapidly resolved by the movement of water from the osmotically sensitive epithelium into the lumen. The responses of the airways to thermal gradients and the response to water loss and transient hyperosmolarity can act as independent stimuli for the airways to narrow. Cooling is a mechanical stimulus that could induce reactive hyperemia of the bronchial vasculature, whereas the response of the epithelium and other cells to changes in ASL volume and osmolarity is the most likely trigger for mediator release that serves as the primary stimulus for sustained bronchoconstriction.[E3,E4]

When air of subfreezing temperature is inspired during exercise, airway cooling causes vasoconstriction of the bronchial vasculature.[E5] On cessation of exercise, when ventilation decreases and the airways rewarm, a reactive hyperemia with vascular engorgement and edema of the airway wall occurs.[E4] This is known as the thermal theory of EIB. It is generally accepted that the thermal theory is inadequate to explain many of the events that occur in the airways after exercise challenge.[E6,E7] In a canine model ligation of the bronchial circulation did not attenuate hyperpnea-induced bronchoconstriction (HIB), indicating that the bronchial vasculature is not the primary mechanism of bronchoconstriction.[E6] In human subjects inspiring warm air after a challenge test with cold air has a modest effect on the amount of bronchoconstriction experienced 5 to 15 minutes after exercise.[E4]

The osmotic theory of EIB developed as it became apparent that cooling of the airways was not a prerequisite for EIB,[E8] changes in ASL osmolarity could be demonstrated with direct delivery of dry air in the peripheral airways,[E9] and the airways of asthmatic patients were sensitive to inhalation of osmotically active substances.[E10-E13] Dehydration of the ASL causes a transient increase in ion content and osmolarity when water from the ASL is evaporated faster than it is returned by means of condensation or from the epithelium or submucosa.[E14,E15] Dehydration of the ASL also results in reduction in ASL volume. Such a reduction in ASL volume reduces mucociliary clearance.[E16] These events have been demonstrated *in vivo* by a marked reduction in mucociliary clearance during dry air breathing both in asthmatic patients and healthy subjects.[E17]

The precise mechanism by which water loss and transient osmotic gradients lead to leukocyte activation is not certain. It is well known that mast cells and eosinophils release mediators in response to shifts in osmolarity.[E18-E20] Changes in ASL volume and osmolarity also trigger cellular signaling events in epithelial cells and the release of regulatory proteins from the epithelium that could be involved in leukocyte activation.[E3]

The osmotic and vascular theories of EIB can operate together under conditions of breathing cold dry air when vascular effects that can result in airway edema amplify the contractile effect of mediator release. As the temperature of the inspired air increases toward body temperature, the osmotic effects of water loss are more important than cooling.[E21-E23]

Exercise itself is not necessary to cause bronchoconstriction; voluntary hyperpnea of dry air induces bronchoconstriction similar to exercise in susceptible subjects.[E24,E25] Thus EVH of dry air containing 4.9% to 5% carbon dioxide is often used as a surrogate for exercise in the diagnosis of EIB, particularly in athletes.[E26-E29]

The EVH test for EIB was developed to evaluate military recruits for EIB.[E30] EVH is recommended by the European Respiratory Society/European Academy of Allergy and Clinical Immunology Task Force[E31] to identify EIB in athletes and is included in the World Anti-Doping Agency assessment of asthma (www.wada-ama.org/Documents/Science_Medicine/). EVH should not be performed on a patient who has an FEV_1 of less than 70% of predicted value and only with caution if FEV_1 is less than 80% of predicted value because of the risk of a major decrease in FEV_1.

Most studies indicate that the subjects who are susceptible to EIB have increased cellular inflammation. The fraction of exhaled nitric oxide is increased among asthmatic patients who are susceptible to EIB,[E32] especially atopic subjects.[E33] Inflammatory lipid mediators are implicated in EIB. In particular, concentrations of the cysteinyl leukotrienes (CysLTs) leukotriene (LT) C_4, LTD_4, and LTE_4 is increased in induced sputum of adults with EIB[E34] and in exhaled breath condensate (EBC) of children with EIB.[E35] Levels of nonenzymatic products of phospholipid oxidation, 8-isoprostanes, are increased in the EBC of patients who have asthma with EIB. Reduction in the formation of protective lipid mediators in the airways, such as lipoxin A_4, can also be involved in the pathogenesis of EIB.[E36] Prostaglandin E_2 (PGE_2) is a key regulatory eicosanoid that inhibits EIB when administered by means of inhalation.[E37] PGE_2 production relative to CysLTs is reduced in patients with EIB.[E38]

The intensity of cellular inflammation in the airways might be an important factor in the susceptibility to EIB because the formation of inflammatory eicosanoids, such as CysLTs and PGD_2, is largely restricted to myeloid cells.[E39] Several studies have associated the degree of sputum eosinophilia with the severity of EIB, especially in steroid-naive asthmatic patients.[E38,E40] A reduction in EIB severity after treatment with an ICS is also accompanied by a reduction in the percentage of eosinophils in sputum.[E40]

Increased expression of mast cell genes has been identified in patients with EIB by using genome-wide methods in asthmatic patients based on induced sputum[E38] and, subsequently, epithelial

brushings.[E41] In epithelial brushings the findings of increased expression of tryptase and carboxypeptidase A3 but relatively low chymase expression mirror the findings in patients with T_H2-high asthma.[E42,E43] The density of intraepithelial mast cells per volume of the airway epithelium measured by using quantitative morphometry in endobronchial tissue of asthmatic patients is markedly increased in subjects who are susceptible to EIB and suggests that mast cell infiltration of the airways is a defining feature of EIB.[E44]

The cellular mechanism leading to leukocyte activation either directly through the movement of water or through a signal from the epithelium in response to this water movement is not known in detail. There is strong evidence that leukocyte-derived eicosanoids, including CysLTs and PGD_2, are released into the airways after an exercise challenge.[E45-E49] CysLT levels are also increased in exhaled breath condensate after exercise challenge and correlate with the severity of EIB.[E47] CysLTs, such as LTD_4, mediate airway narrowing at a lower concentration than other mediators, such as PGD_2, histamine, or methacholine (Fig E2).

Mast cells and eosinophils are the leukocytes most strongly implicated as a source of mediators in patients with EIB.[E44,E48,E49] Mast cells generate PGD_2, CysLTs, and histamine, whereas eosinophils are also a major source of CysLTs and eosinophilic cationic protein. These leukocyte-derived products are known to mediate airway smooth muscle contraction, sensory nerve activation, and mucus release and increase microvascular permeability (MVP), leading to airway edema.[E50] Although early studies found only small increases in histamine in arterial plasma in response to exercise,[E51,E52] recent studies with induced sputum have confirmed that mast cell degranulation with the release of histamine and tryptase occurs during EIB.[E45,E53,E54] Pharmacologic inhibitors indicate that histamine is responsible for bronchoconstriction early after mannitol challenge, whereas CysLT release is responsible for sustained bronchoconstriction.[E55] After EVH challenge, levels of $9\alpha,11\beta$-PGF_2, the metabolite of PGD_2, are increased in urine, and PGD_2 release can be inhibited by pretreatment with a cromone or a high dose of ICS.[E56,E57]

There is strong evidence that CysLTs play a causative role in EIB through pharmacologic studies with $CysLT_1$ antagonists and 5-lipoxegnase inhibitors.[E58,E59] $CysLT_1$ receptor antagonists modify the maximum decrease in FEV_1 and the time of recovery after EIB.[E58,E59] The 5-lipoxegnase inhibitor zileuton administered 4 times daily for 2 days reduced the decrease in FEV_1 after exercise challenge by approximately one half.[E60] These results clearly demonstrate a role for CysLTs in the pathogenesis of EIB but also indicate that protection from EIB is incomplete, suggesting that other mediators might play a role. Histamine antagonists have been observed to have inconsistent activity on EIB.[E45,E61-E63]

Many mediators increase MVP,[E64] an event that contributes to bronchoconstriction through leak of proteinaceous material into the airways and edema of the airway wall. An increase in MVP after exercise has been demonstrated by a change in sputum-serum ratio of albumin.[E65] The increase in this ratio has been shown to relate to the severity of EIB. Vascular endothelial growth factor and angiopoietin 2, which alter MVP, have been related to the severity of EIB when measured in the airways after exercise challenge.[E65,E66] An increase in MVP could act to amplify airway narrowing caused by ASM contraction in the context of EIB. There is increasing evidence in athletes of hyperpnea leading to mechanical stress on the airway epithelium. Increases in both serum and urinary concentrations of pneumoprotein club cell (Clara cell) CC16 levels have been observed after swimming in elite swimmers.[E67,E68] In symptomatic recreational summer athletes increases in CC16 levels were observed in urine after EVH and mannitol,[E69] suggesting it is the osmotic stress that disrupts the epithelium in these subjects in contrast to that observed in elite swimmers.[E67]

The airways contain abundant sensory nerve endings within the epithelium that can be activated directly by changes in osmolarity or in response to other mediators in the airways in a process that involves neurokinin release. Although sensory nerves send signals from the airways to the central nervous system, they can also act locally through a process called retrograde axonal transmission, leading to bronchoconstriction and mucus release. Eicosanoids, such as CysLTs, can either directly activate or alter the activation threshold of sensory nerves.[E70] In dog and guinea pig models of HIB, leukotriene antagonists inhibit both the release of neurokinins and HIB, whereas neurokinin receptor antagonists inhibit the development of HIB without altering neurokinin levels consistent with leukotriene-mediated bronchoconstriction that occurs through sensory nerve activation.[E71,E72] In human subjects the effects of neurokinin 1 antagonists have been mixed in exercise and hypertonic saline models,[E73,E74] possibly because of the predominance of the neurokinin 2 receptor in human subjects that binds to neurokinin A.[E75] In human subjects release of the major gel-forming mucin MUC5AC after exercise challenge is associated with CysLT levels in the airways, and CysLT and neurokinin A levels in the airways are correlated after exercise challenge, supporting a role for sensory nerve activation in this process.[E76]

In approximately half of patients with EIB, there is an interval of refractoriness lasting approximately 1 to 3 hours during which additional exercise produces less bronchoconstriction.[E77-E79] This bronchoprotective effect might be additive to the protective effect of pretreatment with a SABA.[E77] The precise mechanism of the refractory period is not fully understood; however, recent findings with mannitol challenge suggest that the refractory period could be explained by tolerance to the effect of mediator release.[E80,E81] A probable explanation for the refractory period is that it induces the generation of protective prostaglandins because the administration of a nonsteroidal anti-inflammatory drug that inhibits the COX pathway reduces the refractoriness to both exercise and LTD_4 challenge.[E82,E83]

VII. PREVALENCE

EIB is reported frequently in asthmatic patients but also occurs in the absence of chronic asthma. EIB is very common in athletes. The prevalence of EIB is significantly influenced by the criteria used for diagnosis. The use of self-reported symptoms to make the diagnosis of EIB will result in significant rates of both false-positive and false-negative diagnoses of EIB.[E2,E28,E84,E85] Self-reported symptoms should not be relied on solely for the diagnosis of EIB without the concomitant use of spirometry and bronchoprovocation challenge to confirm the diagnosis.[E2,E28,E84,E86] The prevalence of EIB can be influenced by age, sex, ethnicity/race, and environmental conditions (eg, air temperature and humidity, allergen content, and pollution) in which exercise is performed.[E2,E85,E87,E88]

Summary Statement 1: In asthmatic patients EIB can indicate lack of control of the underlying asthma. Therefore treat the

uncontrolled asthma to obtain control of EIB. [Strength of Recommendation: Strong; Evidence: D]

Summary Statement 2: A diagnosis of EIB should be confirmed by demonstration of airways reversibility or challenge in association with a history consistent with EIB because self-reported symptoms are not diagnostic. [Strength of Recommendation: Strong; Evidence: B]

The occurrence of bronchoconstriction, especially with symptoms during or after exercise, is one of the common characteristics of asthma, but it also occurs in the absence of other clinical features of asthma. In asthmatic patients EIB in itself is a marker of poor control and suggests the need to initiate or step up therapy.[E89] The prevalence of EIB varies considerably, depending on a multitude of factors, including whether chronic asthma is present, the severity and control of asthma if it is present, environmental conditions, type of testing, and demographics factors.[E2,E89]

EIB is a common disorder in children.[E90,E91] The prevalence of EIB has been reported to be 10% in schoolchildren.[E92] However, estimates of up to 20% have been reported.[E92] Overall, there is a paucity of data from cohort studies in children examining changes in the prevalence of EIB over time and virtually no data in adults.

Researchers[E93] exercised 15,241 children using a 6-minute run and a decrease of 15% for peak flow as an indicator of EIB. 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.

A study using EVH reported a presumed prevalence of EIB of 19.4% in 212 adults without a history of asthma.[E94] Similar findings were documented in another cohort of 136 recreationally active subjects in whom EIB was documented in 13% of the cohort by using EVH.[E95] Subjects with a family history of asthma might have a higher prevalence of EIB.[E96] EIB is also more frequent in atopic subjects,[E97,E98] including those with allergic rhinitis,[E99] and after viral respiratory tract infections and other respiratory diseases.[E100] It is unclear what the relationship is between the natural history of EIB when not associated with chronic asthma and the subsequent development of chronic asthma.

The frequency and severity of asthma can vary by sex, with male subjects having greater frequency during childhood but female subjects having more severe asthma during adulthood.[E101-102] In contrast to the above findings,[E93] another study[E103] did not demonstrate sex differences in patients with EIB. However, these investigators found that with increasing age, the frequency of EIB decreased.

The frequency of asthma and EIB can also vary by sex in elite athletes. In winter sports female subjects appear to exceed male subjects in the prevalence of EIB. In US Olympic winter sports the prevalence of EIB by using an exercise challenge test was 26% in female and 18% in male athletes, with a combined percentage of 23%.[E104] When using EVH as a surrogate challenge for EIB, other studies failed to find such a difference in prevalence between the sexes.[E30,E105] Using questionnaires and methacholine challenges, investigators[E106] found that the prevalence of both exercise-associated asthma symptoms and BHR was higher in female than male athletes.

Data suggest there can be racial/ethnic differences in the prevalence of EIB. A standardized free running test with peak flow monitoring demonstrated that African Americans had a higher prevalence of EIB than white subjects (13% and 2%, respectively).[E107] When assessing 9-year-old children with cycle ergometry in Great Britain, ethnic differences in EIB were also evident, with Asian children (originating from the Indian subcontinent) having a prevalence 3.6 times higher than that of white inner-city children.[E108]

Summary Statement 3: Evaluate EIB in elite athletes by using objective testing. [Strength of Recommendation: Strong; Evidence: B]

No test for EIB is fully sensitive or specific, and thus no test is sufficient to substantiate or exclude the diagnosis of EIB in all athletes. Additional variability can be caused by seasonal and environmental influences, which might affect the ability to detect BHR.

Reports of the occurrence of asthma symptoms in elite athletes have varied from none to 61%,[E109,E110] depending on the sport and environment.[E84,E104,E109-E119] In fact, higher prevalence rates are reported in certain populations, such as elite endurance athletes, and in unique environments, such as competitive skaters and cross-country skiers.[E119-E121] Some investigators suggested that endurance athletes, whether summer or winter, had considerably more symptoms than athletes participating in less aerobic sports.[E109,E110] Overall, this study suggested that, based on symptoms, as many as 1 in 4 athletes had EIB. By using a questionnaire in recreational athletes, a similar prevalence of asthma symptoms was reported.[E122] However, these data do not suggest that the subjects who report asthma are the same as those who have a positive exercise challenge test result. However, a similar prevalence of EIB in Winter Olympics athletes has been reported based on objective data by using an exercise challenge.[E104] Certain populations have a higher than expected prevalence based on unique circumstances, such as the high prevalence of EIB in skaters (20% to 35%) that has been attributed to high emission pollution from ice-cleaning equipment and cold dry air.[E113,E114] A similar example is the extremes of cold dry air, such as that to which cross-country skiers are exposed, which might increase the prevalence of EIB to 30% to 50%.[E123] Similarly, another study found as many as 78% of elite cross-country skiers have symptoms, BHR, or both.[E124]

Athletes who participated in the 1996 Summer Olympics also had variations in EIB prevalence, which might have depended on the sport in which they participate. For example, long-distance runners were found in one study to have a prevalence of 17%, whereas speed runners had a prevalence of 8%.[E125] Whether these differences are significant might depend on how the test was performed rather than on a difference in the sports for athletes who expend a similar amount of work. By survey, none of the US Olympic divers and weightlifters had symptoms, whereas 45% of mountain bikers experienced symptoms, which is consistent with the hypothesis that endurance sports have a higher prevalence of associated EIB during sport participation.[E110]

Poor air quality can also be associated with a high prevalence of EIB in athletes.[E126] In swimmers chloramines above the water can trigger EIB. Interestingly, swimmers with longer duration of exposure (>100 hours of chlorinated pool exposure) tend to have a higher prevalence of EIB.[E127] Discontinuation of swimming resulted in a decreased incidence of EIB.[E128] As noted previously, the high prevalence of EIB in skaters (20% to 35%) has been attributed to high emission pollution from ice-cleaning equipment and cold dry air.[E129,E130]

Athletic fields and school playgrounds in an urban environment might present a major health concern. Daily measurements (62 days) of air pollutants at a university soccer field in proximity to major highway traffic showed extremely high levels of airborne particulate matter that were related to significant decreases in lung function in soccer players.[E131] High levels of ambient ozone, as well as emissions and particulate matter from vehicular traffic, have been shown to enhance the EIB response in asthmatic patients.[E132]

Seasonal variation of EIB is also described in Olympic athletes[E97] and the general population.[E133,E134] For example, when using a 6.5% decrease in FEV_1 with running, 28% of runners had probable EIB. Of these runners, 22% had EIB that occurred only in the winter, and 7% had EIB only during the pollen season.[E97] A seasonal difference was also demonstrated in another investigation,[E135] which found that 35% of runners training in the cold reported an increased prevalence of EIB compared with summer, when the prevalence was less. Data collected from the Summer Olympics between the years 1992 and 2008 have documented an increasing percentage of elite athletes reporting asthma. This trend follows a similar increase noted in the general population.[E136]

Summary Statement 4: Perform a standardized bronchoprovocation (exercise or a surrogate) challenge to diagnose EIB because the prevalence of EIB will vary with the type of challenge and the conditions under which the challenge is performed. [Strength of Recommendation: Strong; Evidence: A]

By examining responses to history questions on the intake forms of athletes participating in the 1996 Summer Olympic Games, as required by the US Olympic Committee, investigators[E110] found 0% to 45% of summer athletes, depending on the sport, answered questions compatible with having EIB. The prevalence varied significantly among different sports, with nonendurance sports having minimal levels and endurance sports having higher prevalence rates. By using the same data extraction method, the same researcher[E109] found that up to 60.7% of athletes participating in Nordic skiing events responded to questions that suggested they had EIB.

The use of self-reported symptoms to make the diagnosis of EIB will likely misdiagnose asthma in patients who do not have EIB and miss persons with the condition. A limitation of determining prevalence by survey is evident in multiple studies[E28,E84,E86] in which results showed participants who had symptoms did not necessarily have a positive challenge result and those who had a positive challenge result did not necessarily have symptoms.

It has also been demonstrated that symptoms are neither sensitive nor specific to suggest a positive EVH test result as evidence for EIB.[E28] This study found that 36% of college athletes without symptoms had a comparable decrease of 10% in FEV_1, and a similar number (35%) of those with symptoms had such a decrease with EVH.[E28]

Another study used different techniques in an attempt to clarify the prevalence of EIB. These investigators challenged 50 elite athletes with and without a history of asthma documented by questionnaire with methacholine provocation and EVH.[E137] The results showed that of the 42 athletes who reported respiratory symptoms, 9 had a positive methacholine test result, and 25 had a positive EVH test result. Methacholine had an excellent negative predictive value but only a 36% sensitivity for identifying those with a positive EVH test result. These findings are consistent with the observations found in 2 more studies, which demonstrated that EIB and asthma symptoms do not correlate well with exhaled nitric oxide levels, results of bronchoalveolar lavage, or challenges with AMP or histamine.[E117,E118]

Elite athletes can have a high prevalence of EIB, which can be associated with extreme atmospheric conditions, such as high levels of pollen, pollution, dry air, and chemicals, particularly in the training environment. EIB can be demonstrated in persons without symptoms, but symptoms are not a sensitive predictor of EIB.[E138] The prevalence of EIB also can be affected by age, sex, ethnicity, urbanization, and, most significantly, the diagnostic method used to detect it.

VIII. DIAGNOSIS

Symptoms of EIB primarily include wheeze, chest tightness and shortness of breath (dyspnea), and cough; however, they can also include chest pain (primarily in children), excessive mucus production, or feeling out of shape when the patient is actually in good physical condition.[E28,E84,E85,E139,E140] Because these symptoms also occur with other conditions, a diagnosis of EIB based only on symptoms lacks any reasonable diagnostic sensitivity or specificity to predict a positive exercise challenge result in adults or children.[E84,E93,E141-E143] Thus the diagnosis of EIB should never be made based on symptoms alone when unaccompanied by data from an objective exercise or surrogate challenge (Fig E1).[E28,E84,E85,E139,E144-E146]

Summary Statement 5: In subjects with no current clinical history of asthma, use an indirect ungraded challenge (eg, exercise challenge or surrogate testing, such as with EVH) for assessing EIB in the recreational or elite athlete who has normal lung function. [Strength of Recommendation: Strong; Evidence: D]

Summary Statement 6: Use an indirect graded challenge (eg, mannitol, if available) for assessing EIB in recreational or elite athletes who have normal to near-normal lung function and who might currently require treatment for the prevention of EIB or asthma. [Strength of Recommendation: Strong; Evidence: D]

Diagnostic challenges used to identify airway hyperresponsiveness are of 2 types classified based on mechanism of action: (1) direct challenges in which a single pharmacologic agent, such as methacholine or histamine, is the provoking substance administered exogenously that acts directly through receptors on airway smooth muscle to cause contraction and (2) indirect challenges in which exercise or a surrogate, such as EVH; inhaled osmotic agents, such as mannitol or hypertonic saline; or inhalation of AMP is the provoking agent that in turn triggers endogenous mediator release that acts to cause airway smooth muscle contraction. These mediators act on specific receptors on bronchial smooth muscle to cause bronchoconstriction. Indirect challenges are more specific in reflecting BHR caused by the presence of airway inflammation and are preferred as a way to confirm underlying asthma and potentially the need for ICSs.[E28,E84,E85,E139,E144-E146] In addition, indirect challenges are recommended for monitoring asthma therapy because BHR is most often associated with inflammation,[E28,E84,E139,E144-E146] which is diminished by ICS therapy.[E85,E146-E149]

Summary Statement 7: Perform an indirect challenge (eg, exercise challenge or surrogate testing, such as with EVH or mannitol, where available) instead of a direct challenge (eg, methacholine) for assessing EIB, recognizing that an indirect challenge is more sensitive for detection of EIB than a direct

(eg, methacholine) challenge. [Strength of Recommendation: Strong; Evidence: B]

Direct challenges with methacholine, an approved agonist, can be performed in an office setting by trained personnel. The challenge, as described in a consensus statement by the ATS,[E145] requires administering increasing concentrations of methacholine by means of inhalation and measuring FEV_1 levels after each dose. Although the direct challenge is used as a screening test for chronic asthma, especially to rule out asthma, it is not useful to detect EIB. This is because it has low specificity for EIB as a result of reflecting the effect of only a single agonist (Fig E3).[E85,E144-E146,E150,E151]

Summary Statement 8: Ensure the ventilation reached and sustained during exercise challenge testing is at least 60% of the maximum voluntary ventilation by using dry medical grade air to achieve an adequate challenge. If ventilation cannot be measured, ensure the heart rate as a percentage of HRmax that is reached and sustained is at least 85% in adults and 95% in children and elite athletes. [Strength of Recommendation: Strong; Evidence: B]

Indirect challenges should also be conducted only by trained personnel using standardized protocols. For example, laboratory-based exercise should be performed as described in the consensus statement published by the ATS.[E2,E145] Such a laboratory challenge controls minute ventilation and water content of inhaled air.[E2,E85,E144,E145] Exercise ramp-up should be brisk within 2 to 3 minutes to reach a heart rate of 85% of maximum and an exercise duration of no more than 8 minutes, of which 6 minutes is maximum exercise, while a maximum heart rate of 95% for children with a preferred exercise duration of 6 minutes. It is preferable to use a source of dry air (medical grade) at 20°C to 25°C to achieve more than 40% of the patient's calculated maximum voluntary ventilation.[E2,E85,E144,E145] Medical air can be supplied directly from a compressed air tank with a demand valve that delivers air at high flow rates or alternatively supplied to a balloon reservoir bag (eg, Douglas bag) fitted with a 2-way nonrebreathing valve before being attached to a mouthpiece or facemask.[E152,E153] Measurement of ventilation should be encouraged because it is the level of ventilation reached and sustained, which is key to providing a maximal stimulus.[E154] This can be measured by using a spirometer that measures minute ventilation of expired air in real time (eg, Bi-directional Universal Ventilation Meter, VacuMed, Ventura, Calif). In the absence of this, maximal heart rate can be used alternatively and is estimated by using the following formula:

$220 - \text{Age (in years)}$[E2];

however, a more accurate equation, which was published recently, to predict HRmax is as follows:

$208 - 0.7 \times \text{Age}$.[E155]

Ideally, the exercise ventilation should be greater than 60% of predicted maximum (ie, >21 times FEV_1)[E2,E144,E145]; very well-conditioned subjects might require the exercise intensity to be greater than 90% HRmax. There might be a need to reach a higher target HRmax of 95% for adolescent children because one study in patients 9 to 17 years of age demonstrated the decrease in FEV_1 was 25.1% at 95% HRmax but 8.8% when the children reached only 85% HRmax (Fig E4).[E139]

Spirometry should be performed at baseline according to the ATS standards of reproducibility before exercise challenge and at predetermined time points after exercise, usually at 5, 10, 15, 30 minutes and occasionally 45 to 60 minutes after exercise. A pre-exercise value is obtained by performing a full forced vital capacity (FVC) maneuver at baseline.[E2,E85,E144,E145] The International Olympic Committee Medical Commission Independent Panel on Asthma recommends that FEV_1 should be recorded beginning as soon as 3 minutes after completion of the challenge to overcome the problem of posttest respiratory fatigue. Reproducibility of FEV_1 after exercise is desirable because at times moderate-to-severe decreases have occurred. A measurement at 1 and or 3 minutes after exercise for reasons of safety might be warranted in persons who are suspected of having large decreases in FEV_1. FEV_1 is often performed without having the patient perform full FVC maneuvers to avoid causing the patient to become tired because of the spirometric efforts (eg, 2-4 seconds of expiration). The highest FEV_1 at each time point is used to calculate the percentage decrease from baseline. A 10% or greater decrease in FEV_1 from the pre-exercise value at any 2 consecutive time points within 30 minutes of ceasing exercise can be considered diagnostic of EIB.[E2,E85,E144,E145,E154] Reproducibility of FEV_1 after exercise becomes essential in cases in which borderline decreases in FEV_1 have resulted. If a greater decrease in FEV_1 is required, such as a decrease of 20% in FEV_1, as in some pharmaceutical studies, then only 1 time point might be necessary to be diagnostic of EIB.

Summary Statement 9: Perform EVH as the preferred surrogate challenge for the athlete without a current history of asthma participating in competitive sports in whom the diagnosis of EIB is suspected. [Strength of Recommendation: Strong; Evidence: D]

Summary Statement 10: If an indirect graded challenge (eg, mannitol) result is negative and EIB is still suspected, an ungraded challenge should be considered. [Strength of Recommendation: Weak; Evidence: B]

The profile of the decrease in FEV_1 after an exercise or EVH challenge should be examined to determine whether the decrease is sustained and not the product of a single measurement that might represent an artifact because of inadequate spirometric effort at 1 or more time points. There might be variability in the airway response to exercise when more than 1 test is performed, particularly in those with milder airway responses, and thus repeat testing might need to be considered in some cases in which EIB is strongly suspected.[E141,E156]

However, there is no single test that will identify all patients with EIB.[E84] Decreases in FEV_1 consistent with EIB can occur in subjects who are subsequently found to have other conditions.[E85] A flat or "truncated" inspiratory flow-volume loop on the flow-volume curve suggests an upper airway dysfunction rather than EIB.[E85] EILD can occur independently or coexist with EIB.

Exercise challenge by treadmill is most easily standardized for office practice or a hospital laboratory. Alternative exercise challenges using cycle ergometry can be more difficult to perform and might provide a suboptimal exercise stimulus compared with the treadmill challenge.[E154] Furthermore, field challenge and free running are challenge tests that are more difficult to standardize.[E2,E85,E142,E144,E145]

Although sport governing bodies require specific cutoff values to diagnose EIB, there is no specific decrease in FEV_1, and there is no single absolute cutoff for a decrease in FEV_1 or change in some other spirometric measure that clearly and unequivocally distinguishes between the presence and absence of EIB.[E85] The ATS has suggested that the postexercise decrease in FEV_1 required

to make the diagnosis must be 10%, whereas other groups have suggested a decrease of 13% to 15% is necessary to make the diagnosis.[E2,E144,E145] A decrease in FEV_1 of 15% after a "field" challenge and a decrease of 6% to 10% in the laboratory have also been recommended.[E2,E85,E144,E145]

Surrogate challenges for exercise in which a hyperosmolar agent, mannitol (graded challenge), or EVH (ungraded challenge) are used are increasingly being recommended by organizations that regulate drug use by elite athletes. EVH should only be performed by highly trained specialists, and all safety precautions should be observed. EVH can cause substantial decreases in FEV_1 in a patient with reduced lung function caused by airway inflammation. The EVH test should be performed with caution, especially in patients with an FEV_1 of less than 80% of predicted value. The EVH test should not be performed on patients in whom FEV_1 is less than 75% of predicted value.[E2,E85,E144,E145] For all these challenge tests, treatments that are effective at attenuating or inhibiting airway hyperresponsiveness should be withheld for an appropriate time before testing to ensure sufficient washout of the drug, so that it does not influence the airway response (Table E1).[E158-E170]

IX. DIFFERENTIAL DIAGNOSIS

Summary Statement 11: To differentiate between EIB and EILD, perform appropriate challenge tests (eg, exercise, EVH, and mannitol for EIB) and potentially flexible laryngoscopy during exercise for diagnosis of EILD. [Strength of Recommendation: Strong; Evidence: B]

EILD, primarily vocal cord dysfunction (VCD) and also other glottic abnormalities, can be elicited by exercise and mimic EIB. Inspiratory stridor is a differentiating hallmark sign with EILD and not with EIB. However, the presence of inspiratory symptoms does not necessarily differentiate athletes with and without EILD.[E171,E172] Flattening of the inspiratory curve on spirometric maneuvers can be seen concomitant with symptoms (Fig E1). EILD can occur alone or with EIB. Failure to respond to asthma management is a key historical feature suggesting EILD.

Since the initial description of VCD as a functional disorder that mimicked attacks of asthma,[E173] VCD and glottis structural abnormalities elicited with exercise have been increasingly recognized. These functional and structural disorders can be grouped as EILD, including (1) paradoxical VCD, (2) exercise-induced laryngeal prolapse,[E174] (3) exercise- induced laryngomalacia,[E175] and (4) variants, including arytenoid collapse while the vocal cords move normally.[E176] EILD occurs in all age groups, especially among young adult female elite athletes.[E177] VCD is more common in middle school– to high school–aged athletes than college-aged athletes.[E178] There is a question as to whether VCD and exercise-induced laryngeal malacia in children and adolescents are separate clinical entities.[E179]

Bronchial provocation challenge results with methacholine, exercise, and EVH can be negative in patients with EILD who do not otherwise have BHR. The onset of breathing difficulties occurs and peaks during exercise with EILD, rather than peaking after exercise with EIB. Medications used to treat asthma, such as β_2-agonists, are ineffective to prevent or reverse EILD. EILD can be suspected based on bronchial provocation challenges with EVH, methacholine, and/or exercise, demonstrating variable extrathoracic airway obstruction.[E180]

Inspiratory stridor with throat tightness during maximal exercise resolves within approximately 5 minutes of discontinuation of exercise in patients with EILD. Inspiratory stridor with EILD contrasts with EIB, in which case dyspnea generally occurs after exercise, peaks 5 to 20 minutes after stopping, and involves expiration rather than inspiration. There can be variations in the timing of the manifestations of EILD symptoms, depending on such factors as the duration and intensity of the exercise.

In patients with VCD, direct observation of vocal cord adduction by means of laryngoscopy and flattening or truncation of the inspiratory portion of the spirometric flow-volume loop are the hallmarks for diagnosis (Fig E1). These findings can be seen only during symptomatic periods. Methacholine challenge can be used to elicit VCD.[E181,E182] Additional evidence of VCD can be suggested by examining a video of the patient recorded while exercising in the natural setting at the time that inspiratory stridor is heard.[E183] Diagnosis can be made directly by using continuous laryngoscopy during exercise challenge.[E184] Spirometry and laryngoscopy with sound recording can be performed during exercise, detecting minor and major aryepiglottic and vocal cord abnormalities.

Exercise-induced laryngeal prolapse has been seen in otherwise healthy athletes and can present with subtotal occlusion of the larynx. This condition can result from mucosal edema from the aryepiglottic folds being drawn into the endolarynx (laryngochalasia).[E174] Laryngoscopic evaluation at rest can be normal, and various laryngeal abnormalities can be elicited only with exercise challenge.[E185]

Laryngomalacia is associated with diminished laryngeal tone, resulting in supraglottic collapse, and is usually a congenital condition.[E186] Laryngomalacia is the most common cause of inspiratory stridor in infants[E187] but might not manifest until later childhood with participation in competitive sports.[E175,E186-E190] It has been questioned clinically whether exercise-induced VCD and exercise-induced laryngomalacia in children and adolescents present as the same clinical syndrome.[E179] Although the typical anatomic features of congenital laryngomalacia (shortened aryepiglottic folds or retroflexed epiglottis) might not be seen, other presentations, such as profound arytenoid redundancy and prolapse, can be seen during nasolaryngeal endoscopy. As in infants with laryngomalacia, supraglottoplasty can improve late-onset disease.[E186,E187] Laryngomalacia can also be seen in adults.[E191]

Concurrent laryngeal abnormalities can be seen in patients with VCD. Laryngoscopy can identify findings suggestive of gastroesophageal reflux disease (GERD), chronic laryngitis, laryngomalacia, vocal cord motion impairment, nodules, and subglottic stenosis, especially in patients in whom exercise induces symptoms.[E192] EILD can coexist with EIB. Inspiratory stridor is the signature clinical feature suggesting EILD rather than EIB.

Gastroesophageal reflux anatomic findings can be seen on laryngoscopy in children and adults with EILD, but whether they are causative or concomitant is difficult to establish. Empiric pharmacologic treatment of GERD in juveniles with VCD has been recommended because posterior laryngeal changes associated with GERD are common in these patients.[E193]

Although laryngopharyngeal reflux can be a contributing factor in many patients with EILD, there is very little supporting objective evidence. The sensitivity and specificity of laryngoscopic examination to diagnose laryngopharyngeal reflux are also controversial.[E194] Although there might be a clinical suspicion of

laryngopharyngeal reflux, there is an absence of an objective gold standard to establish this diagnosis. Although great attention has been given to EILD and other dysfunctional breathing disorders in the differential diagnosis, therapeutic strategies might require a multidisciplinary approach, including speech therapy and addressing possible psychophysiologic stress.[E195]

Summary Statement 12: To determine whether exercise-induced dyspnea and hyperventilation are masquerading as asthma, especially in children and adolescents, perform cardiopulmonary exercise testing. [Strength of Recommendation: Moderate; Evidence: C]

Exercise-induced respiratory symptoms have been described as an "epidemic" among adolescents.[E196] EILD and exercise-induced hyperventilation are common, and the prevalence is uncertain, as described primarily in uncontrolled case reports.[E197,E198] Chest discomfort perceived as dyspnea during vigorous exercise can be associated with hypocapnia from hyperventilation without bronchoconstriction, especially in children and young adolescents previously given a diagnosis of and having been treated for EIB.[E140,E199-E203]

It has been demonstrated that exercise-induced lactic acidosis is causally involved in hyperventilation. However, lactic acidosis does not represent the only additional stimulus of ventilation during intense exercise. Sensory input from exercising muscles, such as muscle afferents, can also trigger hyperventilation.[E204,E205]

Idiopathic hyperventilation is a poorly understood condition in which patients have sustained hyperventilation, hypocapnia, and dyspneic drive.[E206]

Perhaps the most common reason for exercise-induced dyspnea in children is physiologic (poorly conditioned) limitation without bronchospasm or underlying disease.[E199] Limits in exercise performance and respiratory system oxygen transport can occur in highly fit adults.[E207] This might be due to flow limitation in the intrathoracic airways because of narrowed hyperactive airways or secondary to excessive ventilatory demands superimposed on a normal maximum flow-volume envelope. In addition, exercise-induced arterial hypoxemia occurs as a result of an excessively widened alveolar-arterial oxygen pressure difference. This inefficient gas exchange might be attributable in part to small intracardiac or intrapulmonary shunts of deoxygenated mixed venous blood during exercise. Finally, fatigue of the respiratory muscles resulting from sustained high-intensity exercise and the resultant vasoconstrictor effects on lung muscle vasculature will also compromise oxygen transport and performance. Exercise in the hypoxic environment of even moderately high altitudes will greatly exacerbate the negative influences of these respiratory system limitations to exercise performance, especially in highly fit subjects.

Dyspnea on exertion is present in obese patients. This dyspnea has been strongly associated with an increased oxygen cost of breathing without bronchoconstriction in otherwise healthy obese women.[E208] Exercise capacity has been variously reported as unchanged in obese female subjects to being reduced at or near maximal effort.[E209]

Cardiopulmonary exercise testing should be performed with close observation to assess the clinical presentation (Fig E1).

Summary Statement 13: Perform spirometry, as well as detailed pulmonary examination, to determine whether shortness of breath with exercise is associated with underlying conditions, such as COPD, or restrictive lung conditions, such as obesity, skeletal defects (eg, pectus excavatum), diaphragmatic paralysis, or interstitial fibrosis, rather than EIB. [Strength of Recommendation; Moderate; Evidence: C]

Dyspnea with exertion in some obese patients might not be a manifestation of EIB.[E210] Idiopathic pectus excavatum can be associated with exercise symptoms, including chest pain, dyspnea, or impaired endurance. Even in the absence of clinical symptoms, restrictive lung defects and lower airway obstruction are common (Fig E1).[E211,E212]

Scoliosis has been associated with decreased exercise tolerance. Patients with mild scoliosis can be asymptomatic at rest but with exercise can have decreased tidal volume, as well as hypercapnia and hypoxia.[E213]

Although diaphragmatic paralysis has a predictable effect on lung function, the symptoms depend on pre-existing heart-lung diseases and can mimic various cardiorespiratory processes, including EIB.[E214,E215]

Patients with interstitial lung disease frequently have dyspnea with exercise. These patients' exercise limitations appear to be related to arterial hypoxemia and not respiratory mechanics. Their dyspnea is often fixed and reproducible.[E216,E217]

Summary Statement 14: Consider a diagnosis of EIAna instead of EIB based on a history of shortness of breath or other lower respiratory tract symptoms accompanied by systemic symptoms (eg, pruritis, urticaria, and hypotension). [Strength of Recommendation: Moderate; Evidence: C]

EIAna is characterized by the exertion-related onset of cutaneous pruritus and warmth, generalized urticaria, and the appearance of such additional manifestations as shortness of breath, upper respiratory tract distress, vascular collapse, and gastrointestinal tract symptoms. This must be differentiated from asthma, cholinergic urticaria, angioedema, and cardiac arrhythmias, which are recognized as exertion-related phenomena in predisposed patients but are distinct from EIAna.[E218] There is variability in the reproducibility of EIAna symptoms given similar testing conditions.

Episodes of food-dependent exercise-induced anaphylaxis (FDEIAna) might or might not be dependent on ingestion of identifiable foods.[E219,E220] The cumulative effect of exercise and food ingestion can trigger the mediator release and anaphylaxis, whereas this is not the case for each of these triggers independently.

Foods reported as predisposing factors range from shellfish, eaten 4 to 24 hours before EIAna, to seemingly benign foods, such as celery, eaten before or after exercise.[E219,E220] Skin testing with foods might be helpful in eliciting the trigger when history taking does not.[E221] Serum tryptase measurements might help in confirming the diagnosis of EIAna.[E221] FDEIAna occurs in both children and adults.[E218-E223]

Wheat gliadin has been identified as the cause of FDEIAna caused by wheat.[E224] It has been further determined that crosslinking between tissue transglutaminase and omega-5 gliadin–derived peptides increases IgE binding. The tissue transglutaminase becomes activated in the patients' intestinal mucosa, and large allergen complexes become capable of eliciting anaphylaxis.[E225] Exercise and aspirin have been shown to increase the levels of circulating gliadin peptides in patients with wheat FDEIAna, suggesting facilitated allergen absorption from the gastrointestinal tract.[E226]

Although skin testing to the specific foods, commercial or fresh food extracts, or crude gliadin is most used, measurement of IgE

levels specific to epitope peptides of omega-5 gliadin or recombinant omega-5 gliadin might be useful as an *in vitro* diagnostic method (Fig E1).[E226,E227]

Oral challenge with gluten alone or along with aspirin and alcohol is a sensitive and specific test for the diagnosis of wheat-dependent EIAna. Exercise is not an essential trigger for the onset of symptoms in these patients.[E228]

FDEIAna can have a delayed onset for an unpredictable number of hours. Therefore it has been suggested that in such patients exercise should be avoided 4 to 6 hours after specific food ingestion. In patients with wheat gliadin–associated EIAna, a gluten-free diet is recommended.[E224,E229]

Susceptible patients might be advised to take an antihistamine before exercise and should carry self-injectable epinephrine, which is the primary treatment for anaphylaxis.[E229]

Summary Statement 15: Refer to appropriate specialists (eg, cardiologist or pulmonologist) to perform cardiopulmonary testing when breathlessness with exercise, with or without chest pain, might be caused by heart disease or other conditions in the absence of EIB. [Strength of Recommendation: Moderate; Evidence: C]

Although the incidence of cardiac-related dyspnea with exercise in young healthy patients is minimal, it remains an important differential in patients with EIB (Fig E1). Idiopathic pulmonary arterial hypertension can occur in both adults and children. Patients with primary pulmonary hypertension can demonstrate peripheral airway obstruction, poor oxygenation, and early physiologic aerobic limits restricting exertion and, in children, documentation of significant reversibility of lower airway obstruction.[E230-E232]

A case report documents how idiopathic pulmonary arterial hypertension can masquerade as asthma. Two adult nonsmokers presenting with wheezing, chronic cough, and irreversible obstructive lung disease were given a diagnosis of adult-onset severe refractory asthma but actually had dilation of the central pulmonary arteries, compressing the mainstream bronchi.[E233]

"Cardiac asthma" can be considered one presentation of cardiac dyspnea caused by cardiogenic pulmonary edema. The pathogenesis might be reflex bronchoconstriction as a manifestation of pulmonary venous hypertension. In distinguishing cardiac from pulmonary dyspnea, the most useful studies include B-natriuretic peptide measurement, echocardiography, and, if needed, a cardiopulmonary exercise test.[E198] Congestive heart failure can present with dyspnea on exertion. Hyperpnea with exercise can occur without lung function impairment. Ventilation-perfusion mismatch in exercise can be enhanced by increased treatment of heart failure.[E234]

Hypertrophic cardiomyopathy is well known to cause sudden death in young athletes, with an annual 1% mortality rate.[E235] Patients can have dyspnea and chest pain that improve with β-blockers.[E236]

Cardiac dysrhythmias can also cause dyspnea with exercise. Supraventricular tachycardia can cause EIB in children.[E199] Young adults with complete heart block can have shortness of breath, dyspnea on exertion, syncope, dizziness, or fatigue.[E237]

Vascular rings of the aorta are rare but can present as asthma. Spirometry in these patients reveals decreased peak expiratory flow and truncation of the expiratory flow-volume loop with normal FVC, FEV_1, and FEV_1/FVC ratio values. Chest radiographs are significant for a right aortic arch.[E238]

Pulmonary arteriovenous malformations and disorders with right-to-left shunts can cause exercise-induced dyspnea because of hypoxemia, without associated bronchoconstriction. Hereditary hemorrhagic telangiectasia, atrial septal defects, ventricular septal defects, and Osler-Rendu-Weber syndrome are among the primary causes. Cardiopulmonary exercise testing, as differentiated from pulmonary function testing for EIB, is an appropriate noninvasive tool to begin and guide the evaluation of these patients presenting with undiagnosed dyspnea.

The evaluation might require procedures, such as cardiac catheterization, to further delineate the right-to-left shunt.[E239,E240] Exertional dyspnea in symptomatic patients with COPD might be due to the combined deleterious effects of higher ventilatory demand and abnormal ventilatory dynamics but not temporally attributable to bronchoconstriction.[E241] Patients with COPD might have evidence of small-airway dysfunction with increased ventilatory requirements during exercise, likely on the basis of greater ventilation and perfusion abnormalities. These abnormalities also involve changes in end-expiratory lung volume and breathing patterns that are more shallow and rapid than in a comparatively healthy cohort.

Although there are reports of exertional gastroesophageal reflux in healthy subjects, most studies have demonstrated no significant correlations between GERD and EIB.[E242-E244]

Although acid reflux can be common in patients with EIB, many patients with exercise-related respiratory symptoms can receive a misdiagnosis of asthma when they truly have exercise-onset GERD (Fig E1).[E245] Some controversies exist in the treatment of GERD and EIB. One study demonstrated that symptoms of acid reflux related to running were relieved by a proton pump inhibitor, but the respiratory symptoms of EIB were not relieved by proton pump inhibitors.[E246] In contrast, other investigators have reported improvements in exercise-related breathing symptoms when patients were treated with proton pump inhibitors.[E245]

Impaired oxidative phosphorylation in working muscle disrupts the normal regulation of cardiac output and ventilation relative to muscle metabolic rate in exercise.[E247] Deficiencies of mitochondrial enzymes cause a number of severe neurologic syndromes in pediatric patients. Isolated myopathies secondary to enzymatic deficiency have been recognized in adults and might be more prevalent than reported previously (Fig E1).[E248,E249]

Summary Statement 16: Refer patients for psychological evaluation when the symptoms (eg, hyperventilation and anxiety disorders) are in the differential diagnosis of EIB. [Strength of Recommendation: Weak; Evidence: D]

Psychological factors can obfuscate the diagnosis in patients with apparent exercise intolerance. Such scenarios, such as subjects, particularly young women, complaining of shortness of breath while running without having stridor, wheezing, or relief with trial bronchodilators, are not uncommon but might be vexing to patients, their parents, and their physicians.

Although VCD and exercise-induced hyperventilation can have functional triggers, differentiating EIB requires subjective and objective assessment.[E250] Mental stress might be one trigger factor in which hyperventilation is seen in patients with asthma-like symptoms with negative asthma test results.[E251] If objective testing does not reveal any bronchoconstriction or other physiologic explanations, then a psychological cause should be considered and addressed with the patient, which might involve a recommendation for psychological consultation (Fig E1).

X. THERAPY

EIB is a reflection of BHR and, in asthmatic children and adults, ordinarily is due to underlying inflammation. EIB in these subjects, most of whom are not elite athletes, might represent inadequacy of overall asthma control.[E252,E253]

The goal of therapy for EIB is to prevent symptoms induced by exercise, to enhance overall control of asthma, and to ameliorate symptoms rapidly when they occur. Pharmacotherapeutic agents that are effective in controlling chronic asthma generally have bronchoprotective activity for EIB. If asthma is otherwise well controlled, bronchoprotective therapy is administered only as needed. This therapy can be delivered by means of inhalation or oral administration minutes to hours before exercise, respectively. Nonpharmacologic therapies can also be helpful in preventing EIB when used alone or in combination with pharmacotherapy; these are described in the "Nonpharmacologic therapy" section.

Pharmacotherapeutic agents act to prevent or attenuate EIB through various mechanisms with different degrees of effectiveness. None of the available therapies completely eliminates EIB. Pharmacotherapy shifts the dose-response relationship to a more favorable position after exercise.[E254,E255] The efficacy of a given agent in protecting against EIB can vary at different times and among different subjects.

Summary Statement 17: Schedule regular office visits with patients because medications can differ in effectiveness over time because of variability of asthma, environmental conditions, intensity of the exercise stimulus, and tachyphylaxis. [Strength of Recommendation: Strong; Evidence: A]

The variability of effectiveness within a subject might be due to changes in airway responsiveness over time, environmental conditions, and intensity of the exercise stimulus.[E256] The variability among subjects might result from differences in baseline airway responsiveness and susceptibility to tachyphylaxis and perhaps genetic differences.[E85] Pharmacotherapeutic studies supported by pharmaceutical sponsors generally have used parallel groups or crossover designs to compare active drugs with placebo or to compare 2 (or more) active drugs.[E256] The primary end point is most commonly the maximum percentage decrease in FEV_1, especially for studies submitted to the US Food and Drug Administration (FDA)[E256] in support of a bronchoprotective end point. Peak expiratory flow has also been used as an end point in some studies but not as a primary end point, and it is used less commonly than FEV_1.

In addition to the maximum absolute decrease in FEV_1 expressed as a percentage of baseline, the results might indicate FEV_1 before and after therapy.[E257] Baseline lung function can also be compared before and after therapy if a bronchodilator response is also being investigated.[E59,E145,E254,E258-E263] Some studies have examined the percentage of subjects protected from EIB after therapy (responder analysis).

The maximum decrease in FEV_1 required to produce a positive test result varies with the situation in which the test is performed. In a clinical setting the decrease in FEV_1 from baseline required to diagnose EIB is usually 10%[E145] or perhaps 13%[E264] or 15%.[E265] As an inclusion criterion in a pharmaceutical trial, a 20% decrease in FEV_1 is usually required to define a positive challenge result (as described in FDA guidance).[E256] In a clinical setting it is desirable to produce as complete protection as possible so that there is no decrease in FEV_1 after exercise with treatment. In a pharmaceutical trial protection might be defined as a less than 10% decrease in FEV_1 after exercise or 50% protection compared with placebo[E266] for patients who are required to have a 20% decrease at the screening visit. When other end points are used (eg, area under the curve [AUC] or time to recovery), the percentage of protection must also be adjusted for the situation in which the test is performed. Protection has been defined in some studies based only on statistically significant differences between responses after pretreatment with active drug compared with placebo. Attempts to define protection that have clinical relevancy have resulted in concepts such as "complete protection" and "clinical protection."[E258,E267] Complete protection can be suggested by predefined decreases in FEV_1 percentage within an accepted reference range (eg, <10% for FEV_1). Clinical protection has been defined as a 50% inhibition of the placebo response to exercise by drug pretreatment.[E263,E266] The 10% decrease is based on the mean plus 2 SDs of the decrease in healthy subjects,[E268] and the 50% protection is based on the coefficient of variation for repeated tests.[E266]

Numerous studies have been assessed in developing the evidence-based recommendations for therapy in this document, but there is little information on the consistency, presence, or absence of drug effect from recurrent testing. Also, most published evidence is from EIB studies in patients with clinically diagnosed (and usually atopic) asthma, and recommendations made herein are based on these data.[E2,E85,E253] Information suggesting possible differences in the pathogenesis of EIB and response to pharmacotherapies in apparently nonasthmatic elite athletes is summarized elsewhere in separate sections ("Pathophysiology" and "Competitive and elite athletes"). It is recommended that this section on therapy be used largely as a starting point on which to base a trial of best therapy for a patient with EIB tempered by the responsiveness and needs of that individual patient over time. Failure to demonstrate inhibition or significant attenuation of apparent EIB by using effective bronchoprotective agents should indicate the need for re-evaluation of the diagnosis.

β_2-Adrenergic receptor agonists

Summary Statement 18: Prescribe inhaled short-acting β_2-adrenergic receptor agonists for protection against EIB and for accelerating recovery of pulmonary function when given after a decrease in pulmonary function after exercise. [Strength of Recommendation: Strong; Evidence: A][E2]

β_2-Adrenergic receptor agonists are the single most effective therapeutic group of agents for acute prevention of intermittent EIB (Fig E1).[E259] They attenuate or protect against EIB in most patients.[E152,E259,E269-E273] Their effectiveness might be due to their action to enhance recovery of FEV_1 to baseline values when given after a decrease after exercise.[E260,E261]

Summary Statement 19: Prescribe a single dose of SABA, LABA, or both on an intermittent basis (ie, <4 times per week) before exercise because this might protect against or attenuate EIB. [Strength of Recommendation: Strong; Evidence: A]

Early investigations of β_2-adrenergic drugs developed for asthma showed that these agents were highly effective in protecting against EIB when inhaled 5 to 20 minutes before exercise.[E262,E269,E274,E275] Protection was found to last from 2 to 4 hours after inhalation, with most studies showing a duration at the lower end of this interval (Table E1).[E163,E270] There appear to be no substantial differences among SABAs currently in

use.[E163,E270] Mast cell stabilizers, as described below, have been used as add-on therapy to supplement SABAs in increasing the degree of bronchoprotection.[E259,E276]

Multiple LABAs are currently in use and differ in their actions, mainly in their onset of effect (Table E1). Formoterol has a more rapid onset of bronchodilator and bronchoprotective action; in contrast, salmeterol requires 15 to 30 minutes.[E271,E272]

Summary Statement 20: Be cautious in daily use of β_2-adrenergic agents alone or in combination with ICSs because this can lead to tolerance manifested as a reduction in duration, magnitude, or both of protection against EIB and a prolongation of recovery in response to SABAs after exercise. [Strength of Recommendation: Strong; Evidence: A][E2]

Prolonged duration of a bronchoprotective effect for as long as 12 hours has been shown for these drugs after the first dose in β_2-agonist–naive patients.[E157,E270,E273,E277-E279] However, many patients are not protected for this entire dosing interval, and the optimal dosing interval for bronchoprotection for EIB might be closer to 6 hours on average.[E157,E270,E277,E278] Prolonged protection with intermittent use of LABAs is sustained,[E157,E277,E280-E282] but daily maintenance use of LABAs (and SABAs) often results in some loss of bronchoprotection ("tolerance") with cross- tolerance to other β_2-agonists.[E278,E283-E289] Moreover, daily use of LABAs and SABAs might actually increase the severity of EIB.[E288,E289] Of additional concern, the degree of tolerance can increase with increasing bronchoconstriction, potentially putting patients experiencing severe asthma attacks at risk of less bronchodilator responsiveness at the time of greatest need.[E290] Therefore only intermittent use of adrenergic agonists is recommended for bronchoprotection.[E2,E85] Although some subjects might have a greater propensity than others to develop tolerance, only a small number of patients are required to demonstrate tolerance,[E285,E288-E293] suggesting that tolerance occurs in most patients. Studies addressing this in subjects with and without the Arg16Gly β_2-receptor polymorphism, which has previously suggested susceptibility to β_2-agonist tolerance, demonstrate that these polymorphisms do not influence tolerance to loss of bronchoprotection to β_2-agonists with EIB.[E294] Importantly, tolerance occurs even when patients are also receiving ICSs (Fig E1).[E153,E284]

The onset of tolerance can be rapid. By means of extrapolation of the effects on methacholine-induced bronchoconstriction[E285] and other challenges, such as AMP,[E295] it can occur within 12 to 24 hours after a first dose.[E285,E295-E297] The degree appears to increase with constant β_2-agonist use before it reaches a plateau.[E285] By means of similar extrapolation, β_2-antagonist sensitivity can recover within 72 hours after the last dose of β_2-agonist.[E166,E285]

Tolerance might not develop when β-agonist use is limited to an interval of 48 to 72 hours.[E166] However, a longer period for recovery might be required for other stimuli, such as allergen challenges.[E298] Tolerance is manifested most strikingly by a decrease in the effectiveness of SABAs[E299] and by a shortening of duration of LABA effects,[E153,E273,E278,E280,E284] with one study demonstrating this in less than 3 hours.[E300] There is also evidence this is manifested by prolongation of recovery from bronchoconstriction.[E285,E288] The presence of tolerance is often missed clinically because a patient is rarely challenged at the point of care; consequently, the shorter duration of protection and the prolonged recovery time are not revealed. Importantly, prescribing additional doses of β_2-agonist aerosol immediately before exercise might unintentionally contribute to further generation of tolerance.

The mechanism or mechanisms by which long-term (daily) use of β_2-agonists lead to tolerance is unclear. A number of observations have led to suggestions for possible mechanisms involved in the development of "tolerance." Long-term exposure of β-receptors to β_2-agonists results in uncoupling and internalization or sequestration in the cells in which they are degraded.[E301] This net loss in the number of available functional β_2-receptors[E302] results in "downregulation" of responsiveness to β_2-agonists, which manifests as a lack of clinical protection to bronchoconstrictive stimuli. Restoration of sensitivity requires resynthesis of the receptor to the active state. This resynthesis is observed clinically within 72 hours of cessation of exposure to a β_2-agonist.[E166,E285]

Stimulation of mast cell β-receptors normally inhibits mediator release. The process of β-receptor desensitization varies markedly among different cell types; bronchial mast cells are more easily desensitized than bronchial smooth muscle cells.[E301,E303] Downregulation appears to occur more readily in mast cells, as can occur with therapeutic administration of β_2-agonists.[E304,E305] For this reason, the clinical effects of downregulation are evident more rapidly on mast cells, with an effect on bronchoprotection rather than on smooth muscle and bronchodilation.[E306] The downregulation of mast cell β-receptors not only enhances mediator release but potentially enhances bronchoconstriction as well.[E288,E304,E305,E307,E308]

This β_2-receptor downregulation or tolerance is demonstrated clinically as a reduction in duration of β_2-agonist bronchoprotection to stimuli, such as exercise, which depends on mast cell mediator release for bronchoconstriction.[E309] Tolerance to bronchodilation after EIB is demonstrated by prolongation of the time of recovery from bronchoconstriction in response to usual β_2-agonist doses.[E285,E288,E289]

Downregulation of the β_2-receptor is accompanied by augmentation of pathways mediated through the LT, histamine, and thromboxane receptors. Activation of these receptors has the added potential to enhance bronchoconstriction.[E310-E312] Also, BHR can be induced by non–mast cell mediator mechanisms involving cholinergic agonists, for example, independently or with mast cell mediator mechanisms.[E313-E315]

Use of LABAs as daily monotherapy to provide overall asthma control is not recommended.[E252] When ICSs alone are not adequate in controlling chronic asthma, LABAs are often combined with ICSs to provide effective maintenance therapy; however, there is no convincing clinical evidence that this combination diminishes tolerance to the bronchoprotective effect of LABAs in asthma or EIB with asthma.[E153,E284,E316] LABAs alone used intermittently, up to 3 times a week, do not appear to be associated with tolerance and can be prescribed for EIB.[E166,E317]

LT inhibitors

Summary Statement 21: Consider prescribing daily therapy with leukotriene inhibitors because this does not lead to tolerance and has been shown to attenuate EIB in 50% of patients. It can also be used for intermittent or maintenance prophylaxis; however, it provides incomplete protection and is not effective for reversing airway obstruction. [Strength of Recommendation: Strong; Evidence: A][E2]

The role of LTs in patients with EIB is to sustain the bronchoconstrictive and inflammatory response, although their role appears to vary significantly among patients. Correspondingly, inhibitors of the LT pathway (LTRAs and lipoxygenase inhibitors) are effective in reducing the severity of the decrease in FEV_1, as well as enhancing recovery of airway narrowing. Furthermore, there is much variability in their effectiveness, from completely blocking EIB in some asthmatic patients to blocking EIB less so or not at all in others. There is a 30% to 80% attenuation of EIB, with approximately 50% of patients being responders.[E257,E318,E319] These percentages can vary, depending in part on the FEV_1 decrease required to make a diagnosis of EIB (>10%, >15%, or >20%) or used to define protection. Most patients do not experience complete protection.[E258] This is not surprising given that other mediators (eg, PGD_2 and histamine)[E48,E320] are involved in EIB.

Various LTRAs have been found to be effective in attenuating EIB.[E58,E321-E324] Most studies have examined specific LTD_4 receptor antagonists, particularly montelukast. Montelukast is approved by the FDA for treatment of EIB in adolescents and adults. Montelukast acts within 1 to 2 hours of oral administration[E62,E324-E326] and has a bronchoprotective activity of 24 hours (Table E1).[E58,E59,E257,E326-E329] Maximum protection might not be retained in some subjects toward the end of this period.[E329] LTRAs also accelerate the time to recovery from EIB.[E58,E299] Although LTRAs are not as effective overall in attenuating EIB as β-agonists,[E258] tolerance does not develop with long-term use.[E58,E286,E287,E330] The variability in effect on EIB suggests populations of responders and nonresponders similar to those shown for the LT effects on overall asthma control (Fig E1).[E331-E333]

A second group of agents that affects the LT pathway by inhibiting synthesis are the lipoxygenase inhibitors. Lipoxygenase inhibitors have been shown to attenuate EIB when given orally,[E60,E160,E334,E335] but the duration of inhibition of these compounds is relatively short,[E60,E160] and they are not currently recommended for this indication (Table E1). Early-stage studies have demonstrated that inhibition of the LT pathway by 5-lypoxygenase activating protein inhibitors can inhibit EIB.[E336]

Mast cell stabilizers

Summary Statement 22: Consider prescribing inhaled cromolyn sodium and nedocromil sodium (currently not available in the United States as a metered-dose inhaler or dry powder inhaler) shortly before exercise; this attenuates EIB but can have a short duration of action. There is no bronchodilator activity. They might be effective alone or as added therapy with other drugs for EIB. [Strength of Recommendation: Strong; Evidence: A][E2]

Cromolyn sodium and nedocromil sodium are 2 structurally unrelated compounds that have no bronchodilator activity but have similar bronchoprotective activity against EIB when inhaled.[E57,E259,E337,E338] Several mechanisms have been proposed for these agents, including interference with mast cell mediator release of PGD_2.[E57,E337,E339] The bronchoprotective effect is rapid[E340] but of short duration (1-2 hours; Fig E1 and Table E1).[E164,E341] These agents can be effective when taken alone or when inhaled shortly before, and perhaps simultaneously with, exercise and might increase overall inhibition of EIB when combined with other drugs used to diminish EIB.[E259,E275,E341,E342] Significant intersubject and between-study variability has been observed in the ability of these agents to attenuate EIB. Some studies found few or no subjects protected, whereas other studies showed complete protection.[E343,E344] The effectiveness of cromolyn might be dose related.[E344-E346] Long-term use of either drug is not accompanied by tolerance. For this reason and because of their excellent safety profiles and rapidity of action, these agents can be used repeatedly to attenuate EIB in responsive subjects.[E259,E347]

ICSs

Summary Statement 23: Consider prescribing ICSs in combination with other therapies because ICSs can decrease the frequency and severity of EIB but not necessarily eliminate it. [Strength of Recommendation: Strong; Evidence: A][E2]

EIB in otherwise symptomatic asthmatic patients is best controlled by maintenance anti-inflammatory treatment alone[E148,E348,E349] or in combination with other short-term preventive treatment.[E252,E318,E350] ICSs improve overall asthma control in most patients with chronic persistent asthma. Use of ICSs is associated with attenuation of hyperresponsiveness to direct and indirect stimuli, including exercise.[E351,E352] The dose-dependent effect of ICSs has been observed shortly after the initial (3-4) weeks of treatment[E148,E353]; however, the effects of ICSs are also time dependent with longer duration (12 weeks) of treatment, demonstrating no difference between different doses inhibiting EIB.[E349] The relationship between control of persistent asthma and bronchoprotection, however, is imperfect (Fig E5).[E89,E354] Nevertheless, the degree of EIB is considered a reflection of asthma control (or lack of control), and in particular, moderate-to-severe EIB strongly suggests the need for reassessment of therapy or another diagnosis.[E348]

Some bronchoprotective effect against EIB with high-dose ICSs has been recorded as early as 4 hours after the first dose in adults.[E56,E355,E356] However, it has also been demonstrated that lower doses consistent with the daily treatment of asthma can have a bronchoprotective effect on EIB in children.[E169] After 1 week of therapy, efficacy begins to plateau[E40,E148,E353]; however, bronchoprotection can increase further over weeks or even months until it reaches its final plateau.[E147,E348,E357] This final plateau can come in the form of complete inhibition of EIB.[E349] Bronchoprotection has been shown to occur in 30% to 60% of asthmatic patients with EIB, with marked individual variability ranging from "complete" protection to little or no evidence of protection.[E147] In the absence of definitive dose-ranging and repetitive studies in individual patients, it is not clear whether this reflects distinct subpopulations of responders and nonresponders (eg, a reflection of genetic differences) or whether this is related to EIB severity.

Allergic rhinitis is a common finding in atopic asthmatic patients, and there is some evidence that effective treatment of nasal congestion and obstruction by nasal ICSs is associated with at least mild reduction in EIB.[E357,E358,E359] To some extent, these findings validate the concept of the unified airway theory, which states that allergic rhinitis of the nose and atopic airway inflammation in asthmatic patients are manifestations of similar pathologic processes in the upper and lower respiratory airways, respectively.[E360] It is unclear whether treating EIB with both intranasal corticosteroids and ICSs leads to more effective treatment of EIB in allergic asthmatic patients compared with ICSs alone.

ICSs do not necessarily obviate the need for acute bronchoprotection against EIB (Fig E1). β_2-Adrenergic agonists can be added intermittently, if necessary, for short-term prevention of EIB.[E260,E261] When maintenance ICSs are not sufficiently effective, LTRAs can be used to obtain added protection with low- and medium-dose ICSs[E318,E361] compared with high-dose ICSs[E319] while also administering β_2-agonists for acute bronchoprotection, if necessary.[E121,E253,E267,E362]

Summary Statement 24: Do not prescribe daily LABAs with ICS therapy to treat EIB unless needed to treat moderate-to-severe persistent asthma. The ICS might not prevent the occurrence of tolerance from daily β_2-agonist use. [Strength of Recommendation: Strong; Evidence: A]

The preponderance of evidence indicates little amelioration of tolerance to β_2-agonist bronchoprotection by ICSs[E153,E284,E299,E316,E363] and that a shortened degree of bronchoprotection remains when ICSs and LABAs are administered together. Nevertheless, one study that assessed the combination of an ICS and LABA (fluticasone and salmeterol) for maintenance therapy in adult patients indicated better bronchoprotection at 1 and 8.5 hours after dosing compared with the same dose of fluticasone alone during 4 weeks.[E153] In that study most patients receiving the combined therapy also exhibited greater complete (<10% decrease of FEV_1) protection and overall asthma control. A somewhat similar study with the same agents in children and adolescents also indicated a small persistent effect of bronchoprotection when the combination was used compared with the ICS alone.[E364] LABAs in combination with ICSs when used on demand compared with a low dose of ICS daily can reduce EIB by a similar magnitude over 6 weeks.[E365]

Anticholinergic agents

Summary Statement 25: Consider prescribing inhaled ipratropium bromide for patients who have not responded to other agents; however, its ability to attenuate EIB is inconsistent. [Strength of Recommendation: Weak; Evidence: A][E2]

Anticholinergic agents have bronchodilator activity[E314] through blocking vagally mediated tone and have been used alone and in conjunction with SABAs with some success in treating acute asthma exacerbations.[E366] However, the efficacy of anticholinergic agents to prevent EIB[E367] has not been consistent in double-blind studies, especially in placebo-controlled trials (Table E1).[E368] Not all patients appear to respond to anticholinergic agents,[E259,E342,E369-E371] and responsiveness can be variable in the same patient.[E370] Studies should be performed to determine the characteristics of the responder population (perhaps based on increased cholinergic contributions to EIB in some patients).[E314,E372]

Methylxanthines, antihistamines, and other agents

Theophylline and aminophylline are methylxanthines that have been used for long-term maintenance therapy to treat persistent asthma. In recent years, these agents have only been used as adjunct therapy to ICSs or similar maintenance therapy when further control of asthma is needed.[E253,E350] Methylxanthines are nonselective phosphodiesterase inhibitors of the cyclic AMP and cyclic guanine monophosphate pathways that play a role in the pathophysiology of asthma. Methylxanthines are mild bronchodilators and modify EIB in some patients, possibly in part due to their bronchodilator action.[E373,E374] However, there are studies that clearly show no benefit from methylxanthines administered orally.[E375] Methylxanthines exhibit a relatively narrow therapeutic index with potentially serious adverse events, such as seizures. Selective phosphodiesterase inhibitors are safer and might have efficacy similar to that of the methylxanthines. One such agent, roflumilast, is a phosphodiesterase 4 inhibitor that has been reported to attenuate mild EIB.[E376]

Caffeine also belongs to this class of drug. When caffeine is ingested, it can attenuate EIB in a dose-response manner, with evidence of high doses of caffeine (6-10 mg/kg) inhibiting EIB.[E170,E377,E378] These studies have led to the recommendation of abstaining from caffeine before performing bronchial provocation testing to identify EIB (Table E1).

Some antihistamines have been reported to attenuate EIB,[E61,E62,E320,E379-E382] although with inconsistent results.[E62,E162] Other antihistamines appear ineffective.[E383] A possible explanation for this variability might relate to differences in the intensity and duration of the exercise stimulus, with greater intensity or more severe EIB required for participation of histamine in the pathogenesis of EIB.[E54] Furthermore, histamine is less potent than the other 2 main mediators (leukotriene and prostaglandins) that contribute to EIB (Fig E2).[E384] In addition, the antihistamine class has pharmacodynamic diversity. For example, antihistamines can inhibit mediator activation and release and act on end organs and other histamine receptors.[E385] Different routes of administration and dosages of antihistamines can also be confounding factors in previous studies.[E386]

However, other evidence suggests that antihistamines used in children with allergic rhinitis and EIB might not be bronchoprotective.[E383] The conclusion is that there is an absence of definitive studies that have determined the effectiveness of nasal or systemic antihistamines used to treat allergic rhinitis for an effect on EIB. It is likely to remain common practice to use antihistamines to treat allergic rhinitis in the hope that there will be some effect on EIB. Definitive studies are still needed to confirm the utility of this practice.

Numerous other compounds have been examined for activity against EIB and might have moderate effectiveness in some situations.[E269] These include calcium channel blockers,[E387,E388] inhaled furosemide,[E389-E391] some α-adrenergic receptor antagonists (oral and inhaled),[E367,E392] inhaled heparin,[E393] and hyaluronic acid.[E394] These agents do not always produce consistent results in preventing EIB. The effectiveness of some of these agents does not necessarily apply to other members of the same drug class, suggesting various mechanisms of action not necessarily related to the obvious mechanisms attributed to each class of drug. The effectiveness of diverse kinds of drugs suggests that there are multiple mechanisms underlying EIB.[E395] Although some of these drugs are not recommended for clinical use against EIB, these and other agents might be useful as probes in studying the possible mechanisms underpinning EIB. In addition, it is important to recognize that these agents can interfere with clinical protocols that seek to examine the effects of other experimental drugs on EIB.

Nonpharmacologic therapy

Summary Statement 26: Use pre-exercise warm-up for EIB since it may be helpful in reducing the severity of EIB. [Strength of Recommendation: Strong; Evidence: A][E2]

Warm-up before exercise was studied on postexercise bronchoconstriction in athletes with EIB. Continuous warm-up before exercise was shown to cause a significant decrease in postexercise bronchoconstriction in some athletes (Fig E1).[E396] This has importance in patient education, and health care professionals should tell patients that pre-exercise warm-up should be done at 60% to 80% HRmax to provide partial attenuation of EIB; this refractory period can last typically from 1 to 3 hours and occasionally for 4 hours.[E79,E397,E398] However, this does not alleviate the need for medications. Albuterol plus a warm-up provides better protection than the warm-up or albuterol alone.[E77,E399]

The mechanisms for this approximately 50% reduction in airway responsiveness in 50% of patients with EIB with repeated exercise after an initial exercise stimulus is not well understood. Initially, the inhibition or refractory period was considered to be due to the effects of depleting bronchoconstrictive mediator from mast cells, although later this was considered to be due to the release of protective prostaglandins.[E400] However, using inhaled mannitol as a model for EIB, which also demonstrates a refractory period after an initial challenge test, has suggested the protective effect might be due to transient tachyphylaxis at the level of the airway smooth muscle to the mediators of bronchoconstriction, rather than mediator depletion.[E81]

Summary Statement 27: Consider with caution the recommendation of reduction of sodium intake and ingestion of fish oil and ascorbic acid supplementation; results are questionable in reducing the severity of EIB. [Strength of Recommendation: Weak; Evidence: A][E2]

Dietary supplementation as a treatment for EIB has generally seen evidence of significant yet incomplete inhibition of the percentage decrease in FEV_1 after exercise with low-salt diets, omega-3 fatty acids, and ascorbic acid (vitamin C) with up to 3 weeks of supplementation.[E46,E401-E406] Although many of these studies have been performed in small numbers of subjects, they are generally sufficiently powered. However, many studies require validation because of the use of exercise protocols that might provide suboptimal dehydrating stimuli to the airways or unnecessarily prolong the duration of exercise beyond the recommendation of 6 to 8 minutes so that the severity of EIB is reduced because of refractoriness (eg, progressive exercise challenge until volitional exhaustion). This might be the reason why many of these studies have demonstrated inhibition to mild airway responses to exercise, which makes it difficult to extrapolate these results to persons with moderate-to-severe EIB and, for this reason, can only be given a weak recommendation. Thus it is strongly recommended that further studies assessing dietary supplementation validate these studies outlined below, and this task should be approached by using the recommended protocols for the diagnosis of EIB (also see the Diagnosis section),[E2,E145] which should also include recommendations for the assessment of pharmacotherapies for the treatment of EIB by regulatory agencies.[E256] If dietary supplements are to be prescribed, they should not be seen as an alternative to established pharmacotherapies.

In a series of studies in subjects with mild EIB, one group of investigators has comprehensively shown that a low-salt diet for 2 to 5 weeks inhibits EIB, whereas high-salt diets worsen EIB.[E401,E404] The same investigators have demonstrated that in elite athletes and asthmatic patients with EIB, a 3-week course of high-dose omega-3 fatty acid supplements inhibits the decrease in FEV_1 with exercise or EVH challenge and reduces associated inflammatory markers.[E46,E403,E405,E406] These findings challenged the initial study assessing omega-3 supplements, which did not demonstrate inhibition on EIB with a similar high daily dose used for 3 weeks.[E407] This negative finding has been reproduced with inhaled mannitol[E408] and EVH[E409] by using similar dose and duration of treatment, leaving the role of omega-3 fatty acids in patients with EIB uncertain, and as such this is currently supportive of a weak recommendation. There also is weak evidence for vitamin C supplementation, leading to attenuation of EIB either acutely or after days or a few weeks of supplementation.[E402,E410,E411]

Competitive and elite athletes

Summary Statement 28: Treat athletes with EIB alone in a similar manner to those with EIB and asthma by using the recommended general treatments for asthma. This might require additional consideration in athletes in whom some governing bodies might have requirements for obtaining permission to receive pharmaceutical agents for competition. [Strength of Recommendation: Strong; Evidence: A]

(http://www.usada.org/substances/prohibited-list/athlete-guide/)

Management of EIB in elite athletes is similar to that for recreational athletes and should include reducing relevant environmental exposures as much as possible; treatment of associated comorbid conditions; appropriate pharmacotherapy for control of symptoms, prophylaxis, and rescue; and patient education.[E121,E412] An individualized exercise prescription considering the athlete's venue might need to be designed by the athlete and the specialist to provide adequate control of EIB or EIB with asthma (eg, swimmers).

Similar to observations in asthmatic patients with EIB, as extensively outlined in this document, studies in athletes with EIB alone have shown the same results in the form of the acute protective effect of a β_2-agonist, the mast cell stabilizer cromoglycate, the leukotriene antagonist montelukast, and an inhibitory effect of high-dose ICSs when given acutely.[E56,E57,E337,E413,E414]

When considering treatment to control EIB, it is recommended that controller pharmacotherapy for athletes who have EIB with asthma should include daily ICSs.[E2,E147] Again, It should be noted that the combination of ICSs plus LABAs is not recommended because of the potential for tolerance to develop with daily use of β_2-agonists. This tolerance reduces the duration of bronchoprotection in exercise afforded by the β_2-agonist and prolongs recovery time with rescue bronchodilator.[E309] In some patients with concomitant moderate-to-severe persistent asthma, however, combination therapy can have added utility. The athlete's performance results should be monitored carefully because spirometry and symptoms alone might not be reliable end points to monitor asthma control. Because objective evidence of EIB is recommended by using indirect tests, it can be useful to repeat these tests after weeks to months on regular ICSs or to objectively assess the acute effect of a treatment to inhibit EIB and demonstrate this effect to the athlete, as has been demonstrated in airway hyperresponsiveness in patients with clinical asthma.[E149,E352]

Athletes engaged in either winter or summer sports with high ventilation rates (eg, swimming, mountain biking, rowing, biathlon, cross country skiing, and skating events) can have respiratory symptoms compatible with those with EIB alone, with or without demonstrating a positive challenge test result indicative of EIB or asthma. It has been proposed that the

repetitive epithelial injury repair cycle in response to breathing high volumes of unconditioned air over long periods can result in changes in the contractile properties of BSM as a result of exposure to plasma-derived products from exudation.[E117,E415,E416] This might be representative of an "airway injury" resulting in a form of overuse syndrome in contrast to EIB, which results from airway smooth muscle constriction from the osmotic release of bronchoconstrictive mediators from resident inflammatory cells (eg, mast cells and eosinophils). In the case of the winter athlete, it is common to see high prevalence of BHR to direct challenge tests, such as methacholine, and low prevalence of BHR to indirect tests.[E417,E418] If airway injury is suspected in an athlete, treatment recommendations can include the limitation of activity rather than introduction of the pharmacologic agents used in the treatment of asthma and EIB.[E419,E420] However, in the summer athlete with allergic sensitization, the conditioning of large volumes of air, which might contain higher levels of seasonal airborne allergen, could lead to airway inflammatory cell recruitment, as well the abovementioned consequences of plasma exudation, leading to passive sensitization of the BSM.[E415] In contrast to the winter athlete, summer athletes generally demonstrate higher rates of BHR to indirect tests and lower rates of BHR to direct tests,[E137,E421] which has led to suggestions that elite-level exercise in these environments in susceptible subjects can promote EIB.[E422]

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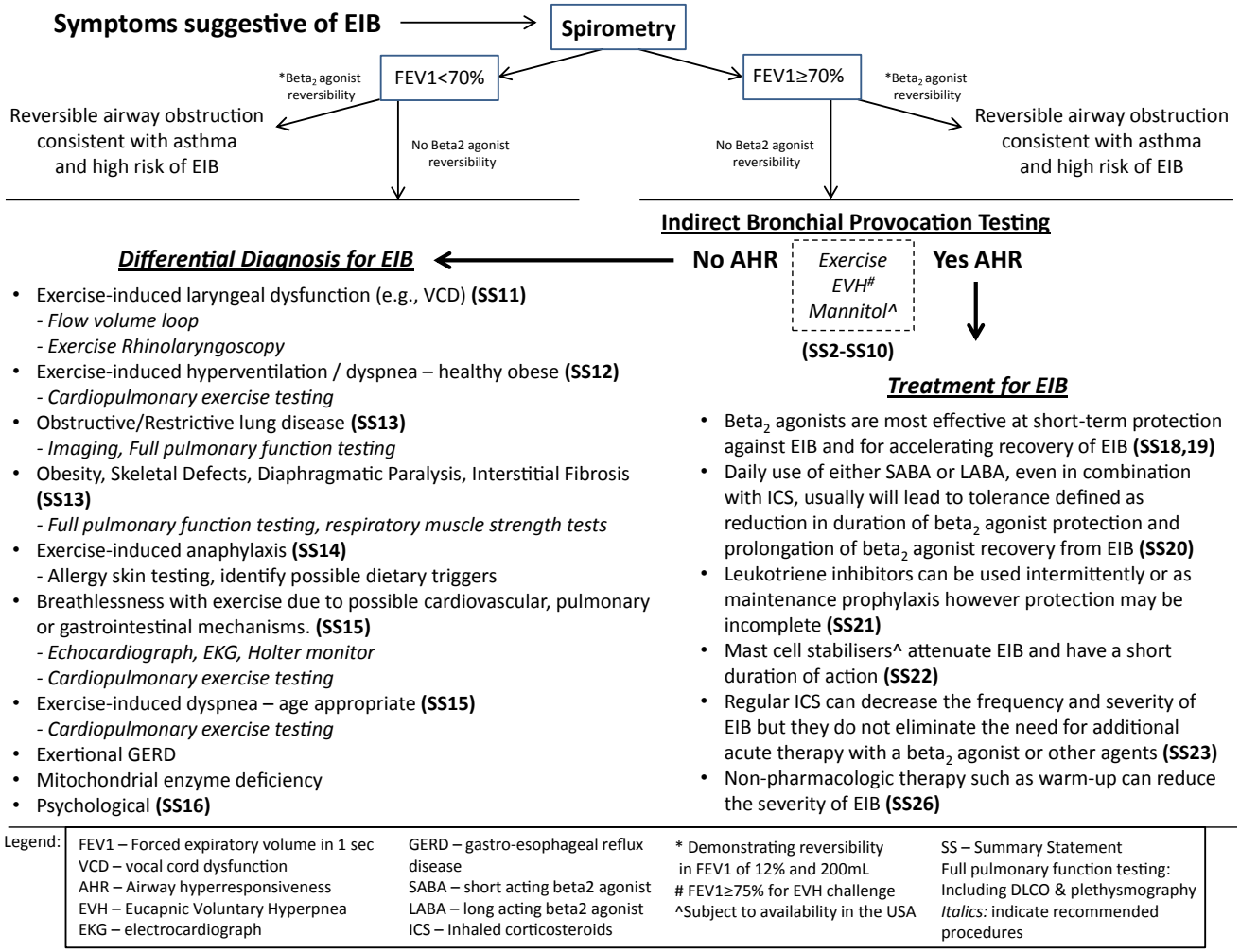

FIG E1. Algorithm for the diagnosis, treatment, and differential diagnosis of EIB.

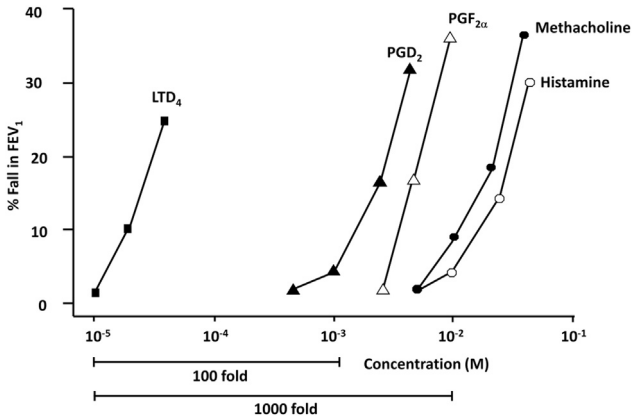

FIG E2. Airway smooth muscle sensitivity to mediators of bronchoconstriction. The potency of mediators of bronchoconstriction that are released in the presence of dry air hyperpnea or osmotic stimuli and then act on specific receptors on airway smooth muscle to cause airway narrowing is shown. These mediators that are endogenously released in the airway, such as leukotrienes and prostaglandins, are significantly more potent than mediators that are exogenously administered to assess airway hyperresponsiveness, such as methacholine. Taken from O'Byrne.[E384]

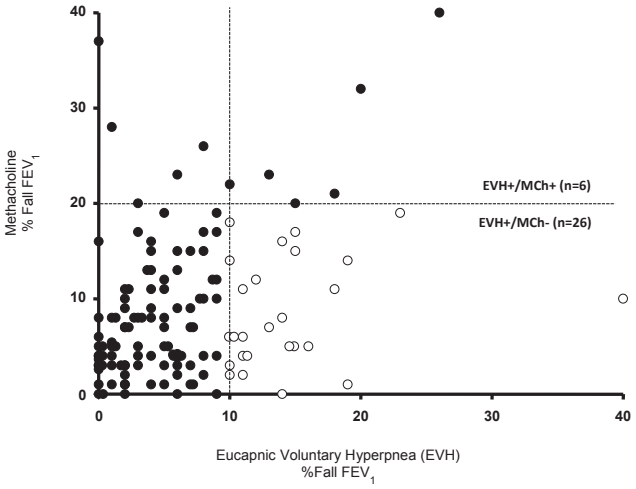

FIG E3. Relationship of airway sensitivity to EVH versus methacholine. The percentage decrease in FEV_1 to a methacholine challenge in relation to the percentage decrease in FEV_1 to EVH challenge in 131 adults reporting symptoms with exercise and no previous diagnosis of asthma. A positive response to EVH documented as a 10% decrease in FEV_1 identified BHR suggestive of EIB more frequently than a 20% decrease in FEV_1 to methacholine. *White dots* highlight those with a positive EVH challenge result and a negative methacholine challenge result. Adapted from Holley et al.[E151]

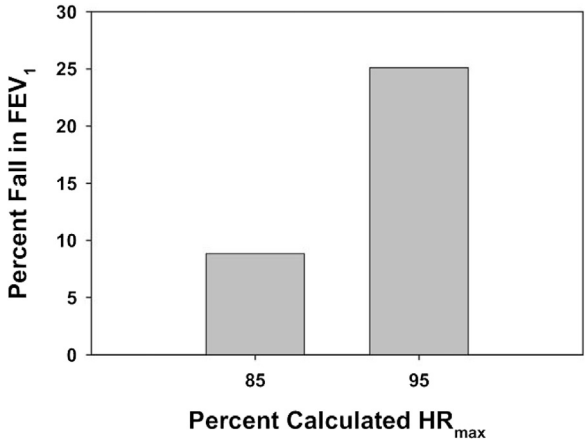

FIG E4. Importance of optimal exercise intensity: highlighting the importance of optimal exercise intensity when assessing EIB. Twenty asthmatic adolescent patients were exercised at 85% of estimated calculated HRmax, resulting in only 9 of 20 having positive results for EIB (mean decrease FEV_1 = 8.84%); however, all 20 asthmatic patients had positive test results after exercise at 95% of HRmax (mean decrease in FEV_1 = 25.11%). Adapted from Carlsen et al.[E139]

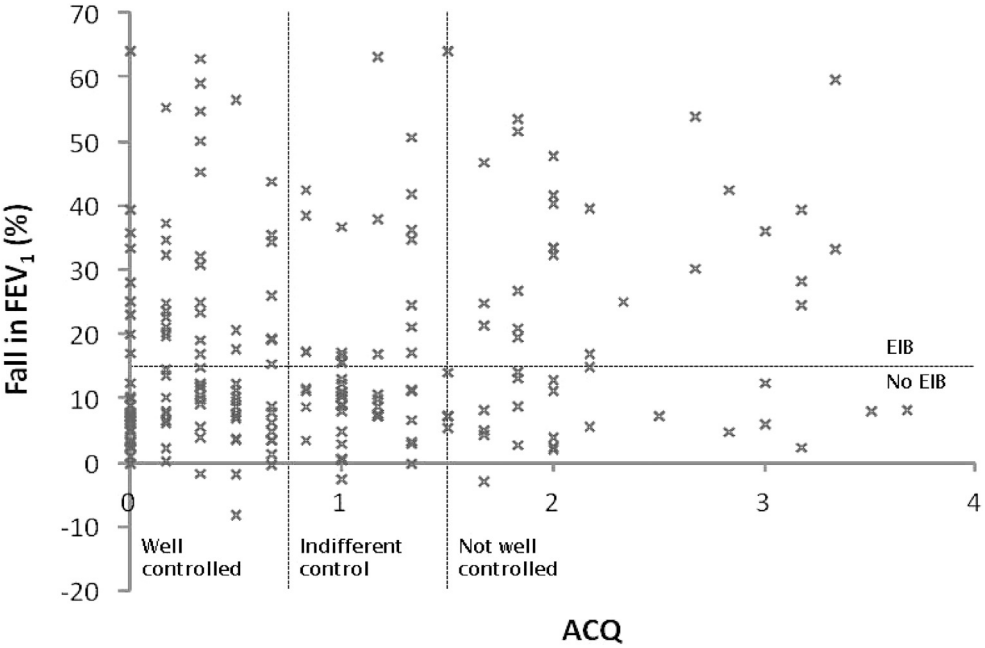

FIG E5. The poor relationship between asthma control measured by using the Asthma Control Questionnaire *(ACQ)* and the percentage decrease in FEV_1 after exercise challenge in 200 adolescents who demonstrated EIB when a 15% decrease in FEV_1 was documented. The cutoff values for asthma control are less than 0.75, representing controlled asthma, and greater than 1.5, representing uncontrolled asthma. Taken from Madhuban et al.[E354]

TABLE E1. Medication withdrawal schedule

Medication/activity/food	Recommended time to withhold before challenge testing	Evidence of maximum duration of protection on EIB	Reference
SABA (albuterol, turbutaline)	8 h	<6 h	E158, E159
LABA (salmeterol, eformoterol)	24 h*	12 h	E158, E160, E161
LABA in combination with an ICS (salmeterol/fluticasone, formoterol/budesonide)	24 h*	NA†	E153
Ultra-LABAs (indacaterol, olodaterol, vilanterol)	≥72 h‡	NA	
ICS (budesonide, fluticasone propionate, beclomethasone)	6 h	NA§	
Long-acting ICS (fluticasone furoate)	24 h	NA‖	
Leukotriene receptor antagonists (montelukast, zafirlukast)	4 d	24 h¶	E59, E62
Leukotriene synthesis inhibitors (zileuton/slow-release zileuton)	12 h/16 h	4 h	E160
Antihistamines (loratadine, cetirzine, fexofenadine)	72 h	<2 h#	E162
Short-acting muscarinic acetylcholine antagonist (ipratropium bromide)	12 h	<0.5 h	E163††
Long-acting muscarinic acetylcholine antagonist (tiotropium bromide, aclidinium bromide, glycopyrronium)	≥72 h‡	NA	
Cromones (sodium cromoglycate, nedocromil sodium)	4 h	2 h	E164, E165
Xanthines (theophylline)	24 h	NA**	
Caffeine	24 h‡‡	NA**	
Vigorous exercise	>4 h	<4 h	E79

NA, Not available.

*A longer duration of withdrawal of up to 48 hours might be warranted in subjects who take regular LABAs to permit recovery of tolerance and prevent delay of recovery to a standard dose of rescue β_2-agonist.[E166,E167]

†Study demonstrates similar efficacy for a LABA acutely when included in combination with an ICS.

‡No evidence exists for the protective effects of ultra-LABAs or long-acting muscarinic acetylcholine antagonists on indirect tests. Thus we recommend testing after complete washout of drug, and for some ultra-long-acting drugs, washout can be up to 10 days. There is evidence of 36 hours of protection of an ultra-LABA on methacholine challenge.[E168]

§Evidence exists for high-dose ICSs to attenuate airway responses to indirect challenge tests in adults (eg, 1500 μg/d),[E56] with evidence for lower standard doses in children.[E169] Thus we recommend testing after complete washout of drug.

‖Based on longer absorption half-life compared with fluticasone propionate.

¶Significant inhibition of EIB is observed at 24 hours after dosing. Thus we recommend testing after complete washout of drug.

#H_1-antagonists demonstrate an overall weak inhibitory effect on EIB[E54]; however, they might have a modifying effect on the airway sensitivity (PD_{15}) to mannitol.[E55] Thus we recommend testing after complete washout of drug.

**In the absence of direct evidence, we recommend testing after complete washout of drug.

††Available data supporting withholding times are from studies assessing the duration of action of drugs on exercise challenge, unless otherwise indicated for EVH.

‡‡High doses of caffeine consumption (>3 cups of coffee) are most effective.[E170]