Allergy 2008: 63: 953–961

DOI: 10.1111/j.1398-9995.2008.01802.x

Review article

Exercise-induced hypersensitivity syndromes in recreational and competitive athletes: a PRACTALL consensus report (what the general practitioner should know about sports and allergy)

Exercise-induced (EI) hypersensitivity disorders are significant problems for both recreational and competitive athletes. These include EI-asthma, EI-bronchoconstriction, EI-rhinitis, EI-anaphylaxis and EI–urticaria. A group of experts from the European Academy of Allergology and Clinical Immunology and the American Academy of Allergy Asthma and Immunology met to discuss the pathogenesis of these disorders and how to diagnose and treat them, and then to develop a consensus report. Key words (exercise with asthma, bronchoconstriction, rhinitis, urticaria or anaphylaxis) were used to search Medline, the Cochrane database and related websites through February 2008 to obtain pertinent information which, along with personal reference databases and institutional experience with these disorders, were used to develop this report. The goal is to provide physicians with guidance in the diagnosis, understanding and management of EI-hypersensitivity disorders to enable their patients to safely return to exercise-related activities.

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Key words: anaphylaxis; asthma; athletes; exercise; rhinitis; urticaria.

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Accepted for publication 26 April 2008

Exercise-induced (EI) hypersensitivity disorders perplex, frustrate and distress both patients and their physicians. Typically, the respiratory (asthma, bronchospasm and rhinitis), cutaneous (urticaria and angio-oedema) or cardiovascular (anaphylaxis) system is targeted. Although most victims survive such an attack, a recurrence is likely to be provoked by exercise under the same conditions and, consequently, future exercise-related activities are often curtailed. In many cases, these disorders are associated with allergic (IgE) sensitivities. The current review of this topic reflects a consensus from working committees from the European Academy of Allergology and Clinical Immunology and the American Academy of Allergy, Asthma and Immunology that will consider clinical features of EI-asthma, -bronchoconstriction, -rhinitis and -anaphylaxis, with the goal of enabling such patients to safely resume their athletic activities.

What are exercise-induced respiratory disorders?

Exercise-induced asthma is defined as lower airway obstruction and symptoms of cough, wheezing or dyspnoea induced by exercise in patients with underlying asthma (1). The same clinical presentation in individuals without asthma is defined as EI-bronchoconstriction. Whether EI-asthma and EI-bronchoconstriction are distinct entities is arguable, because they present similarly and share a pathophysiological mechanism (see below). Asthma flares in athletes significantly impair performance.

Exercise-induced rhinitis is characterized by itching, sneezing, rhinorrhea and/or postnasal drainage, nasal congestion and occasional anosmia provoked by exercise (2). Rhinitis is frequently accompanied by eye, ear or throat symptoms. Underlying noninfectious rhinitis can be classified according to its aetiology, allergic (IgE-mediated) and nonallergic, and to its clinical presentation, intermittent/persistent and mild/moderate/severe (ARIA classification) (2). The prevalence of underlying rhinitis in athletes is comparable to that in nonathletes (Table 1). Allergic rhinitis affects ~25% of adults in Europe and up to 40% of children globally (3, 4); the latter group is commonly encouraged to participate in sports. Athletes with rhinitis, particularly congestion, often have disturbed sleep, daytime somnolence, fatigue and impaired performance.

Exercise induced asthma manifests in nearly all uncontrolled asthmatics and in the majority of children with asthma (5). EI-asthma/bronchoconstriction is not only most prevalent in elite athletes (6), particularly those who participate in endurance events such as cross-country skiing, swimming, road cycling and long-distance running, but also more prevalent among speed and power competitors such as ice hockey and track and field athletes than in recreational athletes (7, 8).

Pathogenesis of exercise-induced respiratory disorders

Hyperosmolar airway fluid formed by evaporation of airway water during exercise is the principal pathophysiological trigger for EI-asthma/bronchoconstriction, and possibly EI-rhinitis (Fig. 1). Hyperosmolarity activates cells in the lower airways to release mediators, causing bronchoconstriction, vasopermeability and mucus hypersecretion (9). Heat loss with reactive airway hyperemia upon rewarming is a secondary pathway of EI-bronchoconstriction (10). Hyperpnoea places the elite athlete at a greater risk because of increased water and heat loss from the airways (11).

The nose protects the lower airway by filtering, humidifying and warming inspired air, so nasal congestion places the lower airway at an increased risk (12). Autonomic reflexes affect nasal congestion by regulating glandular secretions and mucosal blood vessel dilation and permeability. Dynamic exercise stimulates α-adrenoceptors that vasoconstrict and reduce nasal resistance (13). Isometric exercise increases nasal resistance in rhinitis patients, but minimally affects nasal resistance in healthy subjects. Autonomic nerves also mediate the contraction and relaxation of bronchial smooth muscle. Cholinergic-parasympathetic nerves stimulate bronchoconstriction, whereas β2-adrenergic sympathetic and/or noncholinergic parasympathetic nerves bronchodilate (14). Intensive training may promote vagal hegemony (15) with resting bradycardia, but increased bronchomotor tone and susceptibility to bronchospasm (16).

The airways of athletes have increased inflammatory cells and levels of histamine, cysteinyl leukotrienes (CysLTs) and chemokines (17). However, these baseline inflammatory changes are not consistently related to lung function or disease exacerbations (18), and may represent

Abbreviations: CysLT, cysteinyl leukotriene; EI, exercise induced; LABA, long-acting β2-adrenoceptor agonist; SABA, short-acting β2-adrenoceptor agonist.

Table 1. Prevalence of rhinitis or seasonal allergic rhinoconjunctivitis (SARC) in athletes. Overview of key studies from a Medline search up to February 2008 (keywords: rhinitis and athletes or sports or exercise)

Reference	Design and methods	Year of study, subjects (*n*)	Rhinitis/SARC* Prevalence
Fitch KD, J Allergy Clin Immunol 1984;73(5 Pt 2):722–7	Retrospective; medical records analysis	1976, Australian Olympics (185)	8.6
		1980, Australian Olympics (106)	7.5
Helbling A, Schweiz Med Wochenschr 1990;120(7):231–6	Cross-sectional; questionnaire	1986, Swiss athletes (2060)	16.8*
Kaelin M, Schweiz Med Wochenschr 1993;123(5):174–82	Cross-sectional; questionnaire	1990, Swiss athletes (1530)	19.7*
Potts J. Sports Med 1996;21:256–261	Cross-sectional; questionnaire	1995, Canadian swimmers (738)	19.0*
Helenius I. J Allergy Clin Immunol 1998;101(5):646–52	Cross-sectional; skin prick tests with medical diagnosis	1996, Finnish summer athletes (162)	29.6*
Weiler J. J Allergy Clin Immunol 1998;102:722–6	Cross-sectional, questionnaire (USOC-MHQ)	1996, US summer Olympics (699)	16.9
Weiler J. J Allergy Clin Immunol 2000;106:267–1	Cross-sectional, questionnaire (USOC-MHQ)	1998, US winter Olympics (196)	13.3
Katelaris CH. J Allergy Clin Immunol 2000;106:260–6	Cross-sectional; skin prick tests with medical diagnosis	1997/8, Australian summer Olympics (214)	41.0/29.0*
Katelaris CH. Clin J Sport Med 2006;16(5):401–5	Cross-sectional; skin prick tests with medical diagnosis	1999, Australian Olympics/Paralympics (977)	37.0/24.0*
Lapucci G. J Allergy Clin Immunol 2003;111:S142	Cross-sectional; skin prick tests with medical diagnosis	2000, Italian summer Olympics (265)	25.3*
Bonadonna P. Am J Rhinol 2001;15(5):297–301	Cross-sectional, questionnaire on cold-induced rhinitis	2001, Italian skiers (144)	48.6
Alaranta A. Med Sci Sports Exerc 2005;37:707–11	Cross-sectional; self reported medical diagnosis	2002, Finnish Olympic athletes (446);	26.5
		Subgroup of endurance athletes (108)	36.1
Randolph C. Med Sci Sport Exerc 2006:2053–7	Cross-sectional; questionnaire (USOC-MHQ)	2003/4, US recreational runners (484)	34.7
Moreira A. Respir Med 2007;101(6):1123–31	Cross-sectional; self reported medical diagnosis	2003, Finnish marathon runners (141)	17.3
Bonini M. Allergy 2007:62:1166–70	Cross-sectional; medical diagnosis	2006, Italian preOlympics (98)	34.7
Macucci F. J Sports Med Phys Fitness 2007;47(3):351–5	Cross-sectional; medical diagnosis	2006, Italian young athletes (352)	22.2
Salonen RO. Environ Int 2008;34(1):51–7	Cross-sectional; self reported medical diagnosis	2007, Finnish young hockey players (793)	18.3
Summary	*16 cross sectional studies, of which 9 with objective medical diagnosis assessment*	*10 328 athletes, from recreational to Olympic level*	*Prevalence ranging from 8% up to 41%*

physical injury secondary to rigorous hyperpnoea that heals with rest (19–21).

Exercise induced asthma/bronchoconstriction is modulated by the baseline condition of the patient (22, 23). Atopy is a major risk factor along with the type of training. The relative risk of asthma increases ~25-fold in atopic speed and power athletes and ~75-fold in atopic endurance athletes compared to nonatopic controls. Specific sport environments markedly increase the likelihood of an EI-respiratory disorder (Table 2) (2, 12, 22, 24).

Diagnosis of exercise-induced respiratory disorders

Patients with EI-asthma should be considered to have underlying asthma that is exacerbated by exercise because of poor asthma control. In those who have underlying asthma under good control, objective inhalation challenge tests for EI-asthma can confirm the diagnosis; those under poor control can be reversed with a short-acting β2-adrenoceptor agonist (SABA) (Table 3) (25–28). The methacholine provocation test can demonstrate bronchial hyper-reactivity even when baseline spirometry is normal and does not necessarily correlate with hyper-reactivity to exercise and surrogate challenges (25, 27). SABAs reverse bronchospasm induced by exercise or other bronchial challenges.

Methods and thresholds to document EI-bronchoconstriction may be different for recreational *vs* competitive athletes, particularly in regulated sports. For recreational exercisers, free running for children or a simple 10 min (1 km) jog for adults may be adequate to document EI-bronchoconstriction (≥10% drop in FEV_1). For others, the exercise challenge should elicit 90% of maximal heart rate or 40–60% of maximal ventilation during 6–8 min of exercise on a treadmill or stationary bicycle (25, 26). For competitive athletes, precise criteria for diagnosing asthma have been set and will continue to be updated by regulatory authorities (Tables 3–5).

The diagnosis of EI-rhinitis is made by history, but can be confirmed with an exercise challenge test and objective measures of nasal obstruction (nasal peak flow, rhinomanometry and acoustic rhinometry), mucociliary clearance

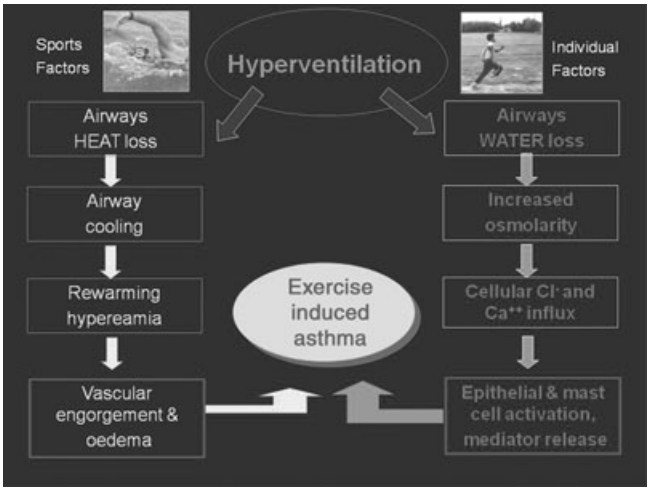

Figure 1. What is the pathogenesis of exercise-induced asthma? Exercise increases ventilation and consequently dehydrates the airways (right flow diagram), which increases the osmolarity of the airway surface water layer. This hyperosmolarity activates epithelial and mast cells, leading to release of mediators causing airway smooth muscle contraction and mucus hypersecretion. Athletes with EI-asthma/bronchoconstriction have increased cellular markers of inflammation in the airway and increased levels of histamine, tryptase, leukotrienes and chemokines, the same biomarkers generally seen in asthma. In addition, heat loss with airway cooling (left flow diagram) stimulates airway receptors and induces vasoconstriction; reactive hyperemia occurs with rewarming that is associated with vascular engorgement and tissue edema, which further diminishes airflow. EI-asthma also may be modulated by pre-existent atopy with bronchial hyper-responsiveness and airway inflammation, by autonomic dysregulation associated with intensive training and by sport-specific environmental factors.

and/or symptoms (29). However, currently, exercise tests are neither standardized nor validated as diagnostic tools in EI-rhinitis. Underlying allergic or nonallergic rhinitis is diagnosed by history, physical examination and assessment of antigen-specific IgE through skin and/or laboratory tests. A nasal allergen challenge is occasionally helpful, although it is primarily a research tool. Rhinitis and asthma often occur together and each should be considered regardless of which one is clinically most apparent (3).

Table 2. Specific sport environments associated with exercise induced hypersensitivity disorders

Runners: hyperosmolarity of the upper and lower airways caused by hyperpnoea, leading to bronchoconstriction, nasal congestion, rhinorrhea and impaired mucociliary function, and hyperosmolarity of the lower, and increased exposures to irritants and pollutants such as diesel exhaust particulates, ozone, NO_2, CO_2 and SO_2. Pollutants adsorbed onto allergenic particles such as pollens may enhance their allergenic potency.
Swimmers: nasal congestion, rhinorrhea and bronchospasm secondary to inhaled chloramines derived from hypochlorite in water disinfectants.
Divers: congestion and rhinosinusitis secondary to barotrauma.
Boxers: repetitive nasal trauma causes increase nasal resistance, impaired secretion clearance, anosmia and hyposmia.
Skiers: bronchospasm and rhinitis secondary to irritant effects of cold dry air.
Figure skaters: ultrafine particulates and NO_2 created by ice grooming equipment can cause rhinitis and bronchospasm.

Treatment of exercise-induced asthma and bronchoconstriction (Box 1)

Most agents effective in the treatment of chronic asthma are likely to be effective in the treatment of EI-asthma and EI-bronchoconstriction. Optimal control of underlying asthma minimizes airway narrowing during exercise (1, 22). Worsening EI-asthma may be a sign of inadequate control of underlying asthma, and 'step up' therapy should be considered. Controlling rhinitis also may improve control of asthma. Reduced nasal congestion should improve sleep and thereby improve quality of life and, most likely, athletic performance. Certain medications for athletes with asthma and rhinitis who participate in regulated competitions are not allowed (Table 5) (30, 31).

Inhaled β2-adrenoceptor agonists (β2-agonists) are most effective in reversing EI-asthma/bronchoconstriction and are also used for prevention. The effectiveness of inhaled SABAs (salbutamol = albuterol, terbutaline) against EI-asthma/bronchoconstriction is optimal ~20 min after inhalation and wanes within a few hours.

Box 1. Allergy and asthma in sports – tips for nonspecialists

Early recognition and a correct diagnosis are the keys for successful management of exercise induced (EI)-hypersensitivity disorders.
Self-reported symptoms of asthma and/or EI-asthma, and baseline spirometry tests are poorly predictive of EI-asthma in competitive athletes. Exercise, methacholine, mannitol or hypertonic saline challenges or a eucapnic voluntary hyperpnoea test, performed by experienced personnel is better.
Treatment of underlying asthma and rhinitis should follow available guidelines. Underlying rhinitis should be assessed and treated in patients with EI-asthma, because rhinitis enhances the severity of asthma and EI-asthma.
Combinations of several types of drugs are frequently needed to fully control EI- asthma in athletes, but for those engaged in competition, physicians also must keep up-to-date on the latest doping regulations both from the World Anti-Doping Agency http://www.wada-ama.org/en/ and International Olympic Committee http://www.olympic.org/uk/organisation/commissions/medical/index_uk.asp
If EI-asthma treatment is not successful, reconsider the diagnoses, because EI-vocal cord dysfunction, EI-arterial hypoxemia, swimming-induced pulmonary edema, poor physical fitness, other lung disorders and cardiovascular illness may present with similar symptoms.
When anaphylaxis presents during exercise, take a careful history of food ingestion over the previous 24 h, paying particular attention to wheat products and shrimp.
Athletes at risk for EI-anaphylaxis must have an action plan to deal with future events, including stopping the exercise at the first sign or symptom, having EpiPen® immediately available and knowing how to use it, assuming the Trendelenburg position for symptoms of hypotension and wearing medic alert information.

Table 3. Criteria set by the International Olympic Committee to document EI-bronchoconstriction in athletes for Beijing 2008. http://multimedia.olympic.org/pdf/en_report_1302.pdf

A *rise* in FEV_1 to bronchodilator ≥12% of the baseline or predicted FEV_1 and exceeds 200 ml
A *fall* in FEV_1 ≥10% from baseline in response to exercise or eucapnic voluntary hyperpnoea
A *fall* in FEV_1 ≥15% from baseline after inhaling 22.5 ml of 4.5 g% NaCl or ≤ 635 mg of mannitol
A *fall* in FEV_1 ≥20% from baseline in response to methacholine: PC_{20} ≤ 4 mg/ml, or PD_{20} ≤ 400 μg (cumulative dose) or ≤ 200 μg (noncumulative dose) in those not taking inhaled corticosteroids (ICS), and PC_{20} ≤ 16 mg/ml or PD_{20} ≤ 1600 μg (cumulative dose) or ≤ 800 μg (noncumulative dose) in those taking ICS for at least 1 month

Note: In the case of an athlete with known but well-controlled asthma, recording a negative result to the bronchial provocation test(s), but still seeking approval for the use of inhaled β2 agonist(s), the following documentation must be included in the submitted medical file: consultations with their physician for treatment of asthma, hospital emergency department visits or admissions for acute exacerbations of asthma or treatment with oral corticosteroids. Additional information that may assist includes: the age of onset of asthma; detailed description of the asthma symptoms, both day and night; trigger factors; medication use; past history of atopic disorders and/or childhood asthma; and physical examination, together with results of skin prick tests or RASTs to document the presence of allergic hypersensitivity. Negative bronchial provocation and allergy test results also must be included with the submission to the International Olympic Committee.

Table 4. Information resources for physicians, trainers and athletes

World Anti-Doping Agency http://www.wada-ama.org/en/ http://www.wada-ama.org/rtecontent/document/2008_List_En.pdf
International Olympic Committee Medical Commission http://www.olympic.org/uk/organisation/commissions/medical/index_uk.asp
International Association of Athletic Federations Medical http://www.iaaf.org/medical/manual/index.html
European Academy of Allergology and Clinical Immunology http://www.eaaci.net/
American Academy of Allergy, Asthma and Immunology http://www.aaaai.org/
KH Carlsen, SD Anderson, L Bjermer, S Bonini, V Brusasco, W Canonica, J Cummiskey, L Delgado, SR Del Giacco, F Drobnic, T Haahtela, K Larsson, P Palange, T Popov, P van Cauwenberge (2008) Exercise-induced asthma, respiratory and allergic disorders in elite athletes: epidemiology, mechanisms and diagnosis: Part I of the report from the Joint Task Force of the European Respiratory Society (ERS) and the European Academy of Allergy and Clinical Immunology (EAACI) in cooperation with GA^2LEN. Allergy 2008;63(4):387–403 http://www.blackwell-synergy.com/doi/full/10.1111/j.1398-9995.2008.01662.x
KH Carlsen, SD Anderson, L Bjermer, S Bonini, V Brusasco, W Canonica, J Cummiskey, L Delgado, SR Del Giacco, F Drobnic, T Haahtela, K Larsson, P Palange, T Popov, P van Cauwenberge (2008) Treatment of exercise-induced asthma, respiratory and allergic disorders in sports and the relationship to doping: Part II of the report from the Joint Task Force of European Respiratory Society (ERS) and European Academy of Allergy and Clinical Immunology (EAACI) in cooperation with GA^2LEN. Allergy 2008;63 (5):492–505 http://www.blackwell-synergy.com/doi/full/10.1111/j.1398-9995.2008.01663.x
Miller MG, Weiler JM, Baker R, Collins J, D'Alonzo G. National Athletic Trainers' Association position statement: management of asthma in athletes. J Athl Train 2005;40(3):224–45. http://www.nata.org/jat/readers/archives/40.3/i1062-6050-40-3-224.pdf

Long-acting β2-agonists (LABAs) (formoterol and salmeterol) protect for up to 12 h after a single inhalation. However, only formoterol acts as fast as SABAs. Therefore, formoterol or a SABA, but not salmeterol, should be chosen to reverse EI-asthma/bronchoconstriction. Inhaled β2-agonists may mask worsening airway inflammation, and should never be used regularly without an inhaled glucocorticoid (1). Also, tachyphylaxis occurs with regular use of β2-agonists (32), reducing their protective effect against EI-asthma/bronchoconstriction, even if used together with an inhaled corticosteroid (1). Therefore, avoiding daily use of inhaled β2-agonists will optimize their rescue or preventive effects when most needed.

Regular treatments with inhaled glucocorticoids and/or leukotriene pathway antagonists control underlying asthma and reduce EI-asthma/bronchoconstriction in most patients (22, 33). Zileuton is a leukotriene synthesis inhibitor, and montelukast, zafirlukast and pranlukast are cysLT receptor-1 antagonists. Importantly, tachyphylaxis to anti-leukotrienes and to inhaled glucocorticoids has not been reported (1). H1-antihistamines and cholinergic antagonists have minimal effects on EI-asthma/bronchoconstriction, whereas cromones administered before exercise reduce EI-bronchoconstriction by ~30%. Xanthines, calcium channel blockers, and inhaled furosemide have modest attenuating effects on EI-bronchoconstriction, but side effects generally relegate these classes to the sidelines (1, 22). In difficult to control EI-asthma/bronchoconstriction, combining inhaled glucocorticoids, oral leukotriene antagonists and/or inhaled β2-agonists may be beneficial (1).

Intranasal corticosteroids, both in nonallergic and allergic rhinitis, reduce all symptoms, even congestion and improve sleep quality (34). Nonsedating antihistamines attenuate the itching, sneezing and rhinorrhea (but not congestion) of allergic rhinitis (35). Nasal sprays containing a sedating antihistamine (azelastine) reduce symptoms, but diffuse across the mucosa and cause sedation (36, 37). Intranasal decongestants act rapidly, but cause rebound congestion (rhinitis medicamentosa), if used regularly. An intranasal anticholinergic (ipratropium) rapidly inhibits rhinorrhea, and is first-line rescue or prophylactic therapy when rhinorrhea is the predominant symptom. Intranasal cromones are not effective rescue agents, and provide minimal benefit when given before exercise. CysLT antagonists benefit both rhinitis and asthma.

Interventions beyond pharmacotherapy in the treatment of EI-asthma, EI-bronchoconstriction and EI-rhinitis could involve allergen/irritant avoidance (when practical) and immunotherapy in patients with specific allergies (1). For exercise in cold air, a mask that

Table 5. Which drugs for asthma and rhinitis are regulated at sporting events?

Stimulants are prohibited during competitions, including oral nasal decongestants (ephedrine, methylephedrine). Intranasal decongestants (oxymetazoline, phenylephrine, propylhexedrine) though monitored, are allowed.
β2-Agonists are prohibited unless a therapeutic use exemption for inhaled β2-agonists in asthma is first obtained, even though inhaled β2-agonists do not enhance the performance of those without asthma. Oral β2-agonists, which are ineffective in EI-bronchoconstriction, are prohibited in regulated competitions.
Sedating antihistamines, though not prohibited, impair performance and should be avoided.
Oral and parenteral glucocorticoids are prohibited, while use of topical intranasal glucocorticoids is allowed, inhaled glucocorticoids in competitions need an abbreviated therapeutic use exemption.
Diuretics, such as furosemide, are prohibited because they may mask the presence of other prohibited drugs. A therapeutic use exemption is not valid if an athlete's urine contains a diuretic in association with threshold or sub-threshold level of a prohibited substance(s).

facilitates warming of inhaled air may help. Infections, gastro-oesophageal reflux, sinusitis and exposure to pollutants and tobacco smoke should be addressed. Warm-up and cool-down exercises might reduce EI-asthma/bronchoconstriction. In light of the pathophysiology, hydration should be encouraged (11).

Exercise-induced urticaria and anaphylaxis

Exercise induced anaphylaxis is a physical allergy, brought on by vigorous to sometimes mild exercise alone (38). A subgroup develops food-dependent EI-anaphylaxis whereby exercise must occur within several hours after ingestion of a food allergen to which the subject is sensitive or, in other cases, after ingestion of any food (39–42). Symptoms of fatigue, pruritus, warmth, flushing and urticaria can progress to angio-oedema, wheezing, rhinitis, gastrointestinal symptoms and cardiovascular collapse (43). Contributing factors may include use of aspirin or NSAIDs, exposure to high pollen levels, insect stings, extremes of temperature and humidity or even stress or menses.

The food allergies most commonly implicated are to wheat (60%) and shrimp (18%), but may be culturally influenced and are usually different from those associated with food allergy alone (peanut, tree nuts, milk and egg) (39, 40). Loss of EI-anaphylaxis susceptibility over time is unusual, but in one 10-year study, episode severity stabilized in 46%, regressed in 47% and worsened in 7% (38).

Pathogenesis of exercise-induced urticaria and anaphylaxis

Anaphylaxis and urticaria develop following release of mediators such as histamine, cysLTs and PGD_2 that vasodilate, enhance vascular permeability and contract bronchial smooth muscle. These mediators are secreted by mast cells and basophils, which can be activated by allergens (44). EI-anaphylaxis and urticaria associated with food-specific IgE may develop in this manner.

In food-associated EI-anaphylaxis, exercise increases the entry of recently-ingested but incompletely-digested food proteins, including allergens, into the circulation, from where they migrate into perivascular and tissue spaces where mast cells armed with allergen-specific IgE reside (39). Increased absorption of gliadin–derived allergens from wheat occurs experimentally with exercise or aspirin ingestion. For those with EI-anaphylaxis without food allergy the pathogenesis is less certain. Some cases occur with exercise alone; others with exercise after ingestion of any food. Anaphylaxis during exercise also may be coincidental to an insect sting (45), or to underlying disease such as systemic mastocytosis (46, 47) with activating mutations of Kit tyrosine kinase (48) that increase the risk for anaphylaxis in general (49). Some cases of EI-anaphylaxis develop in athletes with cholinergic urticaria who elevate their body temperature with exercise, with cold-induced urticaria who exercise in cold conditions, and with chronic urticaria who have IgG anti-IgE receptor autoantibodies and coincidentally exacerbate during exercise. Other cases of EI-anaphylaxis/urticaria may occur in the context of idiopathic anaphylaxis (50).

Diagnosis of exercise-induced urticaria and anaphylaxis

Anaphylaxis should be diagnosed by the clinical consensus criteria proposed in 2005 (43). Exercise and the identification and timing of foods ingested during the preceding 24 h are noted in the history. Measurements of IgE against relevant allergens should be performed by skin testing (including to fresh fruits and vegetables) and/or laboratory tests. An 'exercise ± food' provocation test can be considered (Box 2). The differential diagnosis of EI-anaphylaxis includes cardiac and respiratory diseases along with appropriate tests. Periodic re-evaluation for loss of sensitivity to food and/or exercise is recommended, as the natural history of food-dependent EI-anaphylaxis is unpredictable (42).

Cold-induced and cholinergic urticarias also are important considerations in the exercise setting (51–53). Cold urticaria occurs on contact with cold air, fluids or objects, placing swimmers or skiers at increased risk. Drowning from cold-induced anaphylaxis may occur in cold water. Cold urticaria can be confirmed if an ice cube placed on the skin for up to 20 min induces urticaria during rewarming. Cholinergic urticaria occurs within minutes after elevation of the body temperature, regardless whether passive (hot shower) or active (exercise), and may progress to include angio-oedema, bronchospasm and hypotension. Notably, the diameters of cholinergic urticarial wheals are < 5 mm, whereas those associated with EI-anaphylaxis are substantially larger. Solar, aquagenic, vibratory, dermatographic and/or pressure physical urticarias also may be associated with EI-anaphylaxis.

Box 2. Patient vignette

A 16-year-old soccer player presents with recurrent anaphylaxis. Anaphylaxis occurs during exercise, but only occasionally. Symptoms include flushing, shortness of breath, wheezing, lightheadedness and vomiting. No consistent precipitant was apparent to the athlete or to his parents or coach. Episodes only occur when exercise follows a meal. A specific food could not be identified by history. Prophylactic medications were not effective at preventing anaphylaxis, which often required an epinephrine injection for rescue. Past history revealed well-controlled asthma and rhinitis that rarely interfered with exercise. Medications include cetirizine (10 mg/day), EpiPen® (0.3 mg IM PRN anaphylaxis), budesonide/formoterol (80 μg/4.5 μg 2 doses BID), and albuterol (2 puffs PRN and pre-exercise). The physical exam at baseline was normal.

Assessment: spirometry was within normal limits. Immediate hypersensitivity skin testing for possible foods was positive to wheat, but historic information to support consumption of wheat before anaphylaxis was inconsistent. Open food challenge to wheat was negative. Exercise challenge while fasting 6 h per ATS guidelines for EI-asthma was negative. Exercise challenge with food excluding wheat resulted in an 8% reduction in FEV_1 without symptoms, interpreted as negative. Exercise challenge following wheat consumption induced anaphylaxis with presyncope, nausea and a significant drop in blood pressure that responded to epinephrine. FEV_1 could not be obtained because of nausea and the need for immediate therapy.

Treatment: avoid ingesting wheat products for at least 6 h before exercise. Always have EpiPen® available, and train the player and his coach and parents to use it properly. Continue current asthma treatment.

Follow-Up: soccer playing resumed without recurrence of anaphylaxis. Occasional EI-asthma occurred but responded well to inhaled albuterol.

Lesson: Food-dependent EI-anaphylaxis can be diagnosed or suspected based on the history, and confirmed by objective tests. Treatment includes prophylaxis (food-allergen avoidance for at least 6 h or general food avoidance for at least 2 h before exercise), and being prepared for rescue interventions (immediate availability and use of intramuscular epinephrine, and Trendelenburg position).

Treatment of exercise-induced urticaria and anaphylaxis (Box 1)

Therapeutic interventions for EI-anaphylaxis/urticaria include preventive and acute measures (43, 49). Prophylactic management for EI-anaphylaxis is to first avoid the trigger(s), particularly foods. Specific food allergens should be avoided for at least 6 h prior to exercise. A dietician may be helpful. When EI-anaphylaxis occurs after ingestion of any food, an abstinence interval of 2–4 h is generally adequate, but individual variation is considerable. For children with food allergy, their teachers, close friends and relatives may need special counseling. Avoidance of β-blockers, angiotensin converting-enzyme inhibitors and angiotensin-receptor blockers should be considered, because these drugs may increase the severity of anaphylaxis. Aspirin and NSIADs, which increase gastrointestinal permeability, also should be avoided. Prophylaxis with H1 and H2 antihistamines may attenuate the urticaria (51), but probably not the cardiovascular and respiratory manifestations of anaphylaxis.

Acute management aims to ameliorate the cardiovascular (hypotension) and respiratory manifestations, these being the principal causes of death (43). This begins with anticipation and development of a personalized emergency plan such as wearing an identifying medical alert device and doing exercise with a trained companion. Patients should learn to recognize their first symptoms and signs of EI-anaphylaxis and immediately discontinue exercise. They should learn to assume the Trendelenburg position to facilitate perfusion of vital organs in the face of hypotension and inject epinephrine (EpiPen® or EpiPen® Jr; Dey L. P., Napa, CA, USA) 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 published guidelines.

Summary

Although much is known about how to diagnose and treat EI-hypersensitivity disorders, much still remains to be learned (Box 3). Exercise is a frequent trigger of different hypersensitivity events (asthma, rhinitis, anaphylaxis and urticaria) that impairs performance. Although infrequent, EI-asthma and EI-anaphylaxis are both causes of sudden death in athletes during exercise. Asthma and rhinitis are more common in competitive athletes because of airway dehydration from hyperpnoea, increased exposure to aeroallergens and airway injury from irritant chemicals and environments. Anaphylaxis triggered by exercise is often associated with recent food ingestion, particularly in those with IgE against wheat

Box 3. Ongoing research and unanswered questions

The Global Asthma and Allergy European Network (GA2LEN) and the National Olympic Committees of the participating countries have an ongoing effort to study the prevalence of asthma and allergic diseases among Olympic athletes by both questionnaires and objective tests.

What are the reasons for an increased prevalence of asthma and allergic disorders in athletes, hyperpnoea alone, an increased exposure to irritant chemicals and allergens, or to all of these conditions?

Do athletes with EI-bronchoconstriction respond to treatment similarly to those with underlying allergic or nonallergic asthma?

How many athletes are in need of medical treatment to master their illness, and be able to perform at an optimum level?

Do athletes with EI-respiratory disorders have an increased risk for incurring permanent airway damage by continuing to train and compete, even if their symptoms are medically controlled?

What are the mechanisms of EI-anaphylaxis when no IgE-related sensitivities to classical food and airborne allergens are present?

Is it possible to induce tolerance to exercise in those with EI-anaphylaxis/urticaria?

Is anti–IgE (omalizumab) efficacious for preventing EI-anaphylaxis?

Will allergen vaccines (immunotherapy) for food allergies become available that cure food-dependent EI-anaphylaxis?

and shrimp allergens. Urticaria in athletes can not only occur with anaphylaxis, but may also be caused by an elevated temperature (cholinergic), exposure to cold environments or other physical stimuli. Early and objective diagnoses of EI-hypersensitivity disorders in athletes permit implementation of effective preventative and rescue strategies that should allow full sport participation.

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