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Exercise induced asthma: An overview

Rama Rao Tadikonda * and Yashwanth Thangadipalli

Department of Pharmaceutical Analysis, CMR College of Pharmacy, Hyderabad, Telangana, India.

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Abstract

Variable expiratory airflow limitation and persistent airway inflammation are features of asthma, a respiratory disease that is common throughout the world. Respiratory disorders are very prevalent among top athletes, affecting 20% to 70% of participants in particular sports. Performance is impacted by the common problem of exercise-induced bronchoconstriction (EIB). The incidence varies according to genetics, training, and sport. Ironically, exercise can improve pulmonary function even while it aggravates asthma. The phenotypes of asthma in athletes vary, which makes management difficult. Increased airway sensitivity, exposure to allergens, pollution, and temperature fluctuations are some of the distinctive features. This review explores the pathophysiology, diagnosis, and management of EIB in athletes.

Objective testing is necessary to diagnose EIB in athletes because baseline lung function tests may show normal findings. Tests for bronchoprovocation and exercise offer accurate diagnosis. Although bronchodilation and spirometry testing are routine, provocation tests are becoming more and more important. Despite obstacles, the best diagnosis is essential for efficient treatment, which enhances quality of life and performance. Managing EIB is in line with basic guidelines for preventing and controlling symptoms and minimizing consequences. Warming up, avoiding triggers, and non-pharmacological methods are crucial. Athletes with asthma benefit greatly from inhaled corticosteroids (ICS), which discourage the use of short-acting beta agonists alone. Leukotriene receptor antagonists (LTRAs) and mast cell stabilizing drugs (MCSAs) are probably good choices. Effective management enables athletes to pursue competitive sports and improves their quality of life.

Keywords: Exercise-Induced Asthma; Allergic Rhinitis; Pathophysiology; Spirometry; Bronchoprovocation

1. Introduction

In the 1st century A.D., Aerates the Cappadocian was the first to define the respiratory symptoms brought on by exercise: "If breathing becomes difficult from running, gymnastics, or any other work, it is called "asthma [1]. The effects of exercise on children's respiratory function were initially described in 1962, along with rigorous exercise tests. The phrases "exercise-induced bronchoconstriction" (EIB) and "exercise-induced asthma" (EIA) are sometimes used interchangeably. According to a consensus reached by the Joint Council of Allergy, Asthma, and Immunology (JCAAI), the American Academy of Allergy, Asthma, and Immunology (AAAAI), and the American College of Allergy, Asthma, and Immunology (ACAAI), exercise-induced bronchoconstriction (EIB) with asthma is referred to as "EIB with asthma," and acute airflow obstruction without asthma is referred to as "EIB without asthma [2]. EIA was defined by a joint task force of the European Academy of Allergy and Clinical Immunology and the European Respiratory Society as asthma symptoms that follow vigorous exercise, whereas EIB was defined as a decrease in lung function that follows activity as measured by a standardized exercise test [3]. While EIA also includes EIB asthma symptoms, we shall refer to EIB as the broncho constrictive response in this review. When the populations are clearly named, the two conditions will be examined separately; otherwise, they are referred to as EIB/EIA. This review aims to give the reader up-to-date

* Corresponding author: Tadikonda Rama Rao

information on this subject, with a specific focus on the asthma phenotype of athletes, along with a paragraph discussing fresh ideas for using exercise as a treatment for asthma. According to some reports, up to 75–80% of people with asthma who are not using anti-inflammatory medication may have an asthma episode brought on by physical activity [4], However, following vigorous exercise, people without an asthma diagnosis may noticeably worsen their lung function, which can occasionally be a risk factor for asthma [5].

Chronic airway inflammation, variable expiratory airflow limitation, and various respiratory symptoms, including coughing, chest tightness, wheezing, and shortness of breath, are the hallmarks of asthma, a complex illness. It affects about 339 million people worldwide, with rates ranging from 4% to 10% in Western nations, while prevalence varies by age group and ethnicity [6, 7]. It takes at least five to eight minutes of constant, high-intensity effort to produce an exercise-induced broncho constrictive response. EIB is typically detected two to ten minutes after vigorous activity, rather than at maximal exercise intensity. However, children experienced EIB during submaximal activity rather than after [8]. Since the emergence of symptoms during exercise frequently leads to avoidance of regular physical activity, people with asthma and EIB may have more difficulties than those with asthma alone. This lowers their overall quality of life. Although it seems to make sense to assume that exercise-induced bronchoconstriction (EIB) could have an impact on athletic performance, the available data does not provide a definitive response [9]. We could not conclusively demonstrate EIB's negative impact on athlete performance. The experimental design, the complexity of performance variables, or the choice of outcome measures are some of the possible causes of this ambiguity. The quality of life for people with EIB can be greatly improved by early detection, a diagnosis verified by lung function tests during exercise, and suitable treatment, which enables them to participate in physical activity even at highly competitive levels. However, there is a great deal of variation in the phenotypes of asthma among athletes, which causes variations in how they react to methacholine challenge tests and asthma treatments, athletes also exhibit increased airway sensitivity, which leaves them more susceptible to environmental triggers such as allergens, air pollution, and temperature changes. These factors can all worsen asthma symptoms and make treatment more difficult [10].

2. EIA and EIB: EPIDEMIOLOGY AND PATHOGENESIS

Even if the exact causation of EIA is unknown, exercise-induced hyperventilation and the alterations it causes in airway physiology are most likely the reason [11, 12]. Higher muscular oxygen demands during exercise necessitate a higher ventilatory rate. The ability of the airways to adjust the inhaled air to the proper moisture and heat levels prior to the air reaching the alveoli is put to the test by this elevated ventilatory rate. Increased breathing of comparatively cold and dry air and heat loss from the respiratory mucosa during vigorous exercise cause osmolarity alterations in the surface of the airways [13].The pathogenic processes of EIA/EIB are likely different in athletes than in asthmatic children, adolescents, or adults [14]. Exercise can be seen as a model of stress since it is a measurable and repeatable stressor that can be altered experimentally [15].

It affects the immune, neurological, and endocrine systems, which in turn activates a number of intricately intertwined mechanisms within the psycho-neuro-immune-endocrine pathways [16].

Traditional explanations for EIA and EIB include the osmolar (also known as airway drying) and vascular (sometimes known as "thermal") hypotheses. Both theories are predicated on the idea that physical exertion causes a noticeable increase in ventilation, which increases the amount of heat and water lost through respiration. A higher intracellular ion concentration results from increased water loss because it raises the osmolality of the extracellular fluid lining the bronchial mucosa. This causes water to flow extracellularly through water channels, aquaporins, and bronchial epithelial cells to "shrink [17]eosinophils, neutrophils, mast cells, and other inflammatory cells, including newly generated eicosanoids, as well as the release of inflammatory mediators [18,19]. The epithelium may play a crucial role in controlling the equilibrium of eicosanoids in the airways by triggering the release of broncho constrictive eicosanoids from inflammatory cells that are in close proximity to one another and by causing changes that decrease the production of the protective PGE2 [20].

According to the "vascular" or "thermal" hypothesis, the first mechanism is airway rewarming following airway chilling. The nose warms (up to 378°C) and humidifies the inspired air during normal tidal breathing, acting as a rebreathing organ. As exercise intensity increases, more ventilation occurs, which results in an increase in respiratory heat loss. The respiratory heat loss and subsequent chilling of the airways are further exacerbated if the air being inhaled is chilly [14,21,22]. The vagal nerve causes bronchoconstriction as a result of reflex parasympathetic nerve stimulation brought on by the cooling of the airways [23]. The bronchial venules first exhibit a reflex vasoconstriction to save heat, but when exercise stops, the enhanced ventilation and the cooling stimulus stop as well, resulting in a rebound vasodilation of the peri bronchial venules. The ensuing mucosal oedema from vasodilation and smooth muscle constriction from nerve stimulation in sensitive people decreases the bronchial lumen's size and increases airway resistance [24]. The primary

cause is now believed to be inflammation brought on by variations in airway osmolarity, and in situations when there is a substantial loss of heat, both the osmolar and thermal mechanisms may cooperate [25].

Additionally, eosinophil and neutrophil infiltration, elevated peptidoleukotriene concentrations in broncho-alveolar lavage fluid, and recurrent hyperventilation challenges from exercise can harm the bronchial epithelium.

The expression of several chemokines and cytokines, including IL-8 and RANTES (Regulated on Activation, Normal T cell Expressed and Secreted), can be increased in cultured human bronchial epithelial cells by experimental exposure to a hyperosmolar medium or by cooling and rewarming. This could indicate a potential mechanism for exercise-induced leukocyte migration into the airways [26,27]. When tested at rest, induced sputum from athletes participating in various sports exhibits a higher quantity of inflammatory cells. Moreover, pro-inflammatory cytokines rise following extended, intense exercise [28]. A multifactorial bronchial inflammatory response involving common pathways of allergy and asthmatic inflammation appears to be possible due to the interaction of hyperventilation, hyperosmolarity, and immunological alterations. Lastly, it's important to take into account how rhinitis affects asthma[29]. According to epidemiological research, even when atopy is not present, asthma and rhinitis commonly coexist [30]. Epidemiological research shows that even when atopy is not present, asthma and rhinitis commonly coincide [31], having a fluctuating prevalence based on the diagnostic standards applied in various investigations. Athletes with hay fever experienced noticeably more frequent exercise-related respiratory symptoms in a Swiss research study, but their care was insufficient [32].

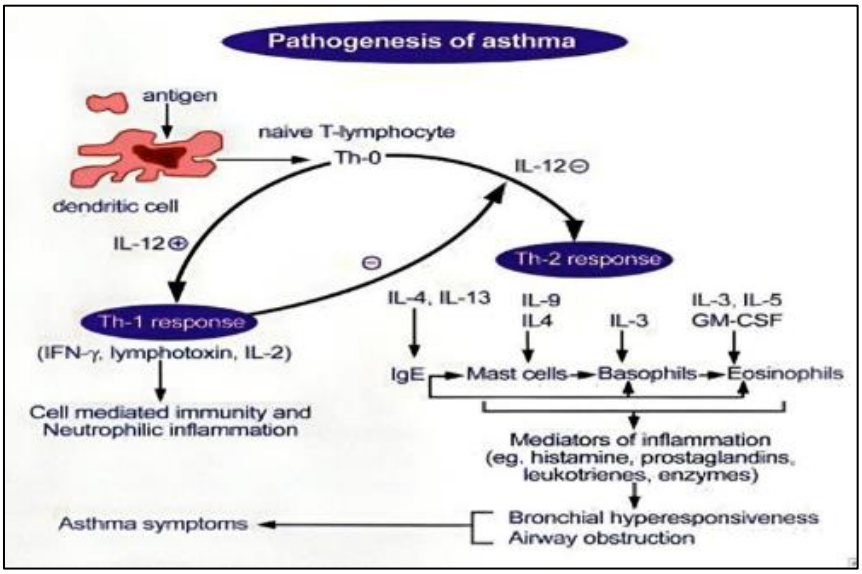

Figure 1 Pathogenesis of asthma [33]

3. Evaluation of EIA

The symptoms of EIA typically appear five to thirty minutes after vigorous exercise and include coughing, wheezing, shortness of breath, and/or chest tightness. More than 10,000 asthma patients who were either taking asthma medication at the time of the study or who had experienced symptoms within the previous year participated in the recent global study, between one-third and half of these patients had EIA symptoms. The existence or manifestation of EIA in people with a history of asthma diagnosis could indicate inadequate therapeutic management of asthma severity [34]. Many adults with asthma may acknowledge that their physical health is not at its optimum or may choose not to seek treatment for the symptoms. Exercise-induced respiratory symptoms are typically not very good indicators of EIA in highly trained persons [35,36]. Prior to beginning treatment, an EIA diagnosis should be established in these people, particularly if they participate in competitive sports [37], because it's crucial that no treatment be administered for a condition that doesn't exist. Before and after receiving a short-acting β-agonist, patients with suspected EIA should have a thorough history, physical examination (including inspections of the throat, ears, and nose as well as cardiac and chest exams), and lung function tests.

Although the mannitol challenge is not yet an authorized method for predicting a successful exercise challenge, preliminary data indicates that it might develop into a valuable test [38]. Methacholine or direct challenges with

histamine (which is likewise not an approved drug) are not the best ways to evaluate EIA. A short-acting β-agonist inhaled within 15 minutes prior to exercise can frequently avoid EIA; according to some writers, the diagnosis of EIA may be made based on the patient's reaction to this therapy. Patients who have already been diagnosed with asthma should continue taking their daily controller medications and pre-exercise therapy as directed. Further testing, such as an exercise challenge or a repeat exercise challenge if one has already been completed, is necessary if these treatments prove ineffective (see differential diagnosis to follow) [39].

Poor medication practice or nonadherence must also be ruled out as a reason for the lack of effectiveness. An exercise challenge is the most straightforward method of diagnosing EIA. We advise conducting a challenge in the setting that typically produces EIA-type symptoms, if at all possible. If a treadmill test is unable to replicate symptoms, a challenge should be conducted at the same exercise intensity and under circumstances that the patient reports typically result in these symptoms (such as at a sporting event) [40]. In the event that a patient who has never had an EIA test is being tested, we advise using a treadmill test where the patient exercises for eight minutes. Exercise should be performed at a level that reaches at least 80% to 90% of the anticipated maximal heart rate during the first two minutes and thereafter at this level for the remaining six minutes. At this workout level, ventilation should be between 40% and 60% of its maximum [41].

It is crucial to understand that in large population studies, the reduction in FEV1 following exercise is normally distributed, which means that there is no precise FEV1 cutoff that can be used to diagnose EIA [42]. After the exercise is over, pulmonary functions should be monitored for 30 minutes to ensure that a delayed reduction in FEV1 is not overlooked [43]. A class of tests known as "indirect airway challenges" includes exercise and EVH. These tests work by triggering the release of endogenous mediators of airway smooth muscle contraction [44]. Methacholine and histamine, on the other hand, cause bronchoconstriction by directly acting on the smooth muscle of the airways. Mannitol, AMP, hypotonic saline, and cold dry air are examples of indirect-acting stimuli that have been used as surrogate challenge agents for EIA. Responses to these stimuli tend to correlate with one another [45].

4. Which sport for the asthmatic?

What advice to provide to athletes with asthma is one of the conundrums that doctors treating these athletes encounter. Athletes who engage in swimming, endurance, and winter sports are more likely to develop EIA/EIB. The osmolar and vascular alterations in the airway, which are essential to the pathogenesis of EIA/EIB, are readily exposed to these athletes by prolonged exercise and extremely low air temperatures. Training styles and atopy are independent risk factors for EIA/EIB; when the two variables are combined in a logistic regression model, atopic speed and power athletes have a 25-fold higher risk of EIA/EIB than non-atopic subjects, long-distance runners have a 42-fold higher risk, and swimmers have a 92-fold higher risk [46].

proving beyond a reasonable doubt that athletes with asthma can compete on an equal footing with their peers. Sports that have a low risk of developing asthma and bronchial hyperresponsiveness are those that require a short physical effort and do not require high ventilatory levels. Medium-risk sports are team sports in general, where aerobic and anaerobic phases alternate and relatively short bursts of high-intensity exercise (usually less than 5 to 8 minutes) reduce the risk of bronchial hyperreactivity. High-risk sports, as previously mentioned, are endurance and winter sports in general (Table 1) [47].

Table 1 Examples of sports and their potential risk of EIA/EIB [48]

Low-risk sports	Medium-risk sports	High-risk sports
All sports in which the athlete performs a<5-8 min effort	Team sports in general, in which the continuous effort rarely lasts more than 5-8 min	All sports in which the athlete performs a>5-8min effort and/or in a dry/cold air environment
• Track and field: • Sprint (100, 200, and 400 m) • Middle distance (800 and 1,500 m) • Hurdles (100, 110, and 400 m)	• Soccer • Rugby • American • football • Basketball • Volleyball	• Track and field: • Long distance (5,000 and 10,000 m) • 3,000m steeplechase • Pentathlon (mixed) • Walks (20 and 50 km)

• Jumps • Throws • Decathlon • Heptathlon • Tennis • Fencing • Gymnastics Downhill • Skiing • Boxing • Golf • Body building • Weightlifting • Martial arts	• Handball • Baseball • Cricket • Field hockey	• Marathon • High-altitude sports • Cycling • Cross-country skiing • Ice hockey • Ice skating • Biathlon

5. Diagnosis of EIA in athletes

For athletes, receiving an EIB diagnosis is extremely important because it has a significant impact on both their performance and general health. However, making a precise diagnosis can frequently be quite difficult, mainly because athletes may display lung function values that seem to be within normal ranges. Furthermore, there isn't a single, widely accepted test for diagnosing EIB. As a result, to properly diagnose and treat this problem in athletes, a thorough strategy combining a number of tests is required. The diagnosis of EIBA in athletes is based on similar concepts as in the general population, with the main focus being on proving airflow limitation. Although symptoms might make EIBA more likely [49]. Giving precise and convincing proof for a diagnosis is essential [50]. because physicians may overdiagnoses if they rely solely on narrative without conducting objective tests for concomitant bronchial hyper-reactivity (BHR) [51].

This can be verified by using spirometry as the main diagnostic method or by requiring challenge or hyperventilation tests. Unfortunately, even in cases when EIB is present, baseline pulmonary function tests usually produce findings that fall within the normal ranges, making them ineffective predictors of the illness in athletes. Therefore, in order to confirm and establish a conclusive diagnosis of EIB, it becomes imperative to rely on objective testing procedures. These examinations seek to validate dynamic changes in airway function, offering a more accurate method of evaluation. Furthermore, the diagnosis is usually confirmed by commonly used tests such as methacholine challenge testing, peak expiratory flows, and spirometry. Conversely, exercise tests are the main method used to assess Eywa, with an emphasis on the particular airway response during bronchoprovocation challenge tests [52,53].

Spirometry and Bronchodilation Test: Spirometry is frequently used in conventional diagnostic procedures to evaluate bronchodilation. According to the most recent guidelines, variations in forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) after bronchodilator responsiveness testing are reported as a percentage difference from the individual's expected value. A positive response is indicated by a change that is greater than 10% of the expected value [54]. But fluctuations in forced expiratory flows (such as peak expiratory flow or forced expiratory flow FEF25–75%) are sometimes very erratic and significantly impacted by variations in FVC. As a result, it is difficult to compare measures taken before and after using bronchodilators. To demonstrate bronchodilator responsiveness, the 2005 pulmonary function test (PFT) interpretation guideline suggested using a combination of absolute and relative changes from the baseline. (BDR), particularly a rise of more than 12% in FEV1 and/or FVC and a change of more than 200 ml [55]. The primary drawback of this strategy is that, in both health and disease, variables like height, age, and sex have an impact on the absolute and relative changes in FEV1 and FVC, which are inversely proportional to baseline lung function.

Provocation to Challenge Tests or Evaluate Bronchial Responsiveness, there are two different kinds of bronchoprovocation challenges direct and indirect. Methacholine and inhaled histamine testing are examples of direct challenges that are thought to be more accurate in determining BHR in asthma and EIBA. Conversely, indirect challenges include tests using inhaled adenosine monophosphate (AMP), hypertonic saline, exercise, eucapnia voluntary hyperpnea (EVH), and inhaled mannitol powder. These indirect challenges are frequently thought to be more accurate in detecting Eywa because they closely mimic the effects of exercise [56]. However, there is presently disagreement on the relationships between exercise tests and other indirect bronchoprovocation tests, and these relationships vary depending on the particular test [57].

Their ability to stimulate inflammatory cells to secrete mediators like leukotrienes, prostaglandins, and histamine which cause the smooth muscles of the airways to constrict is the cause of their increased efficacy. Laboratory exercise testing and other indirect challenges provide objective standards for precise diagnosis and care. False-negative test results could come from inconsistent application of a standardized methodology, which includes appropriate exercise intensity, duration, and exposure to dry air. Fractional exhaled nitric oxide (Feno) is an alternate method of diagnosing asthma. An Feno level of 40 ppb provides good specificity, making it beneficial for confirming a diagnosis of EIB, according to a recent multi-center retrospective analysis involving 488 athletes. However, Feno shouldn't be utilized in place of indirect bronchial provocation testing in athletes due to its limits in sensitivity and predictive qualities [58].

6. Environmental issues

Performance in many sports can be influenced by a variety of environmental factors. Due to the practically daily repeated periods of high minute ventilation during the intensive physical activity of training and competitions, typical for top athletes, they will have a higher exposure to possible contaminants and allergens in the environmental air. For many sports, different environmental elements could be significant. Cold air may be a detrimental environmental factor for cold-weather sports like biathlon and cross-country skiing [59].

Different environmental elements or contaminants might be significant for different sports. Organic chlorine products made from chlorine used to sanitize the pool water are most likely hazardous for water sports played in swimming pools [60], and as previously mentioned, airway inflammation and bronchial hyperresponsiveness are common in competitive swimmers [61]. Indoor ice rinks that use propane or gasoline-powered ice resurfaces and edgers frequently have high levels of CO_2, NO_2, and ultrafine particles [62,63]. Participating in outdoor sports can expose an athlete to environmental contaminants, and pollen and mound can affect an athlete's performance and the existence of EIB in allergic athletes. Traffic pollution may have an impact on the quality of the air on sports fields [64].

7. Diagnosis: current guidelines

When coughing, wheezing, and phlegm occur along with expiratory dyspnoea and audible and sibilating rhonchi on lung auscultation following at least five minutes of vigorous activity, EIA should be considered. Specific validated questionnaires can assist in screening athletes for allergies [65]. The use of inhaled corticosteroids (ICSs) and inhaled β2-agonists in international competitive sports required objective testing to receive approval from the World Anti-Doping Association (WADA) or the International Olympic Committee. However, as of January 1, 2012, ICSs and the inhaled b2-agonists formoterol, salbutamol, and salmeterol were removed from the list of drugs that were prohibited, and their use in sports is now unrestricted. According to some claims, a field exercise test is most likely to replicate the symptoms of an actual activity [66].

8. Anti-doping: current regulations

The WADA imposed stringent guidelines on the use of asthma medications in sports for many years. Although there was initial concern that these medications would enhance performance, it is now widely acknowledged that inhaled steroids and inhaled b2-agonists do not enhance performance following multiple investigations on the maximal performance in healthy volunteers following inhalation of both short- and long-acting b2-agonists. Small but significant gains in isometric quadriceps contraction and swim ergometric sprint performance were shown in a recent trial that combined three b2-agonists (salbutamol, formoterol, and salmeterol) at WADA-permitted dosages. However, swimming performance did not improve in a demanding 110-meter race [67].

Since January 1, 2012, all ICSs and the inhaled b2-agonists formoterol, salbutamol, and salmeterol have been removed from the banned list. The use of leukotriene antagonists, inhaled steroids, inhalation ipratropium bromide, and the inhaled b2-agonists salbutamol, salmeterol, and formoterol is currently unrestricted. However, inhaled terbutaline is prohibited in competitive sports, and its usage requires objective documentation of AHR, EIB, or bronchodilator reversibility. It is forbidden to take oral corticosteroids or intravenous β2-agonists. You can find the list of prohibited medicines on the WADA website (www.wadaama.org), which is typically updated annually [68].

9. Treatment

The same worldwide criteria that apply to people with general asthma symptoms should also apply to athletes' EIA and asthma treatment. Since physical activity is seen to be crucial for children's development and growth as well as for their self-perception, mastering EIA is a primary goal of treatment for asthma in both adults and children, according to all

international criteria. It was discovered that in children with asthma, psychological functioning and fitness were correlated [69]. Since the osmolar and vascular changes mentioned above ultimately lead to inflammation, anti-inflammatory therapy with inhaled steroids is frequently sufficient and successful to provide satisfactory EIA/EIB management [70]. It should be mentioned that the only anti-inflammatory medications that promote the healing of respiratory epithelium are ICSs [71].

As demonstrated by the phenotype of "athlete's asthma," ICSs lessen the harm brought on by frequent training and competition, allowing athletes to become experts in their sport and enhancing their long-term prognosis [72]. However, after three months of treatment, budesonide 800 mg/day did not improve cross-country skiers' performance [73].

10. Conclusion

EIA/EIB are quite prevalent, and competitive athletes—particularly those participating in endurance sports—have a significantly higher prevalence of them. It is still up for debate whether swimming is an "pathogenic" or "non-pathogenic" sport for kids, but there is enough data to conclude that competitive swimmers are more likely to have asthma and bronchial hyperresponsiveness. Now that there is solid evidence linking immune-mediated airway inflammation, epithelial damage, and elevated parasympathetic activity to EIA/EIB pathogenesis, new treatments in the form of new medications and different strategies centered on various therapeutic approaches based on various phenotypes and endotypes may result. Furthermore, despite being the cause of EIA/EIB, exercise can also be a novel cure for it, as shown by murine models and early human research. As such, exercise recommendations ought to be part of the treatment guidelines for EIA/EIB.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest

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