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EAACI POSITION PAPER

Diagnosis and management of allergy and respiratory disorders in sport: An EAACI task force position paper

Oliver J. Price[1,2] | Emil S. Walsted[3,4] | Matteo Bonini[5,6] | John D. Brannan[7] | Valérie Bougault[8] | Kai-Håkon Carlsen[9,10] | Mariana Couto[11] | Pascale Kippelen[12] | André Moreira[13,14] | Helena Pite[15] | Maia Rukhadze[16] | James H. Hull[3,17]

[1]School of Biomedical Sciences, Faculty of Biological Sciences, University of Leeds, Leeds, UK
[2]Leeds Institute of Medical Research at St James's, University of Leeds, Leeds, UK
[3]Department of Respiratory Medicine, Royal Brompton Hospital, London, UK
[4]Department of Respiratory Medicine, Bispebjerg Hospital, Copenhagen, Denmark
[5]Fondazione Policlinico Universitario A. Gemelli – IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy
[6]National Heart and Lung Institute (NHLI), Imperial College London, London, UK
[7]University of Newcastle, Callaghan, Australia
[8]Université Côte d'Azur, LAMHESS, Nice, France
[9]Division of Paediatric and Adolescent Medicine, Oslo University Hospital, Oslo, Norway
[10]Faculty of Medicine, University of Oslo, Institute of Clinical Medicine, Oslo, Norway
[11]Allergy Center, CUF Descobertas Hospital, Lisbon, Portugal
[12]Division of Sport, Health and Exercise Sciences, College of Health, Medicine and Life Sciences, Brunel University London, UK
[13]Centro Hospitalar Universitário de São João, Porto, Portugal
[14]Epidemiology Unit (EPIUnit), Laboratory for Integrative and Translational Research in Population Health (ITR), Basic and Clinical Immunology, Department of Pathology, Faculty of Medicine, University of Porto, Porto, Portugal
[15]Allergy Center, CUF Descobertas Hospital and CUF Tejo Hospital, CEDOC, NOVA University, Universidade NOVA de Lisboa, Lisbon, Portugal
[16]Centre of Allergy and Immunology, Tbilisi, Georgia
[17]Institute of Sport, Exercise and Health (ISEH), Division of Surgery and Interventional Science, University College London (UCL), London, UK

Correspondence
Oliver J. Price, School of Biomedical Sciences, Faculty of Biological Sciences, University of Leeds, Leeds, LS2 9JT, UK.
Email: o.price1@leeds.ac.uk

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Abstract

Allergy and respiratory disorders are common in young athletic individuals. In the context of elite sport, it is essential to secure an accurate diagnosis in order to optimize health and performance. It is also important, however, to consider the potential impact or consequences of these disorders, in recreationally active individuals engaging in structured exercise and/or physical activity to maintain health and well-being across the lifespan. This EAACI Task Force was therefore established, to develop an up-to-date, research-informed position paper, detailing the optimal approach to the diagnosis and management of common exercise-related allergic and respiratory conditions. The recommendations are informed by a multidisciplinary panel of experts

EAACI Working Group: Allergy, Asthma and Sports.

Task Force Chair: Dr Oliver J. Price.

Task Force Secretary: Dr Maia Rukhadze.

including allergists, pulmonologists, physiologists and sports physicians. The report is structured as a concise, practically focussed document, incorporating diagnostic and treatment algorithms, to provide a source of reference to aid clinical decision-making. Throughout, we signpost relevant learning resources to consolidate knowledge and understanding and conclude by highlighting future research priorities and unmet needs.

KEYWORDS
allergy, exercise, immunology, physiology, sport

1 | INTRODUCTION

Allergy and respiratory disorders are common in young athletic individuals, with an estimated prevalence of up to 40% and 20%, respectively.[1,2] The reason individuals engaging in regular exercise are potentially at greater risk of allergic sensitization remains to be fully established; however, it is thought that an interplay exists between genetic predisposition, neurogenic-mediated inflammation, epithelial sensitivity and environmental factors associated with regular high-intensity exercise.[3–5] These include chronic sustained exercise hyperpnoea and repeated exposure to noxious environmental pollutants or irritants such as chlorine derivatives in swimming pools, cold dry air in winter sports and aeroallergens in outdoor summer sports.[6] Furthermore, prolonged intense exercise, characteristic of certain high-level sports, has been shown to be associated with changes in several parameters of innate and adaptive immunity, including a Th2 shift and transient immunodeficiency, that may contribute to the development of allergic disease (see Kurowski et al.[7]).

In the context of elite sport, it is essential that allergy and respiratory disorders are identified in order to optimize health and performance.[8,9] It is also important, however, to consider the potential impact or consequences of these disorders, in recreationally active individuals, engaging in structured exercise and/or physical activity (i.e., outside the setting of professional or competitive sport) to maintain health and well-being across the lifespan. Indeed, physical inactivity is now recognized as a potential cause of chronic disease,[10] and thus, the importance of controlling allergic and respiratory symptoms and optimizing disease management to help reduce barriers to exercise and physical activity engagement, within the wider general population, should not be overlooked.

The European Academy of Allergy and Clinical Immunology (EAACI) has previously commissioned a comprehensive series of position statements concerning exercise-induced hypersensitivity syndromes in athletes.[11–13] However, these reports were published over a decade ago and screening tools, diagnostic methodologies and treatment strategies have evolved significantly during this period. Specifically, research conducted over the past decade has shed light on the fact that a broad differential diagnosis exists for allergic and respiratory symptoms and that a substantial proportion of individuals have evidence of co-morbid illness; that is conditions often co-exist in the same patient.[14]

This EAACI Task Force was therefore established, to develop an up-to-date, research-informed position paper, to describe the optimal approach to the diagnosis and management of common exercise-related allergic and respiratory conditions. The recommendations are informed by a multidisciplinary panel of experts including allergists, pulmonologists, physiologists and sports physicians. The report is structured as a concise, practically focussed document, incorporating pragmatic recommendations and diagnostic and treatment algorithms, to provide a source of reference, to aid clinical decision-making. Throughout, we signpost relevant learning resources (i.e., clinical guidelines, practice parameters, review articles and online supplementary materials), to consolidate knowledge and understanding and ensure best practice is upheld and maintained.

1.1 | Practical approach to clinical assessment

The evaluation of an individual reporting allergic or respiratory symptoms occurring in association with sport or physical activity should begin with history and examination. From a practical point of view, it is often helpful to evaluate the individual during or post-exercise (i.e., attend a specific training session and environment where symptoms typically present), or alternatively, request a 'selfie-type' video, with appropriate consent, for review.

In the majority of cases, the clinical assessment of a young athletic individual will be normal at rest/when not directly exposed to the relevant allergic stimuli, and thus, specialist provocation tests are required to objectively confirm or refute a diagnosis (Figure 1). It is important to recognize that while some routine tests (e.g., spirometry) are available at most primary care centres, other more advanced diagnostics (e.g., skin prick testing, cardio-pulmonary exercise testing [CPET] and bronchial provocation challenges) will usually require referral to secondary or specialist care.

Clinical presentation, diagnostic methods and non-pharmacological and pharmacological management strategies for the most prevalent allergic and respiratory conditions encountered are shown in Tables 1 and 2 but covered in further detail below. In all cases, the approach to diagnostic work-up and management (i.e., methodologies, protocols, interpretation and treatment strategies) should align with established international guidelines, but with due consideration for the annually updated

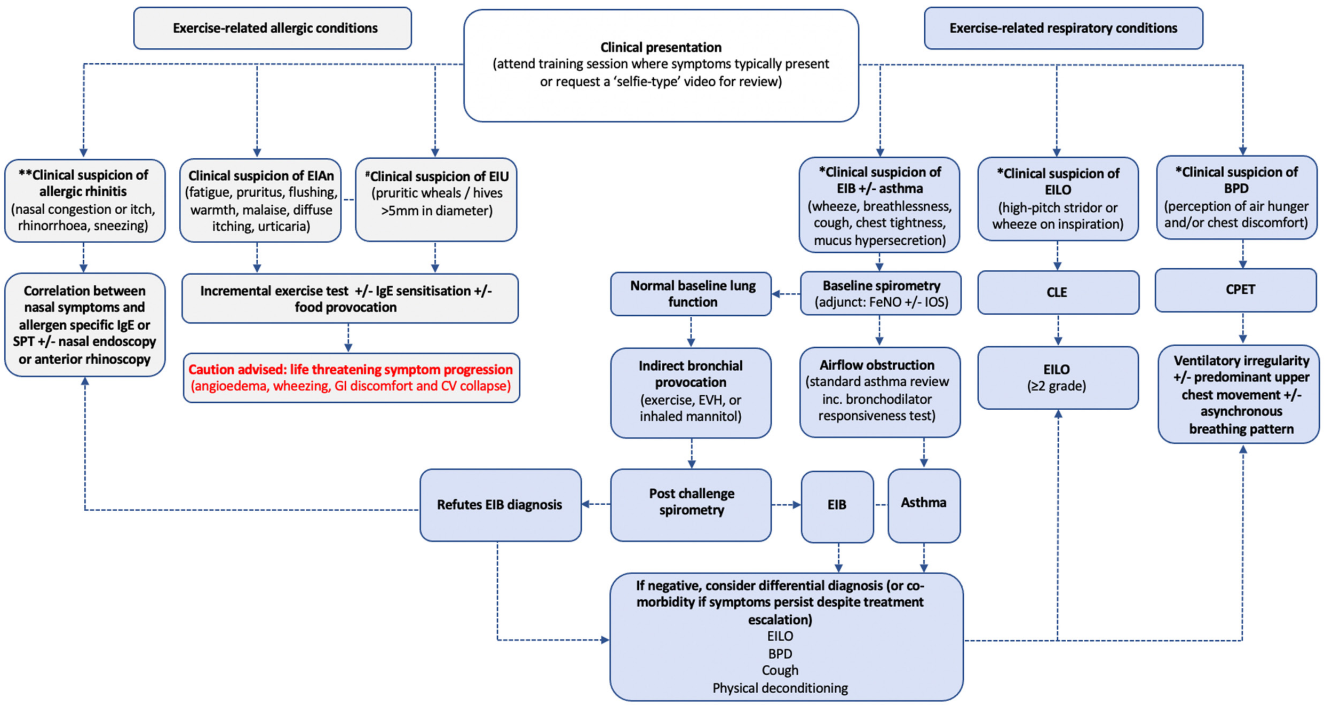

FIGURE 1 Diagnostic algorithm for the assessment of exercise-related allergic and respiratory conditions. #Denotes consider passive warming test to help differentiate cholinergic urticaria; *denotes consider potential co-morbidity between EIB ± asthma, EILO, BPD; **denotes consider potential co-morbidity between allergic rhinitis and EIB ± asthma. Asthma (≥12% increase in FEV_1 post bronchodilator); BPD, Breathing pattern disorder; CLE, continuous laryngoscopy during exercise; CPET, cardio-pulmonary exercise testing; CV, cardiovascular; EIAn, exercise-induced anaphylaxis; EIB, exercise-induced bronchoconstriction (≥10% fall in FEV_1 post exercise and EVH or ≥15% fall in FEV_1 from baseline or 10% fall in FEV_1 between two consecutive doses for inhaled mannitol); EILO, exercise-induced laryngeal obstruction; EIU, exercise-induced urticaria; EVH, eucapnic voluntary hyperpnoea; FeNO, fractional exhaled nitric oxide; GI, gastrointestinal; IgE, immunoglobulin E; IOS, impulse oscillometry; SPT, skin prick test.

World Anti-Doping Agency (WADA) regulations, when caring for professional or competitive athletes: www.wada-ama.org/en/what-we-do/the-prohibited-list.[15]

It is important to note that in response to a serious adverse or life-threatening event (e.g., acute asthma exacerbation or severe anaphylactic reaction), the care afforded to an athlete should always adhere to conventional management guidelines. In this scenario, athletes are required to submit a retroactive therapeutic use exemption (TUE) (with supporting documented evidence of the incident) to avoid a potential anti-doping rule violation.

2 | DIAGNOSIS AND MANAGEMENT OF ALLERGIC DISEASE

2.1 | Allergic rhinitis

The nasal mucosa plays an important role in the context of exercise, in terms of humidifying and warming air and acting as a barrier to encounter and respond to environmental particles such as allergens, pathogens or irritants.[16] Nasal symptoms can arise from either mucosal dysfunction (primarily due to rhinitis) or deformity of the anatomical structures.[16] Allergic inflammation is the most common cause of chronic rhinitis and responsible for symptoms of nasal obstruction, rhinorrhoea, nasal itch and sneezing.

A recent systematic review reported that the prevalence of allergic rhinitis in athletic individuals ranges between 21% and 56%.[17] It is thought that strenuous exercise may contribute to the development of allergic sensitization, due to a potential shift in T lymphocytes towards type 2 sub-types, following repeated strenuous exercise.[18,19] Other pathophysiological factors include a potential interplay between neurogenic regulation, nasal inflammatory changes induced by heavy exercise, direct epithelial damage and repeated exposure to allergens, cold-air, and noxious environmental pollutants during regular training.[20,21] This theory is supported by the fact that athletic individuals engaging in aquatic and winter-based sports appear to be particularly susceptible.[17]

The diagnosis of allergic rhinitis is typically established from a thorough history implicating an association between symptoms and the environment. The Allergy Questionnaire for Athletes (AQUA) is often employed to identify allergic disease,[22] but a final diagnosis should be based on a clear correlation between typical nasal symptoms and a positive allergen-specific immunoglobulin E (IgE) or skin prick test.[23,24] To confirm nasal inflammation, clinical examination via nasal endoscopy is currently recommended. However, in the scenario nasal endoscopy is unavailable, anterior rhinoscopy is an alternative

TABLE 1 Diagnostic assessment and management strategies for allergy in sport

Allergic disease	Clinical presentation	Diagnostic assessment	Management strategies	
			Non-pharmacological	Pharmacological
Allergic rhinitis	• Nasal obstruction, rhinorrhoea, nasal itch and sneezing	• Clinical history and correlation between nasal symptoms and allergic sensitization • Nasal endoscopy or anterior rhinoscopy • Nasal cytology to confirm nasal inflammation	• Trigger avoidance or preventive strategies (e.g., nose clip in swimmers) • Saline nasal douchings • Turbinoplasty (considered in medically resistant, reversible nasal obstruction due to turbinate hypertrophy)	• Intranasal corticosteroids • Antihistamines • Antileukotrienes • Decongestants • Cromoglycates • Oral corticosteroids (considered in short courses or in cases of severe therapy-resistant allergic rhinitis) • Allergen immunotherapy
Exercise-induced anaphylaxis	• Fatigue, pruritus, warmth, flushing and urticaria that can progress to angio-oedema, wheezing, rhinitis, gastrointestinal discomfort and cardiovascular collapse	• Incremental exercise test • Identification and timing of foods ingested during the preceding 24-h • Assessment of IgE sensitization against relevant allergens and an 'exercise ± food' provocation test should be considered	• Individuals should learn to recognize their first symptoms and signs of EIAn and immediately discontinue exercise • Individuals with EIAn should exercise with someone who is also familiar with the use of an adrenaline autoinjector, to carry a mobile phone, to be near emergency medical facilities and to wear some sort of medical alert identification (e.g., bracelet) detailing the problem • Consider avoidance of beta-blockers, angiotensin-converting-enzyme inhibitors, angiotensin-receptor blockers and NSAIDs • Avoid specific food allergens for at least 6-h before exercise (FDEIAn)	• Acute treatment: Trendelenburg position to facilitate perfusion of vital organs in the face of hypotension and administer adrenaline intramuscularly into the lateral thigh to improve airflow and vascular integrity • Once medical emergency personnel become involved, the management of anaphylaxis should align with established guidelines
Exercise-induced urticaria	• Pruritic wheals/hives typically >5 mm in diameter (with or without angioedema) that develop during or post-exercise	• Incremental exercise test • Positive test defined as wheals for 10-min post-test • Passive warming test should be conducted 24-h post-exercise to rule-out cholinergic urticaria	• Education on symptom recognition (i.e., when to stop exercise) and treatment plan • Specific food avoidance pre- and post-exercise in case of food-dependent-EIU	• Non-sedative antihistamines (up to 4 times per day in non-responders)

Abbreviations: EIAn, exercise-induced anaphylaxis; EIU, exercise-induced urticaria; FDEIAn, food-dependent exercise-induced anaphylaxis; IgE, immunoglobulin E; NSAIDs, non-steroidal anti-inflammatory drugs.

TABLE 2 Diagnostic assessment and management strategies for respiratory disorders in sport

Respiratory disorders	Clinical presentation	Diagnostic assessment	Management strategies	
			Non-pharmacological	Pharmacological
Exercise-induced bronchoconstriction	• Wheeze, breathlessness, cough, chest tightness, mucus hypersecretion	• Baseline spirometry and bronchodilator responsiveness testing • Presence of resting airway obstruction should prompt a standard asthma review in accordance with international guidelines • Indirect bronchial provocation challenge (exercise testing, EVH, inhaled mannitol) in those with normal resting lung function • Adjunct tests: baseline skin prick testing and FeNO, and IOS pre and post indirect bronchial provocation • Consider co-morbidities: EILO, BPD	• Warm-up prior to exercise to induce refractory period • Scarf/snood or heat and moisture exchange mask • Dietary supplementation: Fish oil (i.e., omega-3 PUFA), ascorbic acid, reducing sodium intake	• Daily (pre-exercise) combined low dose ICS + fast acting LABA • Leukotriene receptor antagonists • Anticholinergics • Mast cell stabilizing agents • Allergen immunotherapy in appropriately selected athletes (i.e., akin to the approach adopted in patients with allergic asthma)
Exercise-induced laryngeal obstruction	• High-pitch stridor (whistle) or snoring-type sound on inspiration (sometimes accompanied by throat tightness or cough) • Beta-2-agonist inhalers have no effect	• Continuous laryngoscopy during exercise • Consider co-morbidities: EIB+/− asthma, BPD	• Reassurance that the condition is benign • Breathing re-training via specialist respiratory physiotherapist • Laryngeal control techniques via specialist speech and language therapist • In rare, selected cases referral to ENT for supraglottoplasty	• If applicable, discontinue inappropriate asthma medication and consider stepping down treatment in individuals with confirmed asthma • Anecdotal reports suggest a trial of inhaled anticholinergics to be successful; however, no robust evidence currently exists to support this theory
Breathing pattern disorder	• Excessive breathlessness disproportionate to the level of physical activity undertaken • Perception of 'air hunger' or inability to take a deep or satisfying breath +/− chest discomfort or tightness during exercise	• CPET • Ventilatory irregularity or increased respiratory rate (i.e., mismatch between minute ventilation and metabolic demand) • Predominant upper chest movement (or asynchrony between upper and lower chest) • Audible and/or excessive oral breathing and • slumped posture or rounded shoulders • Consider co-morbidities: asthma ± EIB, nasal and reflux disease, anxiety or mood state disorders	• Physiotherapy-led breathing re-training (progressing from rest to sport-specific tasks)	• Nil relevant

(Continues)

TABLE 2 (Continued)

Respiratory disorders	Clinical presentation	Diagnostic assessment	Management strategies	
			Non-pharmacological	Pharmacological
Cough and exercise	• Persistent or troublesome cough during and/or post-exercise	• Initial assessment should focus on ruling out underlying allergic or respiratory disease as a potential cause • Systematic investigation based on suspected causes with specific attention on the intensity of exercise and training environment	• Review and manage as per recommendations in the general population[119]	

Abbreviations: BPD, Breathing pattern disorder; CPET, cardio-pulmonary exercise testing; EILO, exercise-induced laryngeal obstruction; ENT, ear nose and throat; EVH, eucapnic voluntary hyperpnoea; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroid; IOS, impulse oscillometry; LABA, long-acting beta-2-agonist; PUFA, polyunsaturated fatty acids.

widely accessible and easy to perform objective test. Further, nasal cytology is a simple diagnostic method to detect nasal inflammation and provides insight into the phenotypic characteristics of rhinitis.[25] A nasal allergen challenge may also be considered if no correlation is observed between the allergic symptoms (i.e., nasal obstruction, rhinorrhoea, nasal itch and sneezing) and the pattern of sensitization.[26]

In athletic individuals, the approach to treatment should conform with up-to-date clinical guideline recommendations in the general population,[23] yet at the same time, interventions should be tailored according to the individual patient. Simple management strategies include avoidance of triggering allergens by following the four P-s concept (predictive, preventive, personalized, participative) of personalized medicine. A diagnostic algorithm for managing an athlete presenting with nasal symptoms has recently been published which permits a systematic approach to assessment, while considering differential diagnoses (see Hox et al.[16]). The recognition of associated or sub-clinical lower airways disease is also important, given the high concomitance with allergic rhinitis in athletes.[27] Despite its efficacy, it has recently been reported that allergen immunotherapy remains underutilized in athletes[28] and should be recommended more often (particularly in severe cases), on the basis that it is the only disease-modifying treatment option that leads to long-term control.[29]

2.2 | Exercise-induced anaphylaxis (and food-dependent exercise-induced anaphylaxis)

Exercise-induced anaphylaxis (EIAn) is a rare and potentially fatal syndrome in which anaphylaxis occurs in conjunction with exercise.[30] A sub-group of individuals develop food-dependent exercise-induced anaphylaxis (FDEIAn) whereby physical activity follows within hours after ingestion of a food allergen to which the individual is sensitive or in some individuals after ingesting any type of food. Signs and symptoms arise due to massive degranulation of mast cells and include flushing, warmth, malaise, diffuse itching, urticaria, which can progress to angioedema, wheezing, gastrointestinal discomfort and cardiovascular collapse.[31]

In Europe, the incidence rates for all-cause anaphylaxis range from 1.5 to 7.9 per 100,000 person-year with an estimated 0.3% (95% CI 0.1–0.5) of the population experiencing anaphylaxis at some point during their lives.[32] It is estimated that EIAn accounts for approximately 10% of all forms of anaphylaxis,[33] and thus, the incidence rate ranges between 2 and 8 episodes per million person-years.

The pathophysiological mechanisms underpinning EIAn have not been fully elucidated (see Ansley et al.[30]). In brief, contributing factors may include the use of aspirin or non-steroidal anti-inflammatory drugs (NSAIDs), severe or uncontrolled asthma, exposure to high pollen levels, insect stings, extreme temperature and/or humidity, or even stress or menses. In the case of FDEIAn, the type of foods involved may vary with age, but also with geographical location. The most common foods are gluten antigen from wheat (omega-5 gliadin), shellfish, celery, cow's milk, mite-contaminated wheat flour and peanuts. Typically, in these patients, the synergistic effect of both inducing factors is necessary for the development of anaphylaxis (i.e., FDEIAn occurs when exercise is undertaken shortly following the ingestion of a specific food allergen).[34] In this context, it is thought that exercise may modify enzyme and cytokine expression, resulting in altered processing and enhanced immunogenicity of different food allergens. In contrast, co-factor triggered food anaphylaxis refers to a condition whereby additional factors (such as exercise, NSAIDs or alcohol consumption) facilitate and promote the reaction. In co-factor triggered food anaphylaxis, allergic reactions are often more severe and/or have a lower allergen threshold.[34]

Anaphylaxis should be diagnosed in accordance with the clinical consensus criteria recently described in the EAACI anaphylaxis guideline.[35] Exercise and the identification and timing of foods ingested in the hours preceding exercise should be noted in the history and an assessment of IgE sensitization against relevant allergens performed. An exercise test-with-or-without food provocation may be considered in centres with expertise in the management of this condition. The differential diagnosis includes cardiac and respiratory diseases along with appropriate tests (e.g., electrocardiography, echocardiogram, spirometry and gas transfer). Periodic re-evaluation for loss of sensitivity to food and/or exercise is recommended, as the natural history of FDEIAn is often unpredictable.

The management of EIAn and FDEIAn includes both preventive and treatment measures. In the case of FDEIAn, specific food allergens should be avoided for at least 6-h before exercise. When FDEIAn occurs after ingestion of any food, an abstinence interval of 2-4-h is generally adequate, but individual variation is considerable.[13] Avoidance of beta-blockers, angiotensin-converting-enzyme inhibitors and angiotensin-receptor blockers should be considered, as these drugs may increase the severity of anaphylaxis. Aspirin and NSAIDs, which increase gastrointestinal permeability, should also be avoided. In addition, it is advisable to deliver a personalized emergency plan such as wearing an identifying medical alert device and undertaking exercise with a trained companion who is aware of the risk and can support management.

Acute treatment measures should aim to ameliorate cardiovascular and respiratory manifestations. Patients should learn to identify their first symptoms and signs of EIAn and immediately stop exercise. Furthermore, they should learn to assume the Trendelenburg position (i.e., supine with their head declined below their feet at an angle of approximately sixteen degrees) in the face of hypotension and self-administer adrenaline intramuscularly into the lateral thigh to improve airflow and vascular integrity. Once medical emergency personnel become involved, the management of anaphylaxis should proceed according to established guidelines (see de Silva et al.[35]).

2.3 | Exercise-induced urticaria (and other activity-related sub-types)

Exercise-induced urticaria (EIU) is considered when physical activity leads to the development of pruritic wheals/hives (with or without angioedema), which typically disappear within a maximum of 24-h without residual lesions.[13,36] It is possible to distinguish between 'classical' EIU from the far more common cholinergic urticaria; a different condition that also occurs in association with exercise,[13,36,37] but appears within minutes after the elevation of body temperature, regardless of whether the heating is passive (e.g., hot shower) or active (exercise). In addition, cholinergic urticaria typically results in wheals with a diameter less than 5 mm, whereas those associated with EIU are usually substantially larger (Figure 2) and evolution to anaphylaxis is more frequently observed.

Similar to EIAn, milder reactions have been described as food-dependent exercise-induced urticaria/angioedema.[38] Other activity-related urticaria sub-types include (i) dermatographic urticaria occurring in response to shearing forces such as rubbing, (ii) cold or heat-induced urticaria (most often observed in aquatic or winter-based athletes), (iii) delayed pressure urticaria as a result of tightly fitted clothing or compression garments, (iv) vibratory urticaria which can occur in road-cyclists, (v) solar urticaria precipitated by ultraviolet and/or visible light, and (vi) contact urticaria in response to a substance that predisposes a wheal reaction.[36,39] Although several urticarial sub-types may simultaneously co-exist, there currently remain limited data concerning the prevalence of 'classical' EIU.

A clinical history of wheals (with or without angioedema) developing after vigorous (or sometimes low-intensity exercise) is often clear. Incremental exercise testing should be performed to confirm a diagnosis of EIU[36] (although caution is advised as the condition can rapidly progress to anaphylaxis). A passive warming test can be conducted to help differentiate cholinergic urticaria. In cases where EIU is associated with the ingestion of food, evaluation of IgE-specific mechanisms should be performed as per EIAn guidelines detailed above.

Treatment with non-sedating H1 antihistamines should be the first-choice symptomatic therapy in EIU, with up-dosing up to four times the standard daily dose in non-responders.[13,40] It is important to stress, however, that this does not necessarily prevent the progression to EIAn. Other preventive treatments lack a robust evidence-based recommendation. Management of other inducible urticarias has previously been revised (see Magerl et al.[36]).

3 | DIAGNOSIS AND MANAGEMENT OF RESPIRATORY DISORDERS

3.1 | Exercise-induced bronchoconstriction

Exercise-induced bronchoconstriction (EIB), in the presence or absence of clinical asthma, refers to the transient narrowing of the lower airways that occurs during, or most commonly following exercise.[41,42] The condition is a key indicator of uncontrolled asthma and often one of the first signs of asthma in children, however, also presents as a distinct clinical entity in approximately one in five otherwise healthy athletic individuals.[2]

It is thought that exercise hyperpnoea precipitates EIB by inducing osmotic changes at the distal airway surface, which causes inflammatory mediator release (e.g., histamine, prostaglanding-D_2 and cysteinyl leukotrienes) from resident, osmotic-sensitive inflammatory cells (e.g., mast cells and eosinophils).[43–45] In individuals with hyper-reactive airways, this inflammatory response ultimately leads to airway smooth muscle contraction and the development of expiratory airflow limitation.[46] In athletes, late-onset EIB (>25 years of age) is common, as repeated sustained exercise hyperpnoea is thought to cause 'airway injury', rendering the airway smooth muscle hypersensitive.[47] However, rather than the traditional type 2 high asthma phenotype, athletes (particularly those participating in aquatic and winter-based sports) often develop a specific 'sport asthma' or non-atopic phenotype.[48]

The diagnosis of EIB is clinically challenging due to the poor predictive value of self-report respiratory symptoms[49–51] and broad differential diagnosis.[52] However, when athletes report typical 'asthma-like' symptoms (i.e., wheeze, breathlessness, cough, chest tightness and mucus hypersecretion), conducting spirometry is

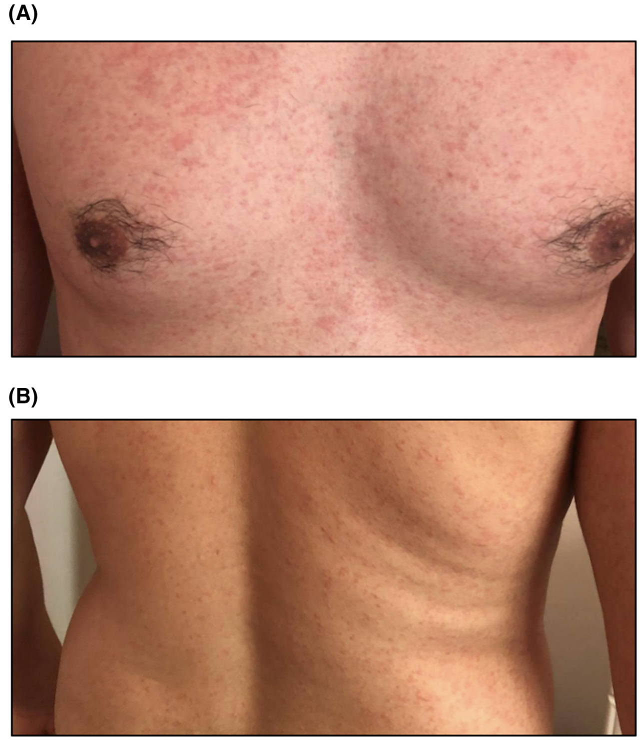

FIGURE 2 Case study example of exercise-induced urticaria in a recreationally active 24-year-old male footballer: (A) upper body; (B) lower back (wheal diameter >5 mm).

recommended.[53] The presence of resting airway obstruction (lower limit of normal defined as −1.64 Z scores [the lower 5th centile][54]) should prompt a standard asthma review in accordance with international guidelines.[55,56]

In those with normal resting lung function and negative bronchodilator responsiveness test, a form of indirect bronchial provocation (i.e., exercise testing, eucapnic voluntary hyperpnoea [EVH] or inhaled mannitol) is recommended to secure a diagnosis.[41,42,57] Despite a lack of consensus regarding the gold-standard methodology and concerns regarding diagnostic cut-off criteria,[58,59] it is widely recognized that EVH offers excellent negative predictive value and is thus considered the optimal approach to detect EIB in highly trained or elite level athletes.[60,61]

A positive diagnosis is typically defined as a pre–post challenge (exercise or EVH) reduction in lung function (i.e., ≥10% fall in FEV_1), with EIB severity classified according to the fall in FEV_1: mild (≥10 to <25% fall in FEV_1), moderate (≥25 to <50% fall in FEV_1) and severe (≥50% fall in FEV_1).[41,42] However, EIB can be a highly variable condition; thus, from a practical perspective, testing should be conducted 'in-season' (i.e., the competitive phase of a sporting season),[55] taking into account environmental conditions (particularly in pollen-sensitized athletes).[62,63] Furthermore, in athletes with mild EIB or a borderline airway response, a single bronchial provocation test is associated with poor test–retest repeatability, and thus, more than one test may therefore need to be performed to avoid misdiagnosis.[64–66]

Due to the aforementioned challenges, several adjunct tests may be considered during diagnostic work-up to aid clinical decision-making. Firstly, it has recently been reported that the AQUA questionnaire offers good sensitivity and thus may have utility to rule out a diagnosis when screening large athletic squads.[67] Secondly, given the strong association between atopy and bronchial hyper-responsiveness (BHR) in athletes,[62] testing for allergic sensitization via skin prick testing may also be a useful predictive tool. Thirdly, resting fractional exhaled nitric oxide (FeNO) (an indirect biomarker of type 2 inflammation asthma, signalling activation of IL-4/IL-13 pathway) may offer value in detecting EIB and/or monitoring the response to ICS therapy (established FeNO thresholds indicating raised eosinophilic inflammation: intermediate [≥25 ppb] and high [>50 ppb]).[68,69] Finally, impulse oscillometry (IOS) (a non-effort dependent lung function test designed to assess airway mechanics via random pressure pulses superimposed over tidal breathing) may offer utility as a supplement to spirometry in those with mild or borderline EIB. Specifically, IOS has previously been reported to provide greater sensitivity to change in airway calibre in comparison with spirometry when employed in conjunction with indirect bronchial provocation.[70–73]

Historically, the administration of a short-acting beta-2-agonist (SABA) prior to exercise has been considered an effective method of protecting against bronchospasm.[74] However, it is now recognized that regular beta-2-agonists therapy can lead to tachyphylaxis and loss of bronchoprotection during exercise,[75,76] and excessive use (i.e., multiple times per day) is also associated with an increased risk of severe exacerbation and asthma-related deaths.[77,78] In light of these concerns, the Global Initiative for Asthma (GINA) now opposes the use of SABA in isolation and instead recommends 'as-needed' (i.e., symptom-driven) or a daily combined low dose of ICS + fast long-acting beta-2-agonist (LABA) as first-line therapy.[55] This approach has previously been shown to be effective in reducing the severity of EIB in adults with clinical asthma.[79]

Other effective pharmacological therapies for EIB include leukotriene receptor antagonists,[80,81] anticholinergics[82] and mast cell stabilizing agents.[83] Allergen immunotherapy may also be considered as a potential therapeutic option in appropriately selected athletes (i.e., akin to the approach currently adopted in patients with allergic asthma) and should align with recommendations in the general population.[84] Non-pharmacological strategies include warm-up prior to exercise which is estimated to be effective in approximately half of individuals with EIB.[85,86] Dietary supplementation with fish oil (i.e., omega-3 poly unsaturated fatty acids),[87,88] or ascorbic acid[89] and reduction in sodium intake[90] can also be considered as adjuncts to pharmacological intervention and should be discussed with athletes. Likewise, when exercising in cold weather, wearing a scarf/snood or heat and moisture exchange mask may help to reduce the severity of EIB.[91,92]

3.2 | Exercise-induced laryngeal obstruction

Exercise-induced laryngeal obstruction (EILO) is a condition characterized by temporary closure of the larynx (upper airway) precipitating stridor and breathlessness on exertion,[93,94] thereby acting to mimic asthma.[95] EILO is estimated to impact approximately 5–7% of adolescents and young adults in the general population (with a two-fold higher incidence in females)[96,97] and up to 30% of athletic individuals referred with respiratory symptoms.[52] In addition, there is also now evolving appreciation that EILO can co-exist in patients with asthma, with recent reports indicating a prevalence of up to one in four people with asthma,[98–100] thus complicating diagnostic precision and confounding assessment of treatment response.

The cause of EILO currently remains unclear; however, it is probable that an interplay exists between several pathophysiological mechanisms. These include mechanical insufficiency due to pressure changes across the laryngeal inlet during exercise and/or inadequacy or laxity of muscles, ligaments or laryngeal cartilage, and/or inappropriate neural reflex control due to direct mechanical or chemical stimulation (e.g., cold-air, aeroallergen and pollutants) of sensory nerve endings (see Halvorsen et al.[94]). Clinical features of EILO include dyspnoea, cough and stridor (i.e., high-pitched whistle on inspiration) that typically occur during high or peak exercise intensity and dissipate rapidly with recovery.[93] For that reason, audio recordings or 'selfie-type' videos have been proposed to offer value in this setting to inform diagnostic work-up and guide referral pathways.[101] Although the assessment of an individual with suspected EILO should begin by obtaining a detailed clinical history, self-reported respiratory symptoms (particularly when employed in isolation) offer limited diagnostic precision (i.e., mimic or overlap with typical symptoms of asthma or EIB) and often lead to misdiagnosis and/or inappropriate treatment with asthma medications.[102]

The gold-standard method to confirm a diagnosis of EILO is continuous laryngoscopy during exercise (CLE)[103]; a technique that involves flexible nasendoscopy, to allow visualization of the laryngeal structures during exercise, usually performed in a laboratory setting (Figure 3). Although the optimal CLE protocol has yet to be established, exercise intensity should be sufficiently intense to provoke symptoms and/or achieve peak aerobic capacity,[94] and the exercise modality should ideally resemble the real-life situation where the patient's symptoms present. To improve ecological validity, it has been suggested that 'field-based' CLE testing may be a suitable and viable alternative.[104,105] Although there is no validated scoring system that differentiates between normal and abnormal responses, EILO severity and sub-type can be graded as mild, moderate or severe[1–3] relative to changes to the glottic or supraglottic aperture (i.e., clinically significant EILO is graded as ≥2).[106] It is important to note, however, that concerns have been raised regarding both the inter- and intra-rater agreement of the EILO visual grading scoring system.[107]

Breathing re-training and laryngeal control techniques are typically considered first-line therapy for people with confirmed glottic-predominant EILO and result in significant improvements in laryngeal obstruction in approximately 60% of cases.[108] It is also important that any other factors that potentially contribute to upper airway irritation and co-morbidities (e.g., asthma, EIB, nasal and reflux disease) are appropriately managed. For individuals that are

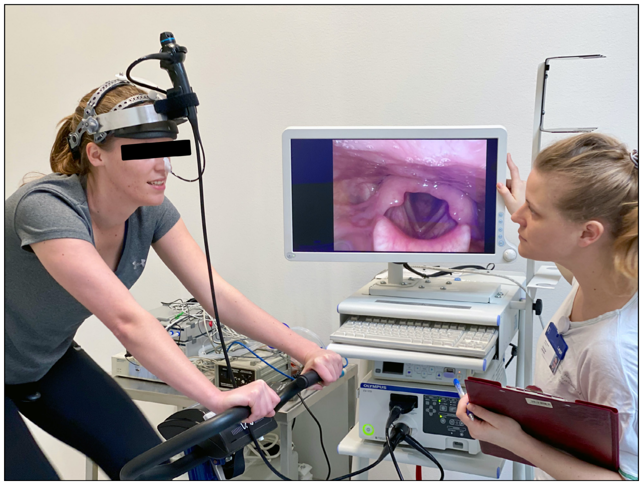

FIGURE 3 Continuous laryngoscopy during exercise. The laryngoscope is placed in situ and secured to a headset via a facemask. The screen provides real-time feedback of the structural and functional behaviour of the larynx in response to incremental exercise.

non-responsive to therapy or have evidence of severe supraglottic collapse and debilitating symptoms, surgical intervention via laser supraglottoplasty has been shown to be a suitable and effective option in selected cases.[109] Inspiratory muscle training has been suggested as potential therapy for EILO, but the efficacy remains unclear on the basis that laryngeal closure has been shown to worsen post-inspiratory muscle training in some individuals.[110] The apparent effect mainly on glottic closure suggests a mechanism of action similar to that of laryngeal control techniques, rather than a benefit from increased respiratory muscle strength. The exercise-induced laryngeal obstruction dyspnoea index (EILODI) is a recently validated patient-reported outcome measure that can be employed to evaluate the efficacy of treatment interventions and change in clinical status over time.[111]

3.3 | Breathing pattern disorder

It is now increasingly recognized that respiratory symptoms may arise from a breathing pattern disorder (BPD) (defined as an alteration in the normal biomechanical pattern of breathing that can result in intermittent or chronic symptoms).[112,113] This maladaptive breathing pattern typically occurs during peak exercise but may also present variably during lower intensity activities. BPD has been reported to occur in approximately 10% of the general population, with a significantly higher incidence in females, and up to 30% of people with asthma.[114]

Clinical features of BPD include excessive breathlessness that is disproportionate to the level of physical activity undertaken. Other typical symptoms include 'air hunger' (i.e., the inability to take a deep, satisfying breath) and/or chest discomfort or tightness (typically exacerbated by either physiological or psychological stress[113]). A reliable objective method for detecting BPD is currently lacking[112]

TABLE 3 Other pathological and non-pathological causes of respiratory symptoms

	Clinical presentation	Diagnostic assessment	Management strategies	
			Non-pharmacological	Pharmacological
Other pathological causes of respiratory symptoms				
Large airway collapse	• Malacia/honking cough • Recurrent infections • Unexplained expiratory wheeze	• Dynamic CT or bronchoscopy with forced expiration[121]	• Physiotherapy to optimize airway clearance and breathing pattern[122] • May benefit from pneumatic splinting with positive pressure in severe cases, but not likely to be possible in an athletic setting	• Nil relevant
Pulmonary embolism	• Pleutiric chest pain • Haemoptysis • Sudden onset dyspnoea • Possible DVT	• Dedicated chest imaging with contrast; that is CTPA.	• Nil relevant	• Anti-coagulation as per international guidance
Pneumothorax	• Sudden onset dyspnoea with unilateral pleuritic chest pain	• Chest image showing air in pleural space	• Review and manage as per international guidelines • Counsel regarding risk of recurrence	
Anaemia	• Malaise, fatigue, history of blood loss or prior anaemia • Symptoms which are predictable and worsen on exertion	• Bloods showing low Hb	• Identify and treat cause	• Iron supplementation, as indicated
Swimming-induced pulmonary oedema	• Acute onset dyspnoea during swimming with clinical features of heart failure, inc. productive cough of white/blood-stained secretions • Audible crackles on auscultation	• CXR may show bilateral infiltrates	• Investigate to detect any underlying cardiorespiratory issues, inc. cardiac dysfunction and hypertension, etc.	• Sildenafil may be appropriate, initiated in specialist centre[123]
Non-pathological causes of respiratory symptoms				
Physical deconditioning	• Exercise limitation +/− dyspnoea	• BMI and waist circumference • CPET	• Lifestyle modification: diet, exercise training and physical activity promotion	• Nil relevant

Abbreviations: BMI, body mass index; CPET, cardio-pulmonary exercise testing; CT, computerized tomography; CTPA, computerized tomography pulmonary angiography; CXR, chest X-ray; DVT, deep vein thrombosis; Hb, haemoglobin.

and thus diagnostic work-up typically involves the exclusion and/or treatment optimization of a pathological problem combined with the positive identification of several distinct ventilatory abnormalities.[115]

It is logical to assess BPD at rest, and when symptomatic, CPET can reveal distinct abnormalities.[115,116] Alternatively, sports-specific, or field-based testing in athletes may improve specificity to help confirm or refute a diagnosis. The most common signs of BPD during exercise include ventilatory irregularity or increased respiratory rate (i.e., mismatch between minute ventilation and metabolic demand), predominant upper chest movement (or asynchrony between upper and lower chest), audible and/or excessive oral breathing, and slumped posture or rounded shoulders.[117] The most effective treatment option for BPD currently includes physiotherapy-led breathing re-training that should progress from rest to sports-specific tasks.[118] The presence of other co-existing conditions that can contribute to BPD (e.g., asthma, EIB, nasal and reflux disease, anxiety, or mood state disorders) should also be considered and managed appropriately.

3.4 | Cough and exercise

Cough is frequently reported by athletic individuals during and/or post-exercise.[119] The presence of exercise-related cough is typically taken to indicate underlying asthma or EIB. However, in many cases, athletic individuals reporting cough do not have objective evidence of BHR or heightened airway inflammation,[120] thus suggesting a more generalized cough hypersensitivity process. Furthermore, there is now improved recognition that cough is a common symptom in other prevalent airway disorders, such as EILO.[52]

In contrast to problematic cough in the general population, exercise-related cough is typically associated with sport-specific environmental exposures (i.e., aeroallergen, irritants and pollutants) and occurs most frequently following high-intensity exercise.[119] Despite several studies evaluating the impact of exercise on cough, there currently remains a paucity of data regarding the optimal approach to diagnostic work-up and treatment. It remains the case that individuals presenting with exercise-related cough should undergo assessment to rule out allergic or asthma-related causes, but due consideration should also be given for a potential contribution from airway reflux, nasal disease and/or a generalized hypersensitivity process.[119] Following an initial assessment, a systematic investigation based on suspected causes of cough should follow, with specific attention to the sporting discipline (i.e., exercise mode and intensity) and training environment.[119] Due to the lack of research in the area, exercise-related cough should be reviewed and managed as per recommendations in the general population (see Boulet et al.[119]).

3.5 | Other pathological and non-pathological causes of respiratory symptoms

The cause of respiratory symptoms (e.g., breathlessness) in young athletic individuals is broad and thus differential diagnoses should be considered when common conditions have been ruled out and/or if the patient remains refractory to standard treatment. This should include consideration for cardiac disease, but other relevant, less common respiratory-related pathological conditions, such as large airway collapse, pulmonary embolism, pneumothorax, anaemia, swimming-induced pulmonary oedema (SIPE) should also be considered. Non-pathological issues such as obesity ± physical deconditioning may also contribute to an increased work of breathing and/or heightened perception of breathlessness (Table 3).

4 | SUMMARY: FUTURE RESEARCH AND UNMET NEEDS

The diagnosis of allergy and respiratory disorders in sport can be difficult and confounded by the poor precision of a standard clinical approach to diagnosis, and thus, objective testing is required to facilitate assessment in order to optimize management. It remains apparent, however, that many of the diagnostic methods detailed in this position paper are currently only available at specialist centres, which precludes widespread implementation. To advance knowledge and understanding and improve the overall care afforded to athletes and recreationally active individuals with exercise-related allergic and respiratory conditions, future research should focus on:

- Developing simple, cost-effective, non-invasive screening tools (e.g., wearable ambulatory technologies and disease-specific smartphone applications) to aid diagnostic work-up inform referral pathways and monitor response to therapeutic intervention.
- Establishing an international registry or collaborative research network to conduct epidemiological studies to evaluate global prevalence estimates and identify relevant risk factors and high-risk groups.
- Reaching widespread consensus regarding optimal diagnostic methodologies and interpretation, with consideration for test protocols and cut-off criteria, according to specific conditions and clinical populations.
- Conducting robust multicentre trials with established protocols and clinical endpoints to evaluate underpinning pathophysiological mechanisms (according to specific disease sub-types and severity) and efficacy of preventative strategies and novel therapeutic interventions.
- Evaluating the impact of allergy and respiratory disorders on physical activity and exercise engagement and how this associates with general health and well-being across the lifespan.

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CONFLICT OF INTEREST

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GUARANTOR STATEMENT

OP confirms responsibility for the content of the manuscript on behalf of all EAACI Task Force members.

IN MEMORIUM

The authors wish to dedicate this position paper to the memory of our friend and colleague, Professor Kai-Håkon Carlsen, who sadly passed away in September 2021.

ORCID

Oliver J. Price https://orcid.org/0000-0001-8596-4949

Emil S. Walsted https://orcid.org/0000-0002-6640-7175
Matteo Bonini https://orcid.org/0000-0002-3042-0765
John D. Brannan https://orcid.org/0000-0001-7243-7998
Valérie Bougault https://orcid.org/0000-0002-2258-6562
Kai-Håkon Carlsen https://orcid.org/0000-0002-3026-8521
Mariana Couto https://orcid.org/0000-0003-4987-9346
Pascale Kippelen https://orcid.org/0000-0002-8443-0248
André Moreira https://orcid.org/0000-0002-7294-9296
Helena Pite https://orcid.org/0000-0002-7300-928X
Maia Rukhadze https://orcid.org/0000-0002-1413-8161
James H. Hull https://orcid.org/0000-0003-4697-1526

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