



CLINICAL REVIEW

Exercise induced bronchoconstriction in adults: evidence based diagnosis and management

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What is exercise induced bronchoconstriction (EIB)?

EIB is defined as “the transient narrowing of the lower airway following exercise in the presence or absence of clinically recognized asthma.”¹ Bronchoconstriction typically develops within 15 minutes after exercise and spontaneously resolves within 60 minutes. After an episode of EIB, there is often a refractory period of about 1-3 hours in which, if exercise is repeated, the bronchoconstriction is less emphasised in 40-50% of patients.²⁻³ EIB can also occur during exercise.⁴⁻⁵

The term “exercise induced bronchoconstriction” is preferred to that of “exercise induced asthma” since asthma is a chronic condition which is not induced by a single bout of exercise. EIB is more likely in people with asthma, but it also occurs in individuals without asthma.¹⁻⁶ EIB is characterised by falls in forced expiratory volume in one second (FEV₁) after exercise, while in people with asthma there is persistent airway inflammation and recurrent symptoms outside of exercise (that is, with allergen exposure or upper respiratory infections). Often, at baseline there is evidence of reversible lower airway obstruction. Pharmacological management for persistent asthma requires daily anti-inflammatory, preventive medications. However, airway inflammation and remodelling also occur in cold weather athletes with and without asthma and EIB.⁷

What triggers an episode of EIB?

EIB typically occurs after high intensity aerobic exercise during which high ventilation (>85% of maximal voluntary ventilation) dehydrates the respiratory mucosa and leads to a transient increase in airway osmolarity, mast cell activation with mediator release (including histamine, serine proteases, prostaglandins, and leukotrienes⁸), and bronchoconstriction. Dry environments exacerbate EIB because of greater respiratory water loss. Exacerbations due to cold air are because of the reduced water content of the air rather than the low temperature. Increased exposure to allergens and respiratory irritants may exacerbate

bronchoconstriction during high ventilation exercise.⁹ EIB may be seasonal in some individuals with atopy,¹⁰⁻¹¹ although research on this association is limited. Figure 1 shows the pathogenesis of EIB and how diagnostic tests and management interventions work.

Who gets EIB?

EIB can occur in children and adults of various fitness levels, ranging from recreational to elite competitors,¹⁵⁻¹⁶ with a reported prevalence of 10-50% or greater in high level athletes, depending on sport and surveillance or diagnostic methodology.¹⁷⁻¹⁸ Individuals who are exposed to high concentrations of airborne particulate matter during high ventilation exercise have an increased incidence of EIB (see box 1).

How does EIB present?

Individuals with EIB typically complain of breathlessness, wheezing, cough, and chest tightness during or after exercise. Athletes may seek medical input because they feel that these symptoms limit their sports performance. However, the non-specific nature of the symptoms can make it hard to reach a firm diagnosis. A systematic review concluded that there are currently no questionnaires with sufficient sensitivity and specificity to diagnose EIB based on symptoms and signs alone.²⁰

How is EIB accurately diagnosed?

Algorithms for the diagnosis of EIB are available (see fig 2).^{1-8, 18-21} Formal diagnosis requires either direct or indirect challenge tests designed to induce bronchoconstriction. Direct challenge uses a nebulised drug to stimulate the airway smooth muscle, whereas indirect challenge attempts to dehydrate the mucosa (see box 2).²² Spirometry before and at 5, 10, 15, and 20 minutes after the stimulus measures the change in FEV₁. A reduction of >10-15% in FEV₁ at two consecutive post-challenge time points is considered diagnostic for EIB, though specific

What you need to know

- Exercise induced bronchoconstriction (EIB) is most common in individuals with asthma but also occurs in those without
- EIB is commonly misdiagnosed because its symptoms (such as shortness of breath, chest tightness, wheezing, and cough) are neither sensitive nor specific
- EIB is most accurately diagnosed by using spirometry to measure forced expiratory volume in one second (FEV₁) before and after a high intensity exercise challenge in dry air or eucapnic voluntary hyperpnoea
- Short acting β agonists are recommended first line treatment for confirmed EIB, used only "as required" rather than daily to avoid tolerance and potential exacerbations
- People with EIB symptoms and a negative bronchoprovocation test or with documented EIB and ongoing symptoms despite treatment should have their management and diagnosis reviewed
- Exercise induced laryngeal obstruction is a relatively common cause of breathlessness in athletes, which may mimic or occur alongside EIB

Methods

We searched Medline for the terms "exercise induced bronchoconstriction" or "exercise induced asthma" or "asthma" and "athlete" or "exercise." We also evaluated our personal archives of peer reviewed references. We gave priority to systematic reviews and meta-analyses, as well as professional society task force and practice parameter papers. When these comprehensive resources were insufficient or published more than five years ago, we used Google Scholar to identify more recent prospective epidemiological studies and randomised clinical trials which cited these references.

Box 1: Athletes who show increased incidence of EIB when exposed to high concentrations of airborne particulate matter during high ventilation exercise^a

- Individuals participating in physical activity in athletic fields and fitness trails adjacent to roads with high traffic volume
- Those who regularly skate at ice rinks where ice resurfacers are powered by fossil fuels
- Risks among winter sports athletes are increased by the dry ambient air
- Swimmers who train in indoor chlorinated swimming pools experience inhalation exposure to chloramines (respiratory irritants that arise from the reaction of nitrogenous waste products with chlorine¹⁹)

recommendations vary (for example, the European Respiratory Society recommends a >12% fall in FEV₁).¹⁸ Diagnostic thresholds are based on a greater post-challenge decrease in FEV₁ than that shown by 95-99% of the healthy population (2-3 standard deviations beyond the mean response).²³ About half of athletes with EIB will have a negative exercise challenge test result, so two tests may need to be done to exclude the diagnosis.²⁴

Challenge tests are designed to trigger a bronchoconstriction and may provoke a severe attack. With the exception of the mannitol challenge, challenge tests should be conducted only in facilities where bronchodilator, supplementary oxygen, resuscitation equipment, and medical staff are readily available in the event of a severe response.²⁹ Direct and indirect challenge tests are contraindicated in patients with baseline impairments in FEV₁ (<70-80% of predicted).

Indirect tests are preferable to direct tests as they replicate the environmental conditions and the pathophysiology, including the inflammatory mediator release, that trigger respiratory symptoms. The most widely used indirect tests are high intensity exercise and eucapnic voluntary hyperpnoea (see box 2). Both tests use high ventilation rates in dry air conditions to dehydrate the respiratory mucosa. High intensity exercise has the advantage of exposing the individual to sport-specific physiological demands, whereas eucapnic voluntary hyperpnoea can be conducted in a controlled manner, which allows for easy standardisation between facilities.

What are the consequences of misdiagnosing EIB?

Diagnosis of EIB based on symptoms without proper adherence to established protocols has led to a high rate of false positive diagnoses, and consequent unnecessary use of bronchodilators.³²

However, individuals with false negative results (box 3) may not receive treatment and may continue to experience EIB. This may take the form of an occasional nuisance or severe impairment that causes them to stop taking part in sport and lose the health benefits of physical activity.²⁰ Though rare, there are reports of asthma related sudden death during sports participation, with one epidemiological study identifying 61 deaths in seven years in the United States.³⁵

What can mimic EIB?

Other conditions can cause shortness of breath during exercise and may be mistaken for EIB. Asthma and exercise induced laryngeal obstruction (EILO, previously called vocal cord dysfunction) are two of the most common (see table 2).³³

Exercise induced laryngeal obstruction (EILO)

Some athletes experience EILO with or without EIB.³⁶ One study reported an incidence of 5% in 370 developmental or elite athletes, with about half of those with EILO also testing positive for EIB.³⁷ Among athletes referred for evaluation of asthma, about 35% had EILO, and, of these, approximately 39% also tested positive for EIB or asthma.³⁸ Thus, EILO and EIB are common comorbidities, but most individuals with EILO may not have EIB.

EILO often produces inspiratory stridor that can be confused with the wheeze of EIB. Stridor associated with EILO occurs during inspiration in the laryngeal region during exercise and resolves quickly after stopping exercise, whereas the wheeze associated with EIB typically occurs during exhalation after cessation of exercise. EILO should be considered in athletes who have symptoms of EIB but who test negative for it in bronchoprovocation testing, or in those who have documented EIB but continue to experience symptoms with exercise despite appropriate management. If EILO is suspected, the diagnosis

Box 2: Challenge tests for EIB*Indirect challenge tests**High intensity exercise challenge*

- Should be performed in a humidity controlled environmental chamber or by having the individual breathe medical grade compressed dry air (<5 mg H₂O/L) throughout the exercise
- Requires sufficient time spent at high intensity activity, with >90% maximal heart rate for the last 4 minutes of an 8 minute exercise challenge¹
- >10% decrease in FEV₁ is a positive test

Eucapnic voluntary hyperpnoea

- Performed with the patient hyperventilating for 6 minutes while breathing from a cylinder of medical grade compressed gas containing 4.9-5% CO₂, 21% O₂, balance N₂²⁹
- Target ventilation of 30×FEV₁ or >85% of maximal voluntary ventilation (MVV), though >60% MVV is generally sufficient
- For individuals who achieve a ventilation >60% MVV
 - 10-19.9% decrease in FEV₁ is a mild response
 - 20-29.9% decrease is a moderate response
 - >30% decrease is severe²⁹

Mannitol challenge

- Provides a safe alternative to the other tests because it allows clinicians to produce bronchoconstriction in a controlled and stepwise manner with increasing amounts of inhaled powdered mannitol, which increases osmolarity until a 15% decrease in FEV₁ occurs.^{18 30} This reduces the risk of severe bronchoconstriction
- Though useful in diagnosis, a negative mannitol challenge result is not sufficient to rule out EIB⁸

Direct challenge tests

- Direct stimulation involves the inhalation of nebulised methacholine in increasing concentrations until a given decrease (generally >15%) in FEV₁ is achieved
- A negative test has a high negative predictive value (>90%) and can potentially rule out asthma and EIB. However, predictive value may be weaker in elite athletes and limits its clinical utility³¹

Box 3: Common causes of false negative challenge results

- Failure to expose the patient to sufficiently dry air²⁷
- Insufficient exercise intensity (that is, <90% of maximum heart rate)²⁷
- Performing a "confirmatory" challenge test while using previously prescribed medication based on symptoms. See table 1 for details
- Using a peak expiratory flow meter as a diagnostic tool instead of a spirometer (lacks appropriate sensitivity and positive predictive value^{33 34})
- Test performed at the wrong time of the year in individuals with seasonal EIB^{10 11}

can be confirmed with laryngoscopy during high intensity exercise,³⁹ and this may be performed simultaneously with a dry air challenge to test for concomitant EIB.⁴⁰

What are the treatment options for EIB?**Non-pharmacological management**

A systematic review and meta-analysis² found that, before vigorous intensity exercise, a warm-up procedure that included continuous high intensity activity (such as 6 minutes of hard uphill running) or sprint interval bouts reduced the later fall in FEV₁. Although individuals vary in their airway response, athletes with EIB may wish to try including some sprint interval exercise (such as six to eight bouts of 30 second sprints with 45-120 seconds rest between²) in their warm-up routine. Individuals with EIB may also try to avoid exercising in areas where they are exposed to high levels of air pollution and airborne allergens, and dry environments when possible.

Should people with EIB avoid exercise?

Exercise is of potential benefit to asthmatic patients with EIB and, if their asthma is well controlled, their exercise should not be limited. A systematic review and meta-analysis revealed that exercise training improved quality of life, reduced symptoms of asthma, decreased EIB and bronchial hyper-responsiveness, and attenuated the fall in FEV₁.⁴¹ Patients with EIB should be encouraged to continue taking exercise while adhering to their

management plan, and should seek further medical evaluation if their symptoms do not resolve.

Pharmacological management

β agonists—People with EIB, with or without asthma, should be prescribed short acting (1-6 hours, depending on drug) β agonist bronchodilators, which should be used only as needed. Long acting β agonists are not used as sole therapy for either EIB or asthma because of the potential risk of severe asthma exacerbations and death.⁴² A systematic review (including studies of adults and children with EIB) found that a single dose of a β agonist was effective in preventing EIB but confirmed that daily use leads to tolerance, which reduces its effectiveness as a rescue medication.⁴³ β agonists can be used before exercise two to four times a week to prevent bronchoconstriction or taken as a rescue inhaler as needed, but they should not be used daily.^{1 8 44} If β agonists are needed more frequently, then a leukotrienes receptor antagonist (such as montelukast) or a daily inhaled corticosteroid should be considered.^{1 8}

Inhaled corticosteroids—Patients with known asthma who also have EIB should be managed with inhaled corticosteroids to reduce airway inflammation. Inhaled corticosteroids are most effective when administered daily and may take up to four weeks to reach maximal effectiveness.^{1 8 44}

Leukotrienes receptor antagonists—These cannot reverse bronchoconstriction but may prevent episodes of EIB if taken

two hours before exercise. Protection can last for 24 hours,^{1 8} but effectiveness varies widely between individuals.⁴⁵

Are any EIB treatments banned in elite athletes? Inhaled corticosteroids and some β agonists are now allowed, within certain limits, by the International Olympic Committee and World Anti-Doping Association (WADA), but some organisations, such as the National College Athletics Association (NCAA), still require a therapeutic use exemption (TUE). Leukotrienes receptor antagonists are allowed. Practitioners should be aware of organisation-specific requirements for documenting diagnosis and management.

What if symptoms persist despite treatment?

Health professionals should review the use of any short acting β agonist to ensure this is not being overused (risking tachyphylaxis) or underused. Inhaler technique should be reviewed. If there is no subjective improvement with treatment, patients should be offered repeat testing with spirometry or a repeat exercise challenge to provide objective measures of lung function and airway hyper-responsiveness. If symptoms persist despite these measures, the diagnosis should be re-evaluated.

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When to refer

- Facilities not available to perform dry air exercise challenge or EVH
- Repeated negative result on properly conducted indirect challenge tests
- Symptoms are not improved despite proper medication use
- Non-reversible airway obstruction

Questions for future research

- Can a screening questionnaire guide clinicians to differentiate EIB from other forms of breathlessness associated with exercise?
- Can EIB phenotypes be categorised according to symptoms (such as individuals who cough but do not wheeze versus individuals who wheeze but do not cough), inflammatory cells or mediators, genetics (such as glutathione S-transferase polymorphisms), or environmental triggers (such as pollutant exposure versus dry and cold air exposure) in order to improve patient specific treatment strategies?
- Why is it that, although EIB and EILO can exist independently, comorbidity is common?
- Tiotropium bromide is used primarily for managing chronic obstructive pulmonary disease. It shows promise as an add-on therapy to decrease exacerbations and improve post-challenge FEV₁ in moderate to severe asthma. Could it be used for prophylaxis or rescue in patients with mild asthma or EIB without apparent asthma?

Tips for non-specialists

- To avoid misdiagnosis, EIB should never be diagnosed on the basis of signs and symptoms alone
- Diagnosis should include changes in FEV₁ before and after a challenge test
- Positive field test results may be used to diagnoses EIB, but a negative field test result does not rule out EIB
- Exercise challenge and eucapnic voluntary hyperpnoea tests should strictly adhere to guidelines and may need to be repeated
- The nature and severity of clinical signs and symptoms of EIB should be fully documented before starting treatment. At diagnosis, clinicians should arrange a time to follow up the patient to determine whether interventions are successful

Additional educational information (freely available)

- Parsons JP, Hallstrand TS, Mastrorade JG, et al. An official American Thoracic Society clinical practice guideline: exercise-induced bronchoconstriction. *Am J Respir Crit Care Med* 2013;187:1016-27—www.thoracic.org/statements/resources/allergy-asthma/exercise-induced-bronchoconstriction.pdf
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Information resources for patients

- American Academy of Allergy, Asthma & Immunology. Exercise and asthma. 2015—www.aaaai.org/conditions-and-treatments/library/asthma-library/exercise-and-asthma.aspx
- Mayo Clinic. Diseases and conditions: Exercise-induced asthma—www.mayoclinic.org/diseases-conditions/exercise-induced-asthma/basics/definition/con-20033156

A patient's story

I have had asthma and EIB most of my life. I also have an Olympic gold medal in women's ice hockey. When I was younger, asthma did not hinder my lifestyle, and it was not a problem training with the US team in ice rinks resurfaced with electric powered machines. However, when we moved our training venue to a site that ice-resurfaced with fossil fuel powered equipment, my troubles began.

My doctors prescribed sodium cromoglicate, montelukast, and a rescue inhaler, and eventually inhaled corticosteroids. I did not like taking that medication, and was repeatedly non-compliant when I would start feeling better. I would then fall back into having asthma and EIB attacks. Just prior to the 2002 Olympics, I left the team and moved to New York City to coach ice hockey. I did not think I needed my medications any more. I was wrong and it was not long before I was having three severe asthma attacks daily and feeling like I was going to die.

I went to my doctor. The first resting spirometry manoeuvre triggered a response on the second, giving 25% predicted FEV₁. I was in trouble! I am now compliant with medication, I have removed all triggers, and have been managing my asthma.

How patients were involved in the creation of this article

A patient story is included in this article

Tables

Table 1 | Guidelines for withholding times of treatments before conducting challenge tests. Modified from Anderson et al²⁵ and Crapo et al²⁶

Intervention	Withholding time
Significant exposure to cold dry air	Day of test
Strenuous exercise	Day of test
Caffeinated foods or beverages	Day of test
Tobacco products	Day of test
Inhaled NSAIDs	6-8 hours
Inhaled short acting β agonist bronchodilators	8 hours
Inhaled corticosteroids (ICS),* anticholinergic bronchodilators	12 hours
Inhaled long acting β agonist (LABA) bronchodilators and ICS-LABA combinations*	24-48 hours
Long acting theophyllines	48 hours
Anticholinergic medications	72 hours
Antihistamines	72 hours
Leukotriene modifiers	2-4 days

NSAID=Non-steroidal anti-inflammatory drug.

*1-2 weeks withholding is necessary to overcome the full effects of inhaled corticosteroids (ICS). However, patients are prescribed ICS because of serious airway dysfunction, and so withholding treatment is not recommended. The withholding times for ICS are meant to reduce the bronchodilatory effects of the corticosteroids rather than the longer term anti-inflammatory effect.

Table 2| Potential causes of breathlessness or exercise intolerance in athletes who do not have asthma or exercise induced bronchoconstriction (EIB)

Condition	Clinical features or specific differentials	Basic diagnostic approach
Upper airway obstruction (primarily EILO)	Pronounced inspiratory stridor, often accompanied by a flattened inspiratory loop; resolves quickly after stopping exercise Failure to respond to EIB management May occur concomitantly with EIB	Continuous laryngoscopy should be performed during an exercise challenge
Inadequate fitness	A physiological limitation to exercise in otherwise normal individuals or obese individuals Relatively intense training regimen results in "shortness of breath" without any pathology Common in team sports (individual less fit than teammates)	Expert evaluation of training regimen
Exercise induced hypoxaemia	Low arterial saturation (<92% SaO ₂) during near maximal exercise causing dyspnoea Physiological limitation to maximal aerobic exercise without cardiometabolic or pulmonary pathology Occurs in about 50% of high level endurance athletes	Near-maximal exercise test with pulse oximetry
Thoracic musculoskeletal pathology	Muscle injury (such as intercostal strain) Costochondritis Skeletal trauma	Musculoskeletal physical examination, radiography
Pneumothorax	Primary pneumothorax (rare, but reported in athletes) Secondary to trauma	Radiography, auscultation
Psychological factors	Sport specific anxiety may result in hyperventilation during exercise or poor quality challenge test Clinical depression General anxiety disorders	Sports psychology assessment Psychological or psychiatric referral
Obesity	Mechanical limitations to ventilation due to excess adipose tissue on the trunk	Body composition analysis; spirometry to detect right shift in flow volume loop or flow limitation
Other factors causing dyspnoea, exercise intolerance, or fatigue	Anaemia Dietary or nutritional deficiencies Inadequate recovery or sleep or overtraining syndrome Medication side effects Mitochondrial myopathy Pulmonary infectious disease Systemic infectious disease (such as mononucleosis, Lyme disease) Cardiovascular, pulmonary, or gastroenterological pathology	Thorough patient history to determine most likely differentials to provide more appropriate diagnostic approach

EILO=Exercise induced laryngeal obstruction.

Figures

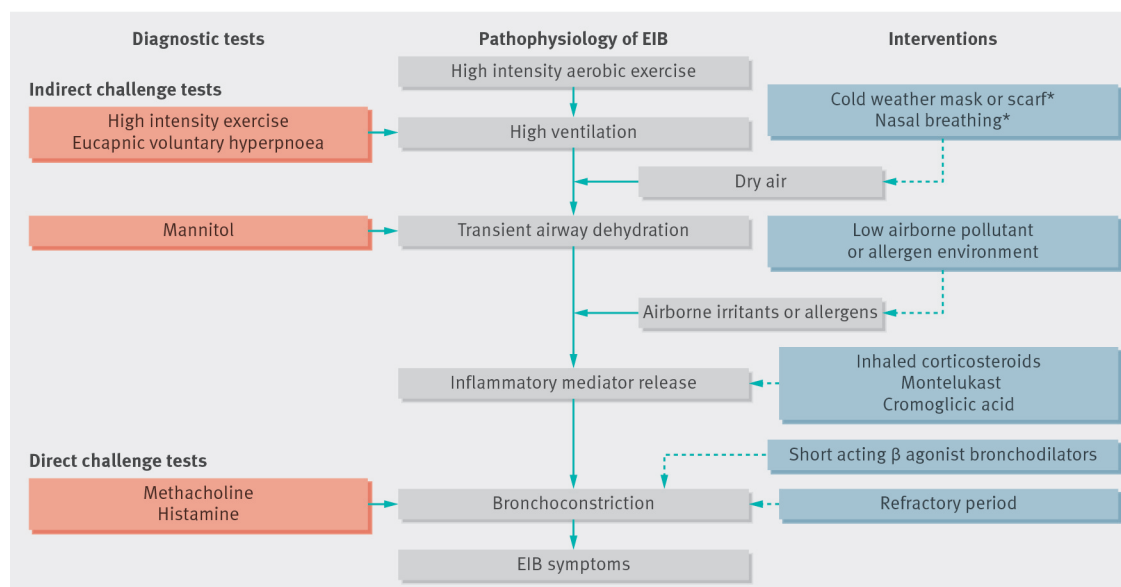


Fig 1 Relation between pathophysiology of exercise induced bronchoconstriction (EIB), triggers of EIB attacks, diagnostic tests, and management strategies. (*Evidence from small studies suggests these interventions may reduce EIB severity,¹²⁻¹⁴ but these may not be practical for athletes engaging in high intensity exercise)

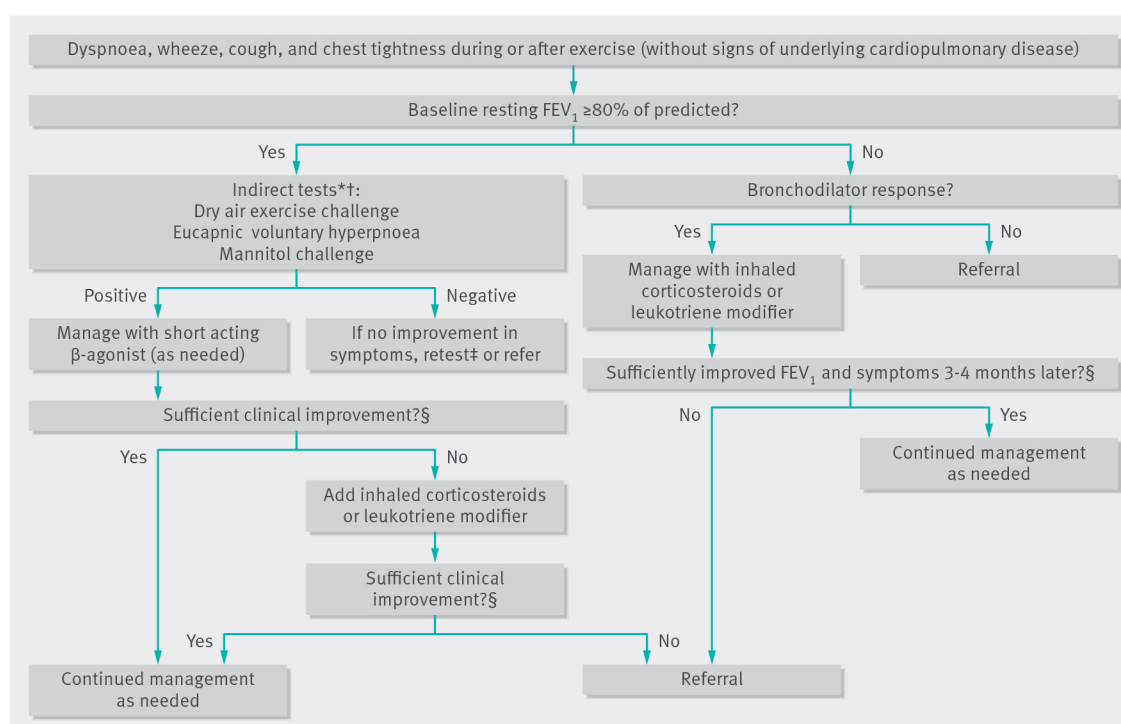


Fig 2 A simplified algorithm for evaluation and management of exercise induced bronchoconstriction (EIB). (*Ensure that a proper withholding schedule is followed (see table 1[¶]). [†]Field tests may be attempted before laboratory tests: a positive field test is diagnostic for EIB, but false negative field tests are common,^{27,28} so laboratory tests should be performed before EIB is excluded. [‡]It may be necessary to perform an indirect test on two separate occasions before EIB can be ruled out.²⁴ [§]Ensure the patient is taking medication as directed.)