

Exercise-Induced Anaphylaxis



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KEYWORDS

- Exercise-induced anaphylaxis • Food-dependent exercise-induced anaphylaxis
- Omega-5-gliadin • Cromolyn sodium • Cholinergic urticaria

KEY POINTS

- Symptoms of exercise-induced anaphylaxis/food-dependent exercise-induced anaphylaxis include extreme fatigue, warmth, flushing, pruritus, and urticaria, progressing to angioedema, wheezing, upper airway obstruction, and collapse.
- Diagnosis of exercise-induced anaphylaxis/food-dependent exercise-induced anaphylaxis is usually based on the clinical history and exclusion of other disorders.
- Exercise challenge (with or without food) is useful when positive, but the symptoms can be difficult to elicit, and the diagnosis can be made without this maneuver. In food-dependent exercise-induced anaphylaxis, allergen-specific immunoglobulin E to the culprit food should be demonstrable.
- Management includes education about safe conditions for exercise, the importance of ceasing exercise immediately if symptoms develop, appropriate use of epinephrine and, for patients with food-dependent exercise-induced anaphylaxis, avoidance of the culprit food for at least 4 hours before exercise.
- All patients should be equipped with epinephrine for self-administration. H1 antihistamines may reduce symptoms in some patients but do not prevent attacks. Oral cromolyn sodium seems to be useful in many cases of food-dependent exercise-induced anaphylaxis. Refractory cases have been treated with misoprostol or omalizumab.

INTRODUCTION

Exercise-induced anaphylaxis (EIA) is a disorder in which anaphylaxis occurs exclusively in association with physical exertion. Food-dependent exercise-induced anaphylaxis (FDEIA) is a similar disorder in which symptoms develop only if exertion takes place within a few hours of eating, and usually only if a certain food(s) is ingested, to which the patient is sensitized.

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EPIDEMIOLOGY

EIA and FDEIA have been reported around the world and in patients of all ages, although adolescents and young adults make up most cases in the literature.^{1–5} Both EIA and FDEIA seem to be rare. In one of the few studies of prevalence, rates of 0.03% and 0.017%, for EIA and FDEIA, respectively, were estimated among Japanese adolescents.³ However, in the author's clinical experience, FDEIA is more common than EIA. Slightly more females than males have been reported to be affected.⁶ Most cases of EIA and FDEIA are sporadic, although there are rare reports of familial cases.^{7,8}

SYMPTOMS AND CLINICAL FEATURES

In both EIA and FDEIA, episodes of symptoms are unpredictable in most patients in that a given level of physical exertion may trigger symptoms on one occasion but not on other similar occasions. Most patients exercise routinely but only develop attacks occasionally.

The signs and symptoms are similar to those in anaphylaxis from other causes. A typical episode begins while the patient is exercising vigorously, with a sensation of warmth and flushing, sometimes accompanied by sudden fatigue.^{9,10} The individual then becomes aware of pruritus, and urticaria often begins to appear on the skin. If the episode progresses (because the patient continues the exercise), lightheadedness or presyncope, gastrointestinal symptoms (nausea, abdominal cramps, diarrhea), angioedema (typically of the face or hands), throat tightness, or bronchospastic symptoms may develop. In severe episodes, patients become hypotensive and collapse. After an episode of EIA or FDEIA, patients may report fatigue or headache lasting a day or so.^{10,11}

If the patient stops the activity immediately at the first awareness of symptoms, there is most often improvement or resolution of the symptoms within minutes. However, not all patients instinctively stop what they are doing. Some may try to “push through” to see if the symptoms will pass, and others may become frightened and try to reach a place where there are other people. Runners may sprint for home. “Pushing through” uniformly results in a worsening of symptoms, and discussing this with patients is an important part of initial management.

Triggering Forms of Exercise

Vigorous forms of exercise, such as jogging, sports involving sudden bursts of sprinting (soccer/football), dancing, and aerobics are most likely to trigger symptoms.¹¹ However, brisk walking or yard work can trigger episodes in some patients, and there are case reports of older adults in whom the physical exertion of crossing a road was sufficient.¹²

Food-dependent Exercise-induced Anaphylaxis

In FDEIA, symptoms occur only when the person exercises within minutes to a few hours after eating. In rare cases, symptoms occur when the food is eaten in the minutes immediately after exercise.¹³ Patients describe episodes in which the combination of the food and exercise precipitates attacks: they can eat the food in question without symptoms if there is no associated exercise, and they can exercise without symptoms if they have not eaten the culprit food. Most patients have symptoms only after eating a specific food, although a few have attacks if any food (usually solids rather than liquids) has been ingested.¹⁴ Rare patients have been described in whom symptoms only occurred if 2 foods were eaten together before exercise,¹⁵ or who only

react to the food in a certain form (eg, tofu vs soy milk).¹⁶ The amount of food ingested may be important in some patients.^{17,18}

The foods most commonly implicated in FDEIAn are wheat, other grains, and nuts in Western populations and wheat and shellfish in Asian populations; however, an array of culprit foods has been reported, including fruits, vegetables, seeds, legumes, and, less often, various meats, cow's milk, and egg.^{1,19–21} Patients should have IgE specific to the culprit food, although this is sometimes difficult to show with standard skin testing or in vitro IgE immunoassays (see later discussion).

Other Factors That May Facilitate Symptoms

Many patients have symptoms more readily in the presence of one or more additional co-triggers, although exercise remains the immediate inciting factor. These include the following:

- Nonsteroidal antiinflammatory drugs (NSAIDs)^{18,22–25}
- Alcoholic beverages^{11,18}
- Premenstrual or ovulatory phases of the menstrual cycle in women^{26,27}
- Extremes of temperature (either high heat and humidity or cold exposure)¹¹
- Seasonal pollen exposure in pollen-sensitized patients¹¹

THEORIES OF PATHOGENESIS

As in other forms of anaphylaxis, mast cell activation and release of various mediators are believed to be responsible for the signs and symptoms of EIAAn and FDEIAn, based on skin biopsies showing mast cell degranulation²⁸ and demonstration of transient elevations in plasma histamine^{29,30} and serum tryptase after episodes.^{31,32} However, the specific changes that occur during exercise and that lead to symptoms, in the presence of food or independent of it, remain unclear. The role of basophils has not been studied. Theories of pathogenesis are summarized in [Table 1](#).

Recent work by investigators in Germany and Japan has shed new light on the pathogenesis of FDEIAn and suggest that this disorder represents a primary food allergy, in which symptoms develop only in the presence of various co-triggers, of which exercise is one but not necessarily an essential one.¹⁸ In a study of 16 patients with wheat-dependent FDEIAn and sensitization to omega-5 gliadin (an allergenic protein in gluten and the best-characterized allergen in wheat-dependent FDEIAn), subjects underwent successive challenges with increasing amounts of gluten-rich bread, combined with alcohol, aspirin, and finally exercise if symptoms did not develop with the other factors. Alcohol, aspirin, and exercise are all known to increase gastric or intestinal permeability. In 14 of 16 subjects, symptoms developed with some combination of the bread, alcohol, and aspirin, without exercise, suggesting that exercise is simply another co-trigger that can augment the clinical expression of an underlying food allergy, rather than an absolute requirement for symptoms. The investigators suggested that the term *augmentation factor–triggered food allergy* might be more accurate than FDEIAn.

DIAGNOSIS

The diagnosis of EIAAn or FDEIAn can usually be made clinically, based on a meticulous history of the events surrounding each episode and exclusion of other disorders that could present similarly ([Table 2](#)).

Important components of the clinical history, physical examination, and laboratory testing, and issues surrounding exercise testing are summarized below.

Table 1 Theories of pathogenesis for EIAAn and FDEIAAn		
Disorder	Proposed Mechanism	References
EIAAn	Abnormalities related to mast cell secretagogues released during exercise (gastrin, endogenous endorphins)	33–35
FDEIAAn	Increased gastric/intestinal permeability during exercise leads to abnormal entry of allergens into the circulation only during exercise. Concomitant intake of NSAIDs, which increase gastric permeability, increases the likelihood of symptoms in patients with FDEIAAn and supports this mechanism	18,23,36,37
	Exercise mobilizes or activates immune cells from gut-associated depots, stimulating proinflammatory responses that are normally countered by antiinflammatory responses when patient is at rest	38
	Exercise results in alterations in blood flow, redirecting blood from away from the viscera to the skin and musculature. This could carry food allergens to tissues containing mast cells that are not tolerant to those allergens, resulting in an allergic reaction during exercise but not at rest.	39
	Patients with FDEIAAn may have dysregulation of the autonomic nervous system	40,41
	Exercise may result in changes in serum osmolality within mucosal tissues, similar to a mechanism that has been implicated in exercise-induced asthma. Hyperosmolality increases basophil histamine release in response to allergens.	42–45
Wheat-dependent FDEIAAn specifically	Exercise may induce changes in the processing of specific allergens, leading to increased allergenicity. Many patients with wheat-dependent FDEIAAn are sensitized to omega-5 gliadin, and exercise activates intestinal enzyme tissue transglutaminase. This enzyme is capable of binding and aggregating gliadin moieties to form large immunogenic complexes that show increased IgE binding.	46–48

Clinical History

It is critical to confirm that exercise/exertion was associated with every instance of symptoms. For suspected FDEIAAn, was there a certain food that was ingested before each episode or is there a food that the patient eats nearly every day (eg, grains)? Did the patient ever have symptoms with exercise first thing in the morning, before eating anything? Did symptoms begin to subside when/if the patient stopped the activity? Have symptoms mostly occurred at certain time of year (peak pollen season) or in certain environmental conditions (high heat and humidity)? Everything the patient ate or drank before each episode should be reviewed (including health drinks, protein bars, or other supplements, which patients often overlook). What medications does the patient take regularly and as needed (especially NSAIDs)? Does the patient have other atopic disorders, especially incompletely controlled allergic rhinitis, asthma, or chronic urticaria? Concomitant uncontrolled allergic disease can lower the threshold for symptoms in some patients.

Physical Examination

No physical findings are unique to patients with EIAN or FDEIAN. Potentially relevant findings include signs of allergic diseases, such as stigmata of longstanding allergic rhinitis. A careful skin examination should be performed to ensure that urticaria pigmentosa, the characteristic skin finding in mastocytosis, is not present. Cardiac examination to exclude abnormal heart sounds or rhythms is appropriate in patients with syncope and near-syncope, as exercise-exacerbated cardiac conditions are in the differential diagnosis.

Laboratory Studies

A baseline serum tryptase level should be measured in all patients. Serum tryptase is normal at baseline in both EIAN and FDEIAN. Elevated values at baseline are suggestive of mast cell disorders. Elevations in serum tryptase or serum or plasma histamine immediately after an episode of symptoms support the diagnosis of anaphylaxis but do not provide information about exercise or food/exercise as the trigger.⁵⁷ Data about how often elevations in these mediators are present after episodes of EIAN and FDEIAN are limited to case reports.

Skin Testing or In Vitro Testing

In patients with suspected FDEIAN, skin testing or in vitro testing for food-specific IgE is essential to the evaluation, because sensitization to the precipitating food(s) is usually demonstrable, with rare exceptions.⁵⁸ If skin testing with a commercial extract yields negative results, skin testing with fresh food (such as wheat flour paste or the wheat product that the patient ingested before an episode) should be performed, because the use of fresh food appears to be more sensitive.^{18,59} For example, in a German series of 17 patients with wheat-dependent FDEIAN, 29% had a positive skin prick test result when tested with a commercial wheat extract, whereas 80% had a positive skin prick test result when tested with a paste of wheat flour.⁵⁹

In a Japanese study of 50 patients with FDEIAN caused by wheat, the sensitivity of the ImmunoCAP (Phadia; Uppsala, Sweden) commercial assay for IgE to recombinant omega-5 gliadin was found to be 80% in patients with positive food/exercise challenges, making this immunoassay more clinically useful than in vitro tests for IgE to wheat (all components), gluten, or other allergens.⁶⁰ IgE to omega-5 gliadin may be positive even when an IgE immunoassay to wheat is negative.⁶¹ In patients known to be sensitized to omega-5 gliadin, skin testing with pure gluten flour, which is rich in omega-5 gliadin, appears to be highly sensitive.¹⁸ However, omega-5 gliadin is not the only wheat allergen to be implicated in wheat-dependent FDEIAN, and some patients are sensitized to other wheat allergens.⁵⁹

Although not a routine part of the evaluation, skin testing or in vitro testing for IgE sensitization to environmental allergens is useful in the evaluation of EIAN if specific co-triggers, such as high pollen counts in a patient with concomitant allergic rhinitis or asthma, are suspected. Optimizing the management of coexisting allergic disorders seems to be helpful in reducing the patient's overall reactivity (see later discussion).

Exercise Challenge Testing

A positive exercise challenge (with food for FDEIAN) confirms the diagnosis, but a negative challenge does not reliably exclude the diagnosis for the reasons described in this section. Some centers with experience in EIAN/FDEIAN perform exercise challenges, with and without the culprit food in cases of suspected FDEIAN. There is no established protocol for exercise challenge to evaluate patients for EIAN or FDEIAN, although the

Table 2
Disorders that may be mistaken for EIA or FDEIA

Disorder	Can Be Confused With	Features That Help Distinguish Disorder from EIA or FDEIA	Helpful Referrals and Testing	Useful References
Cholinergic urticaria	EIA	Symptoms usually limited to skin but can become systemic. Cholinergic urticaria lesions are small, pinpoint hives on an erythematous skin (vs larger hives with EIA). Triggered by shifts in body temperature or sweating: occurs during exercise but also during passive changes in body temperature or sweating, such as hot showers, saunas, or strong emotions. Not consistently related to eating or a specific food, although spicy food can be an occasional trigger.	Passive warm water exposure or passive heating and cooling should elicit symptoms of cholinergic urticarial.	49,50
Postural orthostatic tachycardia syndrome	EIA	Tachycardia develops with change from sitting/lying to standing posture. Symptoms with exercise are common and consistent. Patients may report palpitations, lightheadedness, headache, abdominal discomfort or nausea, fatigue, inappropriate sweating or flushing. However, urticaria, throat tightness, asthmatic symptoms should not be present. Edema may be present, but should be gravitationally dependent.	Cardiology referral, abnormal tilt table testing, abnormal 24-h urine sodium excretion	51
Cardiovascular events	EIA	Patient may present with flushing, lightheadedness, syncope, tachycardia. However, urticaria, angioedema, throat tightness, and asthmatic symptoms should not be present.	Cardiology referral Holter monitor Stress testing	52

Exercise-induced bronchoconstriction	EIA _n	Can mimic EIA _n because patient may have chest symptoms, cough, flushing. Patients can report throat tightness and stridor if there is accompanying vocal cord dysfunction. However, urticaria and angioedema should not be present. Symptoms of exercise-induced bronchoconstriction often peak 10–15 min after the completion of exercise.	Response to prophylactic albuterol taken before exercise and other asthma medications. Formal exercise testing with pulmonary function sometimes needed.	53
Exercise-induced gastroesophageal reflux disease (GERD)	FDEIA _n	Can mimic EIA _n or FDEIA _n because patient may have throat symptoms, flushing, and chest symptoms. However, urticaria and angioedema should not be present. Careful history may reveal that patient also has some symptoms of GERD unrelated to exercise.	Gastroenterology referral Response to H ₂ antihistamines or proton pump inhibitors.	54
Mast cell disorders • Systemic mastocytosis • Monoclonal mast cell activation syndrome • Mast cell activation syndrome	EIA _n or FDEIA _n	Symptoms triggered by a variety of situations and not limited to exercise. These include exposure to medications (eg, NSAIDs, narcotics), physical factors other than exercise (massage, extremes of temperature), ingestion of spicy food or alcohol, surgical instrumentation, emotional stress, infections, hymenoptera stings and other toxic exposures. Urticaria pigmentosa (or other less common cutaneous signs of mast cell disease) may be present on skin	Elevated serum tryptase when patient in baseline state Mutational analysis of KIT showing a codon 816 mutation (eg, Asp816Val), usually in bone marrow or peripheral blood	55,56
Idiopathic anaphylaxis	EIA _n or FDEIA _n	Not consistently related to exercise (this can be difficult to determine if patient has had just 1 or 2 episodes)		

standard Bruce protocol for stress testing, with the addition of spirometry before and periodically during the procedure, has been used by several groups.^{3,25} However, one difficulty surrounding the use of challenges is that symptoms of EIA and FDEIA can be difficult to elicit, and studies have reported variable rates of success in eliciting symptoms.^{1,3,17,18,25,30,49} Thus, a negative test result does not necessarily exclude FDEIA. The amount of food, processing, the interval between food ingestion and exercise, and the intensity of the exercise may all be contributing variables.^{1,17,18,57} The likelihood of eliciting symptoms at the time of exercise challenge can be increased by administering greater amounts of food, NSAIDs, or alcohol before exercise.^{18,60} Challenge procedures are not done at the author's center, largely for reasons of medical legal liability surrounding the deliberate induction of anaphylaxis. If pursued, exercise challenge procedures should be performed by allergy specialists with the expertise, staff, and equipment available to treat anaphylaxis, and informed consent should be obtained from the patient or caregiver.

Food Avoidance as a Diagnostic Tool

Based on the author's experience that FDEIA is the more common disorder, attacks may be assumed to be food dependent until proven otherwise. The author initially advises avoidance of eating for 4 hours before exercise in nearly all cases. If no further attacks occur, then the period of fasting before exercise can be gradually reduced over time. If symptoms recur as the restrictions are removed, then this provides further useful information, and the evaluation can then focus on the foods that were eaten in those situations. In particular, the patient should be questioned again about snacks, candy, protein bars, and other things they might have eaten that were not part of a formal meal, as patients tend to overlook these items. Also, they may have tolerated a small amount of a certain food on other occasions before exercise, and thus do not think of it as a potential culprit. However, the amount of food can be important in some patients, and a small amount of food may provoke symptoms on one occasion and not another.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of EIA and FDEIA includes several disorders (see [Table 2](#)).

MANAGEMENT

The management of EIA and FDEIA must be individualized for each patient, to some extent, depending on the severity and frequency of symptoms, the importance of food or other co-triggers, and the patient's desire to continue participating in the particular sports or types of exercise that trigger symptoms. Randomized trials of therapies for EIA or FDEIA are lacking. The literature is limited to case reports and small series. The authors' approach is described here.

Management of both EIA and FDEIA involves the following components:

- Educating the patient about the importance of stopping exercise immediately at the first sign of symptoms
- Preparing the patient to self-administer epinephrine if needed
- Ensuring that future exercise takes place under safe conditions
- Identification and avoidance of causative foods (in FDEIA)
- Avoidance of co-triggers (eg, NSAIDs, high humidity)
- In some cases, medications to help prevent or reduce symptoms

Management does *not* involve advising the patient to refrain from exercise on a permanent basis. Avoidance of the triggering activity often is prudent in the period between the onset of symptoms and the initial evaluation, but it should not be necessary once the details of the case are understood.

Management of FDEIA is relatively straightforward in cases in which a specific food can be clearly implicated, because avoidance of that food before exercise is all that is required to prevent attacks. However, even in this situation, there are several issues that may arise (see later discussion).

Patient Education and Access to Epinephrine

Patients must become vigilant for the earliest symptoms of their attacks (usually extreme fatigue, flushing, and pruritus) and must stop exercising immediately when these appear. At the first sign of symptoms, the patient should stop all activity, get an epinephrine autoinjector ready at-hand, and, if lightheaded or dizzy, lie down in a nearby and safe location. If symptoms do not immediately begin to improve, epinephrine should be administered without delay. Some patients additionally carry a dose of orally dissolvable antihistamine, which is helpful for milder symptoms, such as isolated urticaria. However, cessation of exercise is the most important early intervention.

It is helpful to formulate a detailed plan with each patient about how he or she will ensure that medications and a cell phone are always accessible when exercising. In the case of children and adolescents, the parent or caregiver should help with this process. Usually these items can be carried in a small pack worn at the waist. Runners, in particular, are hesitant to carry bulky items, and addressing this issue up front can prevent noncompliance. Such patients often prefer the newer epinephrine auto injectors that are similar in size to cell phones and fit in the arm bands and clothing pockets designed for cell phones. Patients involved in team sports cannot usually have these items on their person, but they should be immediately accessible at the sidelines or held by the coach. Having these items locked in a locker is not adequate.

Other Precautions When Resuming Exercise

- Once evaluation for causative foods and other co-triggers has been completed, patients may resume exercise gradually, starting with a low-level exertion that will probably be tolerated, and gradually to increase their activity over weeks to months.
- Warming up before exercise was identified as helpful in a retrospective series of patients with EIA.¹¹ The patient should choose an activity that consistently allows for a warm-up period.
- Patients with EIA should exercise with a companion or in a supervised setting at all times, at least for the first months after the diagnosis until the physician and patient have a sense for whether the attacks will be controllable. The companion/coach should be educated about the signs and symptoms of anaphylaxis and be capable of administering epinephrine.
- The physician should ask the patient if there are any situations in which he or she would be reluctant to stop exercise. This issue arises with adolescents participating in team sports (eg, competitive cheerleading) in which they are an essential member. In this situation, the patient may be tempted to push through mild symptoms against medical advice for the sake of the team. It is better to avoid these situations by choosing appropriate activities or making a plan in advance for how the patient could be rapidly removed and a substitute put in place.
- As with prevention of anaphylaxis of any etiology, patients should avoid certain medications going forward, such as β -blockers and ACE inhibitors. Medication

lists should be reviewed regularly at follow-up visits to ensure that other providers have not prescribed the same medications. NSAIDs should be avoided for 24 hours before exercise in patients with FDEIAn.²⁴

Food Avoidance in Patients with Food-dependent Exercise-induced Anaphylaxis

Patients with FDEIAn should avoid the culprit foods for at least 4 hours before exercise. Exercising in the morning, before eating anything, is a simple way to comply with this restriction. Some patients can restrict the food for fewer hours and others require longer periods (eg, 6 hours).

Avoidance of the culprit food can be difficult in certain scenarios:

- Patients who have symptoms with even mild exertion, such as brisk walking, may have to avoid the culprit food completely, rather than only before exercise. Similarly, children, who run and play unpredictably throughout the day, may need to avoid the culprit food completely.
- Adolescents may need help from parents and clinicians to devise a list of safe foods that they can have on hand, especially for snacking before and during sports practices.

Avoidance of Relevant Co-triggers

- Patients whose attacks follow ingestion of NSAIDs can avoid these agents altogether or at least refrain from exercise for 24 hours after taking one of these medicines.
- Those affected by high humidity or high pollen counts can exercise in an air-conditioned, indoor setting during critical times of year. Allergen immunotherapy can reduce sensitivity to pollen, although this has not been specifically studied in patients with EIAAn and concomitant pollen allergy.
- Maximal management of any concomitant allergic disorders, such as allergic rhinitis and asthma, is also helpful.

Preventative Therapies

Prophylactic pharmacotherapy is not needed in cases in which behavior can be modified and co-triggers avoided. However, this is not practical in all cases, and prophylactic pharmacotherapy is sometimes warranted.

Cromolyn Sodium in Food-dependent Exercise-induced Anaphylaxis

Case reports suggest that high-dose cromolyn sodium taken orally before food ingestion can be useful in preventing attack in patients FDEIAn.^{16,62–64} The patients in these cases have included children and young adults with FDEIAn who were advised to avoid exercise for 4 hours after eating but found it difficult to comply with this restriction. Oral cromolyn sodium was administered 20 minutes before the midday meal in case there was unexpected exercise in the afternoon.⁶³ In a report of 2 children, this approach appeared to prevent the children from having symptoms when they did exercise after eating. The children only had symptoms on days when they forgot to take the cromolyn sodium. Over time, both children resumed unrestricted exercise after eating, managing the disorder with cromolyn before the preceding meal.⁶³

In 2 case reports of adult patients with wheat-dependent FDEIAn, premedication with cromolyn sodium prevented absorption of wheat allergen into the blood in one patient⁶⁴ and prevented an increase in plasma histamine in another.⁶² However, in another case report of wheat-dependent FDEIAn, 100 mg of sodium cromoglycate taken 1 hour

before food/exercise challenge prevented neither symptoms nor absorption of gliadin into the blood.⁶⁵ Of note, the dose used in this report (100 mg) was low for an adult.

Until better data are available, it seems prudent to offer this therapy to patients with a clear warning that the efficacy has not been well defined. It is explained to patients that this approach should NOT be considered a reliable alternative to avoidance of the culprit food but rather an additional protective measure.

Cromolyn sodium comes in an oral formulation (Gastrocrom) in the United States, in ampules of 100 mg/5 mL. The dose used in the reports previously described of children was 100 mg taken before eating. The dose for adults is 200 mg, which is the dose used in the author's practice. We advise patients to take cromolyn sodium in water 30 minutes before any meal that could be followed by exertion and up to four times daily.

H1 Antihistamines

Premedication with H1 antihistamines to prevent EIA_n has not been systematically studied. Clinical experience suggests that antihistamines do *not* prevent symptoms, and some clinicians prefer not to initiate antihistamines due to concern for masking early symptoms. However, H1 antihistamine premedication may reduce the severity of episodes in some patients,¹⁰ particularly if they have coexistent allergic rhinitis that is incompletely controlled. Thus, these agents can be prescribed empirically to patients who have not already tried them and discontinued later if there is no apparent benefit after explaining the pros and cons to the patient. The author's approach is to continue antihistamines if the patient presents already taking these medications for other allergic disorders (eg, allergic rhinitis) but to focus on identifying the relevant foods and/or other co-triggers, as antihistamines do not seem to have a dramatic impact on EIA_n or FDEIA_n.

Other Agents

Case reports suggest that misoprostol (a synthetic analogue of prostaglandin E1),^{65,66} or omalizumab⁶⁷ can be helpful for patients who have not responded to other measures. The author knows of no studies evaluating the use of oral corticosteroids or leukotriene-modifying agents in EIA_n or FDEIA_n.

PROGNOSIS

Few fatalities are attributed to EIA_n or FDEIA_n. Literature review found 4 reported fatalities.^{68–71} Of these, one had autopsy findings suggesting concomitant bowel ulceration, 2 patients had fatal attacks before the disorder was recognized as exercise related (and both had significant asthma as a comorbidity), and a fourth fatality occurred after ingestion of the known culprit food combined with alcohol, exercise, and no access to epinephrine. Thus, each of these cases had extenuating circumstances.

Fortunately, most patients with EIA_n or FDEIA_n do well, reporting fewer attacks over time.^{11,19} This is likely caused by a combination of recognition of early symptoms, modifications in exercise habits, and avoidance of culprit foods and other co-triggers.

SUMMARY/FUTURE CONSIDERATIONS

EIA_n and FDEIA_n are uncommon and unpredictable disorders that usually affect otherwise healthy and active individuals. Diagnosis depends heavily on suggestive clinical features and exclusion of other possible disorders. Treatment and prevention are focused on identification of foods and other factors that are relevant for each patient. Important areas for future investigations include standardization of a

diagnostic approach (including safe and consistently effective challenge protocols), clarification of the pathogenesis of these disorders, and controlled trials to define the efficacy of pharmacotherapy.

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