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REVIEW

Anaphylaxis attributed to exercise: considerations for sports medicine specialists

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Abstract

Anaphylaxis is an unanticipated, acute, and sometimes life-threatening systemic reaction with variable clinical presentations that is typically mediated by immunoglobulin E and causes degranulation of mast cells and basophils. The onset of symptoms can occur within minutes or hours after exposure to a known or suspected trigger, and reactions sometimes progress very rapidly, which can lead to death. One trigger of anaphylaxis in younger adults is moderately intense physical exercise, which has been termed exercise-induced anaphylaxis (EIA). Although rare, EIA should be recognized as a distinct and potentially life-threatening form of physical allergy, and is often undetected or inadequately treated. The ingestion of specific foods, including seafood, tree nuts, and wheat, or a nonspecific meal consisting of multiple food components shortly before or after physical exertion, is sometimes, but not always, the principal precipitant of EIA. This article briefly explores the current hypotheses on the role of immunoglobulin E, response mediators, and physiologic changes that bring on EIA, and discusses the current recommendations for diagnosis, including allergen challenge and laboratory testing, emergency care, and long-term prevention and patient follow-up. Accurate diagnosis of EIA is critical to providing lifesaving therapy and care plans to patients at risk. With respect to the medical management of EIA, mainstay therapy with epinephrine is described. For those with a known history of EIA, a comprehensive anaphylaxis action plan is central to successful patient management. Furthermore, patient education is necessary to heighten awareness of the signs and symptoms of EIA and appropriate strategies for allergen avoidance and self-management of anaphylactic episodes with self-injectable epinephrine.

Keywords:

Anaphylaxis, epinephrine, exercise-induced anaphylaxis, food-dependent exercise-induced anaphylaxis

History

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Introduction

The term *anaphylaxis* stems from the Greek words *ana* (“against”) and *phylaxis* (“protection”), and was first coined by Charles Robert Richet in 1902, who won the Nobel Prize in Medicine or Physiology, and by Paul Portier, who described a set of symptoms that was the opposite of immunity [1]. At present, international consensus (accounting for all guidelines published between 2010 and 2014) on the definition of anaphylaxis recognizes that it is a serious, generalized or systemic, allergic or hypersensitivity reaction that can be life-threatening or fatal [2]. However, in practice, it is often difficult to delineate the essential manifestations of this systemic, and sometimes very rapid, hypersensitivity reaction because these reactions have varied mechanisms and clinical presentations [3]. In some cases, suspicion of anaphylaxis is lessened when an allergic or other trigger cannot be immediately identified. A detailed history is paramount for determining an accurate diagnosis, and it entails eliciting information about all exposures and events in the hours preceding the symptom onset, such as known allergies; exercise; ingestion of prescription, nonprescription, and recreational drugs; ethanol intake; acute

upper respiratory tract infection; exposure to environmental extremes; emotional stress; travel or other disruption of routine; and premenstrual status in females [4].

From 2 recent nationwide, cross-sectional random-digit-dial surveys in the United States ($n = 1000$), it was estimated that the prevalence of anaphylaxis in the general population is $\geq 1.6\%$ (respondents with very likely anaphylaxis) but may be as high as 5.1% (respondents with probable anaphylaxis) [5]. By today’s US population estimate (319 million), a conservative estimate of how many people are affected by anaphylaxis would be > 5 million. Patients in both surveys reported that the most common triggers were medications (34%), foods (31%), and insect stings (20%). Furthermore, care patterns suggested that 42% sought treatment within 15 minutes of onset, 34% went to the hospital, 27% self-treated with antihistamines, 10% called 911, 11% self-administered epinephrine, and 6.4% received no treatment [5]. Unfortunately, a significant unmet need in care was identified because 52% of respondents with reactions had never received a self-injectable epinephrine prescription, and 60% did not currently have epinephrine available for self-administration.

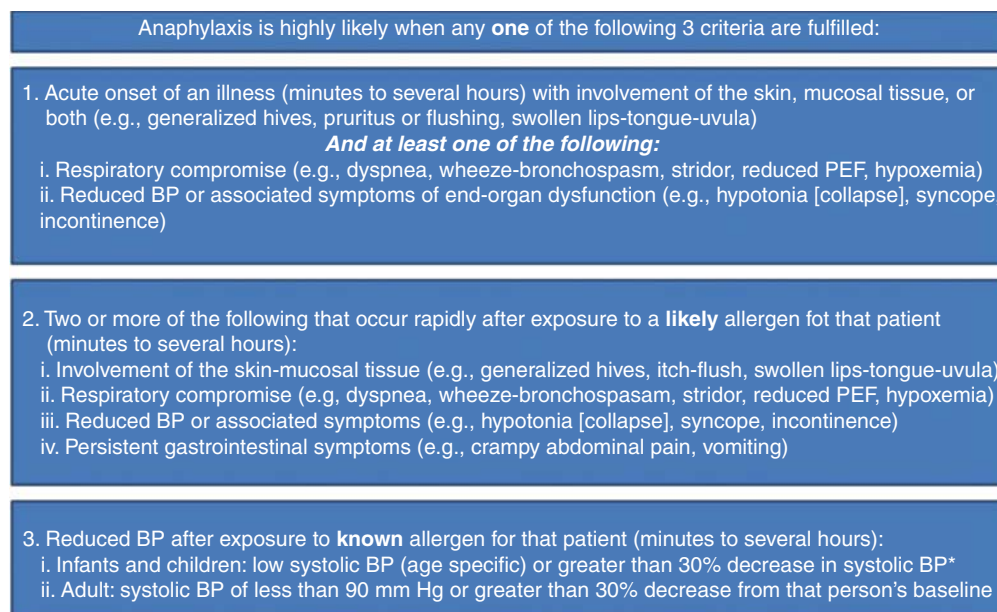


Figure 1. NIAID/FAAN clinical criteria for anaphylaxis.

*Low systolic blood pressure for children is defined as < 70 mmHg from 1 month to 1 year, < (70 mmHg + 2 × age) from 1 to 10 years, and < 90 mmHg from 11 to 17 years.

Abbreviations: BP = Blood pressure; PEF = Peak expiratory flow.

Anaphylaxis commonly targets the skin, respiratory tract, gastrointestinal tract, and cardiovascular system, and in practice an anaphylactic reaction involves ≥ 1 system. For example, ≥ 1 of the following may occur: hives; respiratory distress; gastrointestinal distress; and hypotension, which can manifest as syncope or hypotonia (collapse). Respiratory symptoms tend to be more common in children, explained in part by the higher frequency of atopy, asthma, and food allergy in this age group, whereas preexisting pulmonary disease is associated with an increased frequency of respiratory compromise from any cause. Cardiovascular and cutaneous symptoms predominate in adults. Whereas dyspnea, profuse diaphoresis, nausea, vomiting, and abdominal pain signal the presence of hypotension, both hypoxia and hypotension may share common symptoms of confusion, collapse, loss of consciousness, and incontinence [6,7]. Furthermore, the more rapidly anaphylaxis develops, the more likely the reaction is to be severe and potentially fatal. Fatalities from anaphylaxis have been reported as soon as 5 minutes from the onset of the reaction [6,8]. Thus, prompt recognition of the signs and symptoms, as well as the severity of these symptoms, is crucial to successful treatment.

The National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network (now the Food Allergy Research and Education Network) jointly developed a consensus on a relatively simple and rapid means to make the diagnosis of anaphylaxis. It was acknowledged that although no criteria would ensure complete sensitivity and specificity, it is believed that the proposed criteria would likely capture > 95% of cases (Figure 1) [9].

Exercise-induced anaphylaxis

One of the most common catalysts of anaphylaxis in younger adults is moderately intense physical exercise. First described in

1979 by Maulitz et al. [10] as a late, hypersensitivity reaction to shellfish induced by strenuous exertion, exercise-induced anaphylaxis (EIA) is a rare, yet distinct, potentially life-threatening form of anaphylaxis. It has been previously reported that 5% to 15% of anaphylactic episodes are associated with some form of exercise [11–13]. In 1 of the recent United States–based surveys mentioned above, EIA was confirmed in 1.5% of patient respondents [5]. It often involves the ingestion of specific foods, most commonly wheat/omega-5 gliadin (60%), celery, or shellfish (shrimp 18%), or the consumption of a nonspecific meal consisting of multiple food components, shortly before or after physical exertion [4]. Less commonly, it may involve concomitant use of ethanol, aspirin, or a nonsteroidal anti-inflammatory drug that enhances intestinal permeability and allergen absorption, or exposure to high pollen levels [4].

In classic EIA, exercise at varying degrees of exertion acts as the immediate trigger to premonitory symptoms of fatigue; diffuse warmth; pruritus; and erythema followed by the appearance of urticarial lesions or angioedema, most typically affecting the face, palms, and soles. An episode of EIA may begin approximately 5 to 10 minutes after initiating exercise, and if not promptly discontinued, may progress to hypotension, gastrointestinal colic, wheezing upper airway obstruction secondary to mucosal edema and smooth muscle spasm, and cardiovascular collapse secondary to hypoxia of respiratory insufficiency [12]. Symptoms of EIA mimic those of anaphylactic reactions caused by allergens such as foods or hymenoptera venom and may appear during any phase of exercise, although in 90% of patients the acute episode occurs within 30 minutes of initiating exercise [14]. When present, EIA-related angioedema typically persists from 30 minutes to 4 hours after the cessation of exercise. Frequency of episodes may vary considerably, from a single event to several annually. It appears that for the majority of

Table I. Physical activities associated with EIA [16].

Reported activity	Number of people (%)
Jogging	219 (78)
Walking	117 (42)
Tennis or Racquetball	78 (28)
Dancing	73 (26)
Cycling	68 (24)
Downhill skiing	18 (6)
Yard work	17 (6)
Basketball	12 (4)
Stairmaster	5 (2)

individuals, the frequency of EIA attacks tends to decrease or remain the same over time [15].

A cross-sectional analysis of 671 individuals with a history of recurrent, exercise-associated symptoms was conducted using a validated, 75-item questionnaire [16]. Subjects met the criteria for EIA if they experienced anaphylactic symptoms, including hypotension or upper airway obstruction, urticaria, or angioedema with physical exertion. Of the 365 respondents to the questionnaire, 279 (76%) fulfilled the criteria for EIA. At the time of study entry, subjects with EIA reported a mean 10.6 years of symptoms, which were most frequently triggered by aerobic activities such as jogging (78%) or brisk walking (42%; Table I). Neither fever nor warm bath or shower reproduced the symptoms of EIA, and these episodes were further distinguished by the absence of exposure to environmental allergens during exercise and by a high incidence of syncope within the study group. Due to the striking similarity of this symptom complex with that elicited by exposure to known allergens, it was recognized as a specific type of anaphylaxis caused by physical exertion.

It has been reported that exercise-induced gastrointestinal complaints occur with a prevalence of between 30% and 50% among long-distance runners, triathletes, and athletes engaged in other strenuous or endurance exercise [17,18]. Symptoms of dizziness, nausea, stomach or intestinal cramps, vomiting, and diarrhea appear with the redistribution of blood flow, as it is shunted from the viscera to skeletal muscle, heart, lung, and brain. However, some symptoms can be life-threatening, such as hematochezia or melena that develops in the hours following a long-distance run.

Approximately 10% of patients experience symptoms of EIA with exercise alone, whereas others do so only if triggered by contributing cofactors such as certain medications, exposure to extreme environmental conditions, or allergenic foods, most commonly wheat, celery, seafood, and tree nuts ingested a few hours prior to exercise [10,19]. In 30% to 50% of cases, EIA occurs only when the subject ingests a

particular food before or sometimes after the completion of exercise, known as specific food-dependent exercise-induced anaphylaxis (FDEIA), as opposed to a meal comprised of various food components (nonspecific FDEIA). However, EIA is better estimated to represent approximately 5% to 15% of all anaphylactic cases, and the prevalence of FDEIA, although not well documented, is assumed to account for between one third and one half of all EIA patients.

Presentation and pathophysiologic mechanisms of EIA

The clinical history of EIA does not differ substantially from that of systemic anaphylaxis triggered by other factors. The diagnosis of EIA is usually made on the basis of the history and exclusion of other disorders, although evaluation for sensitization to food allergens, particularly grains and seafood, can be performed. Reactions have a similar progression of events from prodromal, to early, to fully developed, to late stage [20]. Prodromal symptoms manifest with fatigue, prostration, and generalized pruritus with erythema. The early stage is characterized by generalized urticaria. As the events progress, fully developed EIA precipitates gastrointestinal symptoms of abdominal cramps, nausea, and vomiting, as well as symptoms of upper airway obstruction, specifically bronchospasm, dyspnea, stridor, and laryngeal constriction [20]. Others report that symptoms of late-phase EIA, marked by frontal headache and fatigue, may present up to 72 hours after onset [14].

Systemic reactions to exercise may occur in 1 of 3 ways (Table II):

Cholinergic urticaria, the symptoms of which are usually limited to the skin of the upper thorax and neck, presenting as punctate wheals of 2 to 4 mm in diameter, with a prominent erythematous flare or halo triggered by an exaggerated response to exercise, emotional stress, or passive elevations in body temperature from such external sources as warm water or increased ambient temperature, and accompanied by a rise in plasma histamine levels. The inciting stimulus may persist anywhere from 15 minutes to several hours [21-23].

Classic exercise-induced anaphylaxis, presenting with symptoms of an acute, systemic, allergic reaction, which may endure for 30 minutes to 4 hours after cessation of exercise. Episodes of EIA are unpredictable and not consistently reproducible with type, intensity, or duration of exercise [12,16].

Variant exercise-induced anaphylaxis, which shares certain similarities with cholinergic urticaria, in that it produces

Table II. Types of exercise-induced allergic reactions [12,16,21-24].

Condition	Rash	Pulmonary symptoms	Progression to shock	Precipitants
Cholinergic urticaria	Small lesions (2–4 mm)	Yes	Rare	Exercise Passive warming
Classic exercise-induced anaphylaxis	Larger lesions (10–12.5 mm)	No	Frequent	Exercise only
Variant exercise-induced anaphylaxis	Small lesions (2–4 mm)	No	Frequent	Exercise only

Table III. Principal mast cell mediators implicated in anaphylaxis [31–34].

Storage vesicles	Newly synthesized cytokines/chemokines	Lipid-derived mediators	Proteases and other enzymes
Histamine	Tumor necrosis factor- α (TNF- α)*	Platelet-activating factor (PAF)**	Mast cell tryptase (MCT)
Proteoglycans:	Interleukin (IL)-1 α and β	Prostaglandin D ₂	Cathepsin G
Heparin	IL-4: Produced by	Leukotriene [LT] B ₄	Carboxypeptidase
Chondroitin sulfate	Th2 Cells [†]	Leukotriene C ₄	Chymase
	IL-5: Produced by		Elastase
	Th2 Cells [†]		Matrix Metalloprotease 9
	IL-6		Plasminogen Activator
	IL-9		
	IL-13: Produced by		
	Th2 Cells [†]		
	CXC-chemokine: IL-8 [‡]	Cysteinyl leukotrienes:	Renin
	Other chemoattractants:	LTC ₄	Tryptase
	Eosinophil chemotactic factors	LTD ₄	
		LTE ₄	
	Granulocyte-macrophage colony-stimulating factor (GM-CSF)	Thromboxane	Arylsulfatase
	Fibroblast growth factor (FGF)		β -hexosaminidase
	Stem cell factor (SCF)		β -glucuronidase

*Proinflammatory mediators such as IL-1 α , IL-8, TNF- α , and TNF receptor I (TNFRI) may act as amplification signals for mast cells.

**Increased levels of this potent, proinflammatory phospholipid have been associated with severity of anaphylaxis.

[†]May play a role in promoting IgE production from B cells and increase target cell responsiveness to vasoactive mediators.

[‡]May recruit proinflammatory cells to site of allergen exposure.

small, punctate, erythematous papules and is associated with increased plasma histamine levels. However, unlike classic EIA, the variant form is provoked only by exercise and accounts for approximately 10% of all EIA cases [24].

Although EIA can develop in individuals with a negative history for asthma or allergy, approximately 50% appear to be atopic [25]. Although the exact pathophysiologic events during exercise that precipitate symptoms of anaphylaxis have not been fully elucidated, as in other allergic syndromes, the majority of EIA symptoms may be explained on the basis of release of mast cell mediators, including histamine, leukotrienes, and prostaglandins. The initiating event in an anaphylactic episode is antigen cross-linking of immunoglobulin E (IgE) bound to the high-affinity IgE cell surface receptor [26,27]. The antigen/antibody complex-dependent receptor aggregation triggers an intracellular signaling cascade, which ultimately results in calcium influx, exocytosis of mast cell granules or secretory lysosomes mediated by membrane fusions proteins, and release of mediators that increase vascular permeability and impair smooth muscle function [26,27]. Degranulation can be mediated by cross-linking of IgE bound to the membrane high-affinity IgE receptor Fc ϵ RI, or by non-IgE-mediated mechanisms [28]. The distinction between these mechanisms can be important diagnostically, but in practice their clinical manifestations and management are largely indistinct. Different combinations of the above mediators may be released in different circumstances.

Activation and degranulation of mast cells causes release of preformed mediators of inflammation, that is, histamine, the proteoglycans, heparin and chondroitin sulfate, the neutral proteases, tryptase and chymase, carboxypeptidase A, and certain cytokines (Table III) [29]. These mediators recruit inflammatory cells and activate complement cascades, among other mechanisms. De novo production of mediators such as leukotrienes, interleukins, tumor necrosis factor- α (TNF- α),

and platelet-activating factor evoke the characteristic clinical features of vasodilation, angioedema, bronchoconstriction, and increased mucus production observed during the various phases of EIA [29]. Physical exercise elicits a subclinical, inflammatory response manifested by increases in the proinflammatory cytokines TNF- α and interleukin (IL)-1 β , followed by a dramatic increase in the inflammation-responsive cytokine IL-6 [30]. During exercise, IL-6 is released into the circulation to a greater extent than any other cytokine. In addition, exercise increases plasma concentrations of glucocorticoid stress hormones, including cortisol, growth hormone, and catecholamines. Additionally, intense physical exercise has the potential to increase production of reactive oxygen species, leading to oxidative stress [30].

Histamine acts through H1 and H2 receptors on multiple organ systems. Its effects on the vascular bed include release of nitric oxide by endothelial cells (H1 receptors) and direct relaxation of smooth muscle (H2 receptors). In the lung, bronchoconstriction is mediated by H1 receptors, whereas stimulation of both H1 and H2 receptors causes increased production of mucus [35]. Pruritus, rhinorrhea, tachycardia, and bronchospasm are caused by activation of the H1 receptors, whereas both H1 and H2 receptors mediate headache, flushing, and hypotension [32,35]. Histamine increases cardiac oxygen demand indirectly by peripheral vasodilation and via direct effects on the heart, including increased contractility, shortened depolarization, and increased heart rate. Histamine can also cause coronary artery vasospasm through the H1 receptor [3,33]. Results from skin biopsies reveal that skin mast cell degranulation occurs during symptomatic EIA episodes [24,36]. It is likely that vasoactive mediators released by mast cells account for the attendant symptoms. Elevated plasma histamine levels have been demonstrated in patients with both classic and variant forms of EIA. Additionally, other products of mast cell degranulation, namely serum tryptase and leukotrienes, have been found at increased levels in symptomatic patients with EIA. These observations

suggest that EIA is a distinct form of physical allergy associated with mast cell degranulation and resultant histamine elevation in the circulation [36].

Additional evidence supports the idea that exercise indeed can lead to a robust inflammatory response characterized by the following:

Increased mobilization, circulation, and activity of leukocytes (neutrophils and lymphocytes) [26,37,38]
 Rapid increase in natural killer cells [38]
 Transient changes in gene expression of peripheral blood mononuclear cells, reflecting a range of proinflammatory and anti-inflammatory responses [26]
 Increased production of anti-inflammatory cytokines IL-6 and IL-10 [34,39]

Furthermore, changes in pH, lactic acid, temperature, PO₂ and PCO₂ can independently alter immune mediators and leukocyte function [26,40]. Some evidence suggests that mast cell degranulation is promoted by such various mediators as creatinine phosphokinase, immunoglobulin E, lactate, as well as activation of the alternative complement pathway [41,42].

Association of foods, drugs, and other triggers with EIA

Foods

In a large percentage of individuals, EIA develops when they exercise within 2 hours of ingesting a known food allergen, presumably due to increased systemic absorption and mediator release [43,44]. This is known as FDEIA, as cited above. Under normal circumstances, such individuals may tolerate the food allergen and may experience minimal exercise-induced bronchospasm, provided that the specific offending agent has not been consumed within several hours of physical activity [43,44]. For food allergens for which exposure is primarily mucosal as opposed to parenteral, reactions are more frequent in atopic compared with nonatopic subjects [45].

Experimental data have demonstrated that atopic individuals appear more prone to induce IgE antibodies when allergens are administered topically than by injection. In one study, exercise was thought to have precipitated anaphylaxis in 19 subjects, of which 6 (32%) were atopic [46]. Two of the 19 cases (10.5%) classified as EIA occurred after ingestion of a specific food. It is thought that the interaction of a specific IgE antibody with a food antigen may lower the mast cell releasability threshold in the presence of exercise [47]. Additionally, changes in cytokine release, characterized by an increased production of IL-4, IL-5, and IL-13 in atopic individuals, not only enhances the mast cell and basophil degranulation, but also sensitizes target organs to mediators such as histamine [48].

Patients with FDEIA usually produce positive results on skin prick tests against the causative food allergens. Thus, the hypersensitivity reactions in such patients are generally thought to be IgE-mediated [49,50]. In patients with FDEIA, physical activity in the postprandial state may provoke mast cells or basophils to release histamine, cysteinyl leukotrienes,

and prostaglandin D₂, thereby enhancing vascular permeability and contraction of bronchial smooth muscle [51,52]. Normal uptake of food proteins occurs through transcellular and paracellular routes. Intestinal epithelia conduct transcellular absorption via endocytosis, after which the protein is digested in lysosomes. The presence of tight junctions between gut epithelia normally restricts paracellular absorption of incompletely digested food proteins. However, in food-allergic individuals, the increased expression of low-affinity, cell-surface, IgE receptors (FcεRII/CD23) facilitates the bidirectional transcytosis of IgE. The food allergen-IgE antibody complex activates gut mast cells by IgE cross-linking, disrupting intercellular tight junctions and facilitating transport of food allergens.

In patients predisposed to EIA, exertion may encourage the alteration of mucosal enzyme activity or barrier function in the gastrointestinal tract, promoting the absorption of food antigens [53]. In FDEIA, exercise also increases the entry of recently ingested but incompletely digested food proteins, including allergens, into the circulation. From there, they migrate into the perivascular and tissue spaces where mast cells armed with allergen-specific IgE reside. Strenuous or prolonged exercise also reduces splanchnic blood flow up to 50%, which might lead to gastric mucosal ischemia and increased intestinal permeability [54]. Gastrointestinal complaints arise as blood flow is shunted from the viscera to skeletal muscle, heart, lung, and brain. Gut ischemia provokes nausea, vomiting, abdominal pain, and (bloody) diarrhea.

With respect to wheat-dependent EIA (WDEIA), tissue transglutaminases (tTGs) in the intestinal mucosa are activated by IL-6 released by contracting skeletal muscle in response to exercise. Wheat protein is fractionated into both gluten and non-gluten proteins that can be further fractionated into ethanol soluble proteins known as gliadins [55,56]. In wheat-derived EIA, IgE antibodies are directed against these storage proteins. Omega-5 (ω-5) gliadin (Tri a 19) was identified as a major allergen in patients with WDEIA and demonstrated the presence of cross-reactive allergens in both rye and barley grains. Tissue transglutaminase modifies proteins into high molecular weight complexes, which strongly bind to IgE. Although no direct evidence of tTG activation in response to exercise exists, many factors released during exercise are known to activate this stress-responsive enzyme. Taken together, tTG can be activated by TNF-α, IL-6, glucocorticoid hormones, and reactive oxygen species, all of which are detectable in individuals who exercise. It has been suggested that these allergen complexes may elicit anaphylactic reactions in patients with WDEIA.

The intensity of exercise and the amount of food ingested may provoke different symptoms from subject to subject and within the same subject on different occasions. Exercise-induced anaphylaxis is not fully reproducible, and individual patients may not always experience symptoms each time they engage in similar, physical activity [14].

Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs, which are commonly used analgesics, are associated with several different types of hypersensitivity reactions, including anaphylaxis [57]. It has

been suggested that these drugs can increase gastrointestinal permeability [58]. This may increase antigen uptake and result in local immune cell degranulation and inflammation response. For example, it is widely accepted that aspirin is a trigger for anaphylaxis in patients with FDEIA [59]. In particular, aspirin has been well demonstrated to induce or aggravate symptoms in patients with FDEIA, leading most authorities to assume that aspirin induces a histaminergic reaction that manifests as an immediate hypersensitivity. However, some studies suggest that, for example in patients with WDEIA, aspirin uptake induces a marked increase in serum gliadin levels, which suggests that aspirin may increase antigen uptake across the intestinal wall. Another study found that exacerbation of FDEIA symptoms by aspirin is not mediated by a direct effect on mast cell/basophil activation [59].

Genetic, environmental, and other factors

In many patients, other precipitating factors have been reported, such as medications, cold or warm ambient temperatures, humidity, the menstrual cycle, and ingestion of dust mites contained in contaminated foods [30]. A family history of EIA has also been associated with the human leukocyte antigen A3B8DR3 or with a possible autosomal dominant inheritance [30].

It is known that increased osmolarity of the intestinal medium increases both IgE-dependent and IgE-independent histamine release from basophils [60]. Potentially life-threatening anaphylactic reactions triggered by physical exercise might result from increased gut permeability and transient serum hyperosmolarity after exposure to a sensitizing food allergen, which may amplify release of immune mediators from basophils and mast cells. Hyperosmolar airway fluid forms when exercise increases ventilation and dehydrates the airways. The evaporation of airway water activates epithelial cells and mast cells in the lower airways to release mediators, causing bronchoconstriction, vasopermeability, and mucus hypersecretion [61]. Hyperosmolar airway fluid formed by evaporation of airway water during exercise is the principal pathophysiologic trigger for exercise-induced asthma/bronchoconstriction, and possibly exercise-induced rhinitis. Hyperosmolarity activates cells in the lower airways to release mediators, causing bronchoconstriction, vasopermeability, and mucus hypersecretion. Heat loss with reactive airway hyperemia upon rewarming is a secondary pathway of exercise-induced bronchoconstriction. Hyperpnea places the elite athlete at a greater risk because of increased water and heat loss from the airways.

Clinical evaluation of EIA in athletes

Exercise-induced anaphylaxis is a diagnosis of exclusion. A strong clinical suspicion, exclusion of other potential diagnoses, and a meticulous clinical history are required for accurate diagnosis. Patient history remains the most important tool in establishing the etiology of anaphylaxis and should elicit information about clinical manifestations; agents encountered before the reaction, such as foods, medications, or insect bites/stings; as well as activities preceding the event.

The physical examination should assist in the determination of whether the patient appears atopic. Allergy questionnaires tailored to athletes may assess a hidden atopic status [62]. The physical examination also should include a detailed assessment of the endocrine, cardiac, and neurologic systems. The respiratory and dermatologic examination should document the presence or absence of asthma or other systemic, medical conditions. In particular, care should be taken to exclude lesions suggestive of mastocytosis. The absence of cutaneous symptoms puts the diagnosis in question because the majority of anaphylactic episodes involve the skin, mucosal tissue, or both. However, the absence of dermatologic signs and symptoms does not definitively rule out the possibility of an anaphylactic episode [63].

Cutaneous warmth, erythema, and pruritus with or without urticaria brought on by physical exertion are highly suggestive of either exercise-induced urticaria or exercise-induced anaphylaxis. A history of atopy offers further evidence to support the diagnosis of EIA. Progression of symptoms to dysphagia, dyspnea, wheezing, dizziness, or syncope is also consistent with EIA, as are later gastrointestinal symptoms of colic, nausea, and vomiting [63,64]. A striking feature of EIA is the failure of an apparently identical exercise program to reproduce an attack with any predictability. This suggests that ≥ 1 additional variables may augment mast cell responsiveness to physical exercise. [20,24,64]. Symptoms that might mimic the general characteristics of anaphylaxis should be excluded, most commonly vasovagal or neurocardiogenic reactions, which are marked by hypotension, pallor, bradycardia, weakness, nausea, and vomiting; hyperventilation syndrome and panic attacks; vocal cord dysfunction; acute respiratory decompensation from severe asthmatic episodes; foreign body aspiration; pulmonary embolism; acute anxiety; myocardial dysfunction; acute poisoning; hypoglycemia; and seizure disorders [3].

Mediators of anaphylaxis and evidence supporting testing

An immunologic feature of anaphylaxis in general is that not all sensitized subjects exhibit clinical reactivity. Although the quantity of circulating IgE antibodies to both food and airborne allergens appears to correlate directly with the probability of clinical reactivity, the exact series of events that occur between contact with an allergen by a sensitized individual and sufficient activation of mast cells to elicit an anaphylactic reaction remains to be elucidated [9]. Although several well-characterized mediators are released upon activation of mast cells, serum tryptase, in general, is not found to be elevated consistently in patients presenting with anaphylaxis, and histamine levels are raised only briefly at the onset of the reaction [9].

Within 5 to 10 minutes of the onset of symptoms of anaphylaxis, plasma histamine levels begin to rise and remain elevated for 30 to 60 minutes. The preferred time to measure plasma histamine, given its short half-life, is between 10 and 60 minutes after symptoms first manifest [65,66]. In a prospective study of 97 adult, emergency department patients with acute allergic reactions, investigators analyzed plasma

histamine and serum total and β -tryptase levels. Increased total tryptase levels, histamine levels, or both were observed in some patients who did not exhibit airway, cardiovascular, or abdominal signs [65]. Elevated levels of plasma histamine > 10 nmol/L and total tryptase concentrations > 15 ng/mL were observed in only 42 (43.4%) and 20 (20.6%) patients, respectively. Detectable amounts of β -tryptase (≥ 1 ng/mL) were observed in 23 patients (23.7%), including 15 [75% (15.5%)] of those with elevated total tryptase levels. Increases in serum histamine were observed more frequently in those patients symptomatic with urticaria, more extensive erythema, abnormal abdominal findings, and wheezing. Increases in total tryptase occurred more frequently only in those patients with urticaria. A multivariate analysis found that urticaria severity was the best single predictor of plasma histamine levels and of either elevated histamine or elevated tryptase levels [65]. In this analysis, serum histamine and, less commonly, tryptase levels increased in only $\approx 50\%$ of the patients presenting to an emergency department with acute allergic reactions. In some cases, classic features of severe anaphylaxis did not reflect systemic mediator release, and the lack of total tryptase elevations in many patients with elevated plasma histamine levels suggested basophil involvement [65].

Tryptase has been widely used as a biomarker of mast cell involvement in atopic patients with asthma and in patients with hymenoptera venom-induced anaphylaxis [67]. An increase from normal (< 10 – 15 ng/mL) to > 20 ng/mL or from an elevated baseline (> 15 ng/mL) by $\geq 20\%$ should be regarded as a relatively reliable indication of mast cell activation. In many patients, basal tryptase levels may not be available at the time of the first event but may only be known after complete resolution of symptoms when the test is repeated [68]. It should be recognized that tryptase levels are seldom increased when anaphylaxis is triggered by food or when hypotension or shock is absent. Serial measurements of total tryptase levels, including measurement in a remission sample taken after complete resolution of the event, might be more helpful than a single laboratory assay [69].

As a diagnostic tool, plasma histamine levels may not be useful if the patient presents ≥ 1 hour after the inciting event. On the other hand, serum tryptase levels peak 60 to 90 minutes after the onset of anaphylactic symptoms, and can persist for as long as 5 hours [66]. The most opportune time to measure serum tryptase is between 1 and 2 hours, but no longer than 6 hours, after symptom onset [70]. As high concentrations of plasma histamine do not indicate whether mast cells or basophils are involved, tryptase levels also may assist in differentiating between a basophilic reaction and mast cell activation [66].

Specific allergen testing

The diagnosis of anaphylaxis may be supported by the results of skin tests or in vitro IgE tests. These laboratory assessments can determine the presence of specific IgE antibodies to foods, medications, and stinging insects. In general, skin testing is more sensitive than in vitro testing and is recognized as the diagnostic procedure of choice for the evaluation

of most IgE-mediated causes of anaphylaxis [3]. Skin prick tests or circulating IgE antibodies for all foods ingested before physical activity assist in identifying the offending agent. In specific FDEIA, IgE test results are positive for the causative food, whereas in nonspecific FDEIA or in EIA alone, the IgE test is usually negative. When the history indicates an isolated allergen, a straightforward diagnosis can be made from a positive skin prick test. Unfortunately, many episodes occur during the consumption of a mixed meal consisting of multiple, unrelated foods or food groups, which can challenge an accurate diagnosis. Skin tests should be performed with caution in order to prevent further sensitization and provocation of attacks.

As an alternative to skin and in vitro testing, the Pharmacia CAP system is a concise test specifically developed for the diagnosis of allergies [71]. A single test may be performed on multiple serum samples, avoiding the inconvenience of multiple in vivo skin prick tests. The test reveals 3 outcomes [71]:

- Concentration of total IgE against a normal adult range of 20 kU/L to 200 kU/L
- Phadiatop screening for inhalant allergens (eg, dust mites, pollens, animal danders)
- Food Mix 5 identifies the 6 most common food allergens: egg white, milk, fish, peanut, wheat, and soya bean

Compared with conventional tests, the Pharmacia CAP can identify antibodies to > 400 global, allergenic substances and binds ≥ 3 times the amount of allergen [71].

Delayed or biphasic nature of anaphylaxis

Recognition of the wide spectrum of signs and symptoms of anaphylaxis and the timing of these reactions is important in clinical practice [3]. Although the time course of anaphylaxis is usually rapid, occurring within 5 to 30 minutes of exposure to the triggering agent, occasionally manifestations of an acute episode do not develop for several hours, or a second reaction could occur (Figure 2) [72].

In one case report, a young male patient with a 5-year history of several episodes of FDEIA to wheat shortly after exercise was described [74]. He developed severe anaphylaxis with loss of consciousness 5 hours after exercise, preceded by a wheat-containing meal. His skin prick test was 4+ positive to wheat, and serum tryptase levels remained elevated for 2 hours after acute symptom onset. This example illustrates that some patients experience delayed onset of anaphylaxis, which can occur anywhere from 24 to 48 hours after the cessation of physical effort. In patients with EIA, and although therapeutic intervention usually interrupted an acute episode within 1 hour of symptom onset, occasionally urticaria or angioedema persisted for several hours [20]. According to the sequence of manifestations, late sequelae in the form of headache could persist for 24 to 74 hours after the inciting event [20].

Depending on the report, recurrent (biphasic) reactions can occur in up to 20% of patients who experience anaphylaxis [3]. A biphasic reaction is generally described as recurrent

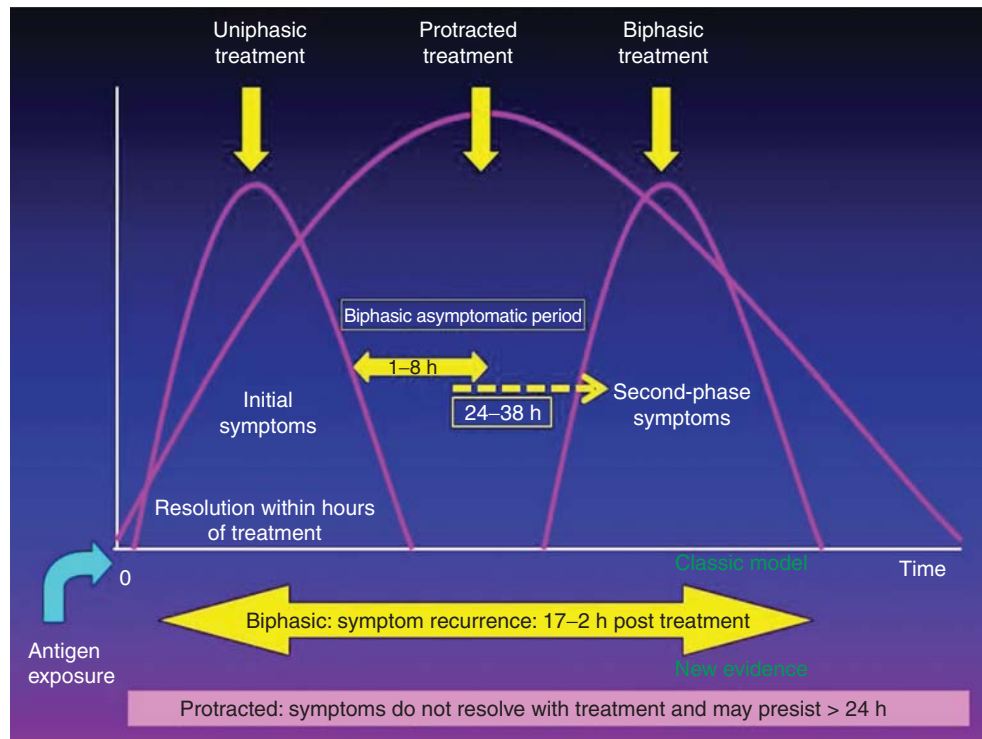


Figure 2. Phases of anaphylaxis.

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anaphylaxis symptoms within 72 hours of the initial event, without reexposure to the inciting allergen. In one study, biphasic reactions occurred within 10 hours of the initial episode and were associated with undertreatment of the initial episode with epinephrine, and initial symptom resolution took longer [75]. In a more recent study of 541 patients with anaphylaxis meant to elucidate predictors of biphasic reactions, the median time between the resolution of initial symptoms and onset of the biphasic reaction was 7 hours. These biphasic reactions were associated with a history of prior anaphylaxis ($P = 0.029$), unknown precipitant ($P = 0.03$), diarrhea ($P = 0.024$), and wheezing ($P = 0.029$) [76].

Treatment and prevention of EIA

Why epinephrine is first

Treatment of EIA or FDEIA follows consensus guidelines for anaphylaxis and is not dependent on the cause [2]. First and foremost, exercise should cease at the onset of symptoms. An anaphylactic reaction results when mast cells and basophils systemically and abruptly release mediators of inflammation. Epinephrine, an α -adrenergic receptor agonist, treats anaphylaxis symptoms by alleviating allergen-induced inflammatory and physiologic effects (Table IV).

For example, the α -adrenergic vasoconstricting effect reverses vasodilation, thus alleviating hypotension and reducing erythema, urticaria, and angioedema [78]. It also has β -adrenergic receptor agonist activity that acts to dilate bronchial airways, increases the force of myocardial muscle contraction (inotropy) and heart rate (chronotropy), which

increases cardiac output, and attenuates the severity of IgE-mediated reactions via receptors on mast cells. [77,79,80]. It is based on these observations and additional supporting evidence that epinephrine is recommended as the therapy of choice in the American Academy of Allergy, Asthma, and Immunology anaphylaxis guidelines, the World Allergy Organization anaphylaxis guidelines, the National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network food allergy guidelines, and a newer consensus recommendation (the International Consensus on Food Allergy) from the International Collaboration in Asthma, Allergy, and Immunology group. [2-4,81,82].

Why antihistamines or corticosteroids are not first

Antihistamines, such as diphenhydramine, easily cross the blood–brain barrier and bind nonselectively to H1 receptors, and interact with adrenergic, serotonergic, and cholinergic receptors. Unfortunately, histamine is only one mediator in an anaphylactic reaction; that is, antihistamines (H1 or H2 blockers) will only affect early mediator release. Other mediators include but are not limited to leukotrienes, prostaglandins, kinins, platelet-activating factor, interleukins, and tumor necrosis factor [83]. And although generalized immune suppression with corticosteroids has the potential to prevent recurrent or protracted episodes, they should never be used in place of or prior to epinephrine, because they are not helpful for acute symptoms [3].

Antihistamines have a longer onset of action and longer time to peak activity compared with epinephrine [84,85].

Table IV. Pharmacology of epinephrine [77].

α_1 -receptor	α_2 -receptor	β_1 -adrenergic receptor	β_2 -adrenergic receptor
↑ Vasoconstriction	↓ Insulin release	↑ Inotropy	↑ Bronchodilation
↑ Peripheral vascular resistance	↓ Norepinephrine release	↑ Chronotropy	↑ Vasodilation
↓ Mucosal edema			↑ Glycogenolysis
			↓ Mediator release

The most compelling evidence against the use of H1 blockers comes from studies looking at the onset of suppression of histamine-induced cutaneous flares. The time to 50% reduction in the flare induced by histamine was 52 minutes for IM diphenhydramine, 80 minutes for oral diphenhydramine, and 101 minutes for oral fexofenadine [84]. As a review of fatal cases in the literature has shown, patients are at risk for death as soon as 5 minutes following allergen exposure. Because anaphylaxis can involve multiple organ systems and occur in < 50 minutes, the onset of action of antihistamines is not compatible with what we know about the pathophysiology of anaphylaxis, and therefore they should not be used as a first-line therapy. This is consistent with current recommendations on antihistamines (and corticosteroids for that matter), positioning them as adjunctive therapies. [3,4,81,82]. There is no evidence that they provide lifesaving treatment (ie, they do not prevent or relieve upper airway obstruction, hypotension, or shock). Antihistamines (IM or IV) may be tried after epinephrine is administered to help control cutaneous and cardiovascular manifestations, such as itching, flushing, urticaria, angioedema, and nasal and eye symptoms [3,4].

Appropriate epinephrine dosing and administration for anaphylaxis

Once an initial assessment is made and clinicians are confident in their diagnosis of anaphylaxis, appropriate treatment should be initiated with an IM injection of epinephrine (into the anterolateral aspect of the thigh [vastus lateralis]), quickly followed by placing the patient in a recumbent position, and the provision of supplemental oxygen or the administration of IV fluids, if needed based on severity of symptoms [3].

Epinephrine is available in different doses and concentrations for delivery by different routes and for different indications, including anaphylaxis and cardiac arrest. Confusion over proper dosing and concentrations for various indications, and inconsistent labeling of epinephrine vials can lead to drug errors, which may result in life-threatening consequences for patients. Labeling of epinephrine concentration is sometimes provided in ratios rather than uniformly as a mass concentrations or percentages. The availability of epinephrine in both 1:1000 and 1:10 000 concentrations can lead to incorrect dosing in an acute setting. Epinephrine for anaphylaxis is given at doses that are substantially lower than those needed for cardiac arrest. If emergency room crash carts are stocked only with prefilled, higher concentration syringes used for IV push during cardiac arrest, clinicians may wrongly give an excessive dose for anaphylaxis if using the stock on the cart in an urgent situation [5].

IM Versus SC administration of epinephrine for anaphylaxis

Positive outcomes resulting from epinephrine use in patients with anaphylaxis are largely dependent on whether it can be rapidly administered and rapidly absorbed. Data suggest that IM administration allows more rapid peak plasma levels compared with subcutaneous (SC) administration [86,87]. In a randomized controlled trial of 17 pediatric patients with a history of food-related anaphylaxis, subjects were given epinephrine by either SC (0.01 mL/kg, maximum 0.3 mL [0.3 mg]) or IM injection (by autoinjector; 0.3 mL [0.3 mg]). In this study, IM administration by autoinjector resulted in greater mean maximum plasma concentrations of epinephrine ($C_{\max}$ = 1802 vs 2136 pg/mL), and did so significantly more rapidly (34 vs 8 minutes; $P < 0.05$) [86]. There were no serious adverse effects. Epinephrine absorption was highly variable in the SC group such that accurate calculation of terminal elimination half-life, clearance rates, or distribution volumes was not feasible [86]. In a randomized controlled, crossover trial of 17 allergic men (otherwise healthy), epinephrine by IM injection (by syringe or autoinjector) in the anterolateral aspect of the thigh resulted in significantly greater peak plasma concentrations compared with either IM or SC injection by syringe in the deltoid (12 222 [IM autoinjector to anterolateral thigh] and 9722 [IM syringe to anterolateral thigh] pg/mL vs 1821 [IM arm] and 2877 [SC arm] pg/mL, respectively; $P < 0.01$ for all IM thigh values vs any arm value) [87]. This study supported the superiority of IM injection of epinephrine into the thigh in adults and that this method may be most effective for patients in life-threatening anaphylactic reactions. No serious adverse events occurred in any child or adult in these studies.

There are several explanations for the variability in epinephrine absorption between IM and SC administration. First, the greater absorption of epinephrine by the vastus lateralis is likely due to greater blood flow compared with that in the skin or deltoid muscle. Another possibility for the more favorable absorption of epinephrine when administered via IM injection may be the vasoconstrictive effects of epinephrine in the skin when given subcutaneously, because this mode of administration can lead to decreased cutaneous blood flow and blanching at the injection site, thus delaying absorption. Lastly, when considering that patients with anaphylaxis may have severe symptoms, and potentially be in shock, peripheral circulation may be compromised and SC injection may not optimally deliver epinephrine systemically. In the adult absorption study, epinephrine delivered by IM injection from an autoinjector provided 4 times higher maximum plasma epinephrine concentration compared with SC injection of epinephrine in the deltoid area [87]. Adverse events are extremely rare when correct doses of epinephrine

Table V. Treatment recommendations at discharge from recent hospital visit for anaphylaxis [3,82].

First-line treatment	Epinephrine autoinjector prescription (2 doses) and training Anaphylaxis education and allergen avoidance strategies Emergency action plan Follow-up with primary care physician Consider referral to an allergy specialist if first presentation or reaction of unknown cause
Adjunctive treatment	H1 blocker: diphenhydramine q 6 h for 2 to 3 days (alternate with nonsedating second-generation antihistamine) H2 blocker: ranitidine twice daily for 2 to 3 days Corticosteroid: prednisone daily for 2 to 3 days

are given by IM administration. The benefits of IM administration include avoiding the need for IV access, providing a greater margin of safety than with IV administration, and the ease of administration. Recent consensus guidelines reinforce the need for epinephrine for outpatient care (Table V) [2,3,82].

Prevention of anaphylaxis

Prevention of EIA and FDEIA is the same as for other triggers and largely by allergen avoidance and self-management via an emergency action plan and an epinephrine autoinjector if necessary [2,3]. However, some strategies to prophylax patients with FDEIA or WDEIA who exercise have been attempted. Strategies prior to physical activity have included the use of sodium bicarbonate, mast-cell stabilization with sodium cromoglycate, combination oral antihistamine plus sodium cromoglycate, H1 receptor antagonism, or H2 receptor antagonism plus leukotriene receptor antagonism [88–92]. Importantly, there is no clear recommendation for these or any other prophylaxis strategies due to the lack of large, randomized controlled trials, and so caution is advised when considering strategies such as these. There is currently no substitute for or contraindication against epinephrine therapy in the event an anaphylactic reaction occurs in a patient.

Conclusion

In the case of EIA, more than 50% of patient athletes describe having ingested food 3 to 4 hours prior to exercising, although variation from 30 minutes to 24 hours have been reported. It is recommended that at least 4 to 6 hours elapse after ingestion of known or potentially causative foods prior to engaging in physical activity at any level of exertion. Patients should also avoid food intake immediately after exercising as well. Patients with confirmed FDEIA should be instructed to avoid allergen-containing foods, including condiments, additives, and preservatives, and to read ingredient labels thoroughly.

Importantly, and although EIA has been recognized as a distinct type of anaphylaxis, acute treatment does not differ from that for anaphylaxis of other etiologies. Proper identification of symptoms and correlation with a history of food allergen ingestion/exercise pattern will aid accurate diagnosis. However, rapid intervention with epinephrine remains the standard of care [2]. Only sporadic case reports in the literature suggest that some EIA patients respond to prophylactic treatment with sodium cromoglycate, H2 antagonists,

antihistamines, leukotriene antagonists, steroids, or sodium bicarbonate. However, insufficient evidence exists to routinely recommend these agents or their combination to patients with EIA or its subtypes to prevent future episodes. Given that early administration of epinephrine for all etiologies of anaphylaxis continues to have the greatest impact on morbidity and mortality, it is imperative that patient athletes, families, and other caregivers be prepared to self-manage anaphylaxis with an epinephrine autoinjector. In the immediate aftermath of an acute episode, supportive care with oxygen, inhaled bronchodilators, and intravenous corticosteroids may also be required while in the hospital, and observation of patients potentially at risk for delayed or biphasic reactions should be provided [2,3,82].

Patient athletes or their caregivers should be provided with detailed instructions and education regarding methods for identification and avoidance of allergens. If a patient is incapable of self-administration of epinephrine by autoinjector, it should be administered by an individual who is appropriately trained on a specific patient's device and can recognize an emergent need. All patients who have experienced anaphylaxis in any of its diverse forms and remain at risk of further allergic reactions should create a personalized emergency action plan that outlines the emergency management of allergic reactions, including the proper use and timing of epinephrine self-administration. An emergency action plan should be specific to the prescribed epinephrine autoinjector and should be updated annually.

Declaration of interest

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