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Recognition and management of food induced anaphylaxis

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Synopsis

Food-induced anaphylactic reactions are common and increasing in frequency. Despite the existence of a consensus definition of anaphylaxis, many cases are missed, recommended treatments are not given and follow-up is inadequate. New aspects of its pathophysiology and causes, including atypical food-induced causes, are still being uncovered. Epinephrine remains the cornerstone for successfully treating anaphylaxis; H1 and H2 antihistamines, glucocorticoids and β -agonists are ancillary medications that may be used in some cases in addition to epinephrine. However, the added utility of these secondary medications in anaphylaxis has not been conclusively demonstrated. Early recognition of anaphylaxis, appropriate emergency treatment and follow-up, including prescription of self-injectable epinephrine, are essential to prevent death and significant morbidity from anaphylaxis.

Keywords

anaphylaxis; food allergy; epinephrine

Introduction

Food allergy is a major cause of anaphylaxis in children, and it appears that the rates of both food allergy and anaphylaxis are increasing in developed countries. Extrapolating the most conservative estimates of anaphylaxis incidence to the overall U.S. population leads to a minimum of 25,000 cases each year.¹ Food allergy accounts for 15–57% of those cases.^{2–7} Widespread deficiencies of concern include significant under-recognition of anaphylaxis and inadequate treatment.^{8–9} One recent report estimated that at least half of likely cases of anaphylaxis are misclassified,¹⁰ and other surveys have found even higher rates of misclassification.^{11–12} Epinephrine, the primary lifesaving drug in anaphylaxis treatment, is used infrequently in emergency settings, and is under-prescribed as a discharge medication.^{8, 13} Recognizing food-induced anaphylaxis, adequately treating the episode, identifying the causative agent, and providing effective recommendations to prevent and or live with food allergies are important aspects of care that need to be improved.

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Definition of Anaphylaxis

Anaphylaxis is a multi-system reaction to allergen exposure. Although the term was coined in 1902¹⁴, pervasive inconsistencies in its application have made interpretation of the literature difficult. In an effort to standardize research of and treatment for anaphylaxis, a joint panel from the American Academy of Allergy, Asthma & Immunology (AAAAI); the American College of Allergy, Asthma & Immunology (ACAAI); and the Joint Council of Allergy, Asthma and Immunology agreed on a consensus definition of anaphylaxis in 2006, and recently revised it.^{15–16} They define anaphylaxis as one of the following:

1. The acute onset of a reaction (minutes to hours) with involvement of the skin, mucosal tissue or both and at least one of the following:
 - a. Respiratory compromise; or
 - b. Reduced blood pressure or symptoms of end-organ dysfunction;
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient:
 - a. Involvement of the skin/mucosal tissue,
 - b. Respiratory compromise,
 - c. Reduced blood pressure or associated symptoms and/or
 - d. Persistent gastrointestinal symptoms; or
3. Reduced blood pressure – after exposure to a known allergen..¹⁶

Although this definition is cumbersome, it highlights the fact that anaphylaxis is not always characterized by severe respiratory and cardiovascular compromise,; persistent abdominal pain and urticaria after ingestion of a likely allergen (for that patient) also meet the definition of anaphylaxis. Generally, anaphylaxis has been understood as an IgE-mediated reaction, although the World Allergy Organization has recommended that non-IgE mediated anaphylaxis-type reactions be included under the term. So far, U.S. consensus panels have rejected that suggestion,¹⁶ and in this review, anaphylaxis will refer to an IgE-mediated syndrome.

Pathophysiology of Anaphylaxis

The initiating event in an anaphylactic episode is the association between allergen and membrane-bound IgE on mast cells and basophils. This leads to aggregation of the high affinity IgE receptor, triggering an intracellular signaling cascade that ultimately leads to calcium influx and degranulation of the cell. Activation of mast cells and basophils causes release of preformed mediators of inflammation (histamine, tryptase, carboxypeptidase A, proteoglycans and some cytokines), and newly generated mediators (leukotrienes, cytokines including TNF- α , and platelet-activating factor). Ultimately these mediators cause the characteristic clinical features of anaphylaxis, including vasodilation, angioedema, bronchoconstriction, and increased mucous production.^{17–19}

Histamine, one of the preformed mediators released by mast cells and basophils, can recapitulate most of the signs and symptoms of anaphylaxis when administered intravenously to humans and laboratory animals.¹⁷ 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, while stimulation of both H1 and H2 receptors causes increased production of mucous. 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.^{13, 16, 20}

Other mediators of anaphylaxis include leukotrienes and other products of arachadonic acid metabolism, including prostaglandins; platelet activating factor (discussed in more detail below); the neutral proteases such as tryptase and chymase; the proteoglycans, including heparin; and various chemokines. These mediators recruit inflammatory cells and activate complement cascades, among other mechanisms.¹⁷

Over the past 5 years, several studies have highlighted the role of platelet activating factor (PAF) in the propagation of anaphylaxis. PAF is a preformed mediator of anaphylaxis released by mast cells, monocytes and tissue macrophages. It is degraded by PAF-acetylhydrolase. In a seminal paper published in 2008, Vadas and colleagues measured PAF and PAF-acetylhydrolase in patients with varying gradations of anaphylaxis severity.²¹ They found significant correlation between PAF levels and the severity of anaphylaxis; all subjects with severe anaphylaxis had elevated PAF levels. In addition, levels of PAF-acetylhydrolase were inversely correlated with severity of anaphylaxis.²¹ Subsequently, Arias and colleagues showed that blocking PAF prevents severe anaphylactic reactions, and, when combined with antihistamines, abolishes nearly all signs of anaphylaxis.²² Further, Kajiwarra and colleagues demonstrated that PAF, by itself, was capable of activating mast cells in the lung and peripheral blood, but not in the skin.²³ The role of PAF-acetylhydrolase deficiency as a risk factor for severe allergic reactions is an area of active exploration.

Diagnosis of Anaphylaxis

There are two components to the diagnosis of food-induced anaphylaxis. The first is the recognition of an anaphylactic event, and the second is the identification of the etiologic agent.

Clinical syndrome

As described above, anaphylaxis involves a combination of cutaneous, respiratory, cardiovascular and gastrointestinal (GI) symptoms. A recent review that collated information on 1,865 patients with anaphylaxis found that skin symptoms are the most common manifestation of anaphylaxis, present in up to 90% of episodes.¹⁶ In this same series, symptoms of both upper and lower respiratory compromise were common, occurring in up to 60% and 50% of published cases, respectively.¹⁶ Perhaps because the GI mucosa is the location of exposure in food-induced anaphylaxis, GI symptoms are much more common in food-induced than in non-food induced anaphylaxis. One series of patients referred to an allergist for anaphylaxis found that only 3.7% of cases of non-food-induced anaphylaxis had GI symptoms, compared to another series where 41% of those caused by foods had GI symptoms.^{16, 24} Hypotension, dizziness and syncope are associated with up to 35% of cases of anaphylaxis in general, but are much less common in food-induced anaphylaxis, where they are rarely found in isolation from respiratory arrest. In severe food-induced reactions, respiratory symptoms predominate, and are responsible for the overwhelming majority of fatalities.²⁵⁻²⁹

The time from ingestion of the food to onset of symptoms is usually on the order of minutes. In published reports the median time from ingestion to symptom onset ranges from less than 5 minutes to 2 hours.²⁴ More severe cases tend to present earlier.^{25, 28-29} Usually, symptoms resolve quickly with appropriate treatment. One area of considerable controversy in the literature is the true frequency of biphasic reactions during anaphylaxis. In a biphasic reaction, symptoms of the initial reaction resolve but are followed by recurrent or new

symptoms hours later. Published reports suggest that this occurs in 5 to 28% of anaphylaxis cases,^{30–33} and some have suggested that biphasic reactions are more common with ingested allergens where allergen absorption may be slower.³⁴ There is also conflicting evidence about whether administration of corticosteroids or time to epinephrine delivery affects the risk for biphasic reactions.^{30–33} In general, the second reaction tends to be less severe than the original reaction.

Atypical Food-Induced Anaphylaxis

Two unusual types of food-induced anaphylaxis, food-dependent exercise-induced anaphylaxis and carbohydrate-induced anaphylaxis, merit special comment. Food-dependent exercise-induced anaphylaxis is a rare cause of anaphylaxis.³⁵ In this syndrome, patients tolerate both the causative food and exercise in isolation, but not together. Typically this syndrome presents in adolescence or in individuals in their 20s, but it can occur at any age.³⁶ The time between consumption of the food and onset of symptoms is frequently longer than in other kinds of food-induced anaphylaxis, as reactions have been reported hours after eating the food. Usually, symptoms begin within 30 minutes of the start of exercise, but can occur at any time during the workout and with any intensity of exercise. The initial stage usually consists of cutaneous signs and fatigue, followed by more generalized symptoms.¹⁶ The most common food to trigger food-dependent exercise-induced anaphylaxis is wheat, followed by other grains, nuts and seafood.¹⁶ Skin prick testing and food-specific IgE can help confirm the diagnosis, although the size of the skin test or level of food specific IgE is usually lower than found in other types of food allergy. The mechanism of exercise-induced anaphylaxis is thought to be increased permeability of the gut to undigested allergens, although this is only speculative. Exercise-induced anaphylaxis can be confused with cholinergic urticaria, where hives occur with heating. Cholinergic urticaria is not typically accompanied by the systemic symptoms that are characteristic of exercise-induced anaphylaxis, and symptoms can be reproduced by passive heating.¹⁶ The current recommendation for prevention of food-dependent exercise induced anaphylaxis is to either completely avoid the food, or to wait at least 6 hours between food ingestion and exercise.¹⁶ Additional important measures are for patients to carry self-injectable epinephrine and exercise with a partner who is aware of the condition and able to assist.

Another unusual type of anaphylaxis to food has been called “delayed anaphylaxis to red meat” or carbohydrate-induced anaphylaxis. This condition has recently been reported in patients living in the South-Eastern United States and Australia who presented with anaphylaxis 3–6 hours after ingesting red meat.³⁷ Commins and colleagues found that these patients had IgE to a carbohydrate found on mammalian serum albumin called galactose- α -1,3-galactose (α -gal). The condition usually begins in adulthood and appears to have a particular geographic specificity. An intriguing hypothesis to explain the age and geographic distribution of α -gal sensitization is that the bite of a tick endemic to this geographic region sensitizes people to the α -gal. Indeed, a history of tick bite is more common in patients with sensitivity to α -gal.³⁸ General practitioners should be aware of this unusual type of anaphylaxis and refer patients to allergists for evaluation if it is suspected.

Severe and Fatal Anaphylaxis

Fortunately, food-allergy induced fatalities remain rare, although fear of fatal reactions contributes to the anxiety that exists in families with a food-allergic child.³⁹ Since Yunginger and colleagues first described a series of deaths from food-induced anaphylaxis in 1998⁴⁰, the most important risk factor for a severe reaction remains a history of asthma. In the series published thus far, the prevalence of a positive history for asthma in fatal reactions has approached 100%.^{25–29, 40} In addition to asthma, several other features of a food allergen exposure appear to convey particular risk. Adolescence is the age at greatest

risk for a fatal reaction, whether from increased reactivity, or, more likely, because of increased risk-taking behavior. Peanuts are the most common cause of fatal reactions, causing 50–60% of fatal reactions. Tree nuts account for another 15–30% of fatal reactions.^{25–29, 40} In two reports from the U.S. and Great Britain attempting to account for as many food-related fatalities as possible between 2001–2006 (U.S.) and 1999–2006 (Great Britain), milk emerged as the next most common cause, accounting for 13% of deaths in each series.^{27, 29} Shellfish; s, fish, eggs, sesame and selected fruits and vegetables account for most of the remaining causes.

Attempts to find other markers that prospectively identify patients at risk for severe reactions have been largely unsuccessful. Although some have found correlations between food-specific IgE titers and/or skin-prick test size and magnitude of clinical reactivity, most have found them to be poorly predictive of reaction severity with food challenge or accidental exposure.^{41–47} This is, perhaps, not surprising, given that the correlation between reaction severity in the clinic and in the community is itself weak (r^2 0.37), likely due to variable exposure doses⁴³. Recent studies of immunotherapy for food allergy offer an interesting opportunity to explore risk factors for reaction at a given dose. Exercise, concurrent illness, and menstrual status were identified as risk factors for unexpected or more severe reactions to a given dose.^{48–50} These findings may not extend to community-based reactions, but it is likely that incident specific factors, such as those mentioned above and concurrent intake of alcohol⁴⁰ are the most important predictors of severe reactions.

Differential Diagnosis of Anaphylaxis

The differential diagnosis of anaphylaxis includes other illnesses that cause acute respiratory distress, syncope, rash and/or GI distress. In children, vocal cord dysfunction, panic attacks and vasovagal reactions (also known as vasodepressor reactions) deserve particular note. Vocal cord dysfunction is caused by abnormal adduction of the vocal cords during inspiration. It can coexist with asthma, and the wheezing and coughing can mimic anaphylaxis. Treatment is speech therapy.⁵¹ Signs and symptoms found in vasovagal reactions, including hypotension, nausea, vomiting and diaphoresis can mimic anaphylaxis, but these reactions lack the typical skin manifestations found in anaphylaxis. In contrast to anaphylaxis, vasovagal reactions are characterized by bradycardia, whereas anaphylaxis is usually, but not always, accompanied by tachycardia.¹⁶ Other causes of flushing, including the “red man syndrome” from vancomycin, should be considered in the differential.

Miscellaneous food-related conditions that can be confused with anaphylaxis include scombroid poisoning, which mimics anaphylaxis closely, as it is caused by consumption of histamine itself, and monosodium glutamate-related flushing, which is not an IgE-mediated condition. Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE mediated disease presenting in infancy. Acute reactions usually include profound vomiting, leading to dehydration, lethargy and hypotension, starting hours after the food is ingested. Awareness of this condition is important, as is the understanding that negative skin prick test or food-specific IgE do not rule it out.⁵²

Laboratory Studies to Confirm Anaphylaxis

Laboratory studies are less helpful in confirming food-induced anaphylaxis than other types of anaphylaxis. Because serum histamine levels are only elevated for 30–60 minutes after onset of reaction, they are not usually measured in any type of anaphylaxis. The most commonly assessed mediator in clinical practice is tryptase. Tryptase levels in the blood peak 1½ hours after onset of symptoms and are measurable for up to 5 hours. However, in reports of severe and fatal anaphylactic reactions to foods, tryptase is less commonly elevated than in other types of anaphylaxis.^{25, 40, 53–55} Because basophils have less tryptase

than mast cells, some have speculated that this is a sign of the central importance of basophils in food-induced anaphylaxis, although this hypothesis has not been confirmed.

Interestingly, in a recent series of 76 cases of anaphylaxis from all causes, including non-food, presenting to the emergency room, two distinctive types of severe reactions were identified: those with predominantly hypotensive symptoms, and those with predominant hypoxia.¹⁸ The authors of this series identified a consistent cytokine pattern, including the presence of IL-6, IL-10, TNF receptor I, mast-cell tryptase, and histamine, in hypotensive episodes, but not in hypoxemic episodes, suggesting either different pathways leading to hypoxemia, or a predominantly local response not reflected in the peripheral blood. Both are plausible explanations for the unique presentation of food-induced reactions. There remains no laboratory test at present that reliably confirms anaphylaxis in food-induced cases.

Identification of Underlying Food Allergy

Clinical history remains the most important tool to identify the cause of an acute episode of anaphylaxis. In contrast to other types of anaphylaxis, many, if not most, cases of reactions to foods occur in patients with a known history of allergy. However, the allergen is frequently hidden in other foods. Common sources of accidental peanut and tree-nut exposure are baked goods, candies, and Asian foods, while milk can be found hidden in chocolate, bread and baked goods.^{25, 29, 56} Knowledge of the epidemiology and natural history of food allergy is helpful in suggesting possible triggers if the diagnosis is not yet established. The most common food allergies in childhood are milk, egg and peanut. Milk and egg allergy are typically outgrown by adulthood, although a significant and perhaps growing minority persist to at least adolescence^{57–58}. In adulthood, peanut allergy remains a common cause of anaphylaxis, and tree nut and shellfish allergies emerge as important causes. Both the epidemiology and diagnosis of food allergy are reviewed in depth elsewhere in this issue.

Referral to an allergist is helpful to both identify the cause of anaphylaxis and help prevent future episodes. At the time of referral, the general practitioner should ensure that the patient has been provided with a prescription for self-injectable epinephrine, given the chance for repeat episodes of anaphylaxis, especially if the etiology remains elusive. For confirmation or exploration of potential allergies, the allergist will either perform specific skin prick testing or test the blood for food specific IgE. All allergy testing needs to be interpreted in the context of a careful clinical history, as false positives are very common. Failure to take into account dietary history and to understand the predictive value of these tests frequently leads to overly restrictive elimination diets.

Management of anaphylaxis

Epinephrine and Other Life-Saving Treatments

Epinephrine remains the mainstay of treatment for anaphylactic reactions. Antihistamines, glucocorticoids and beta-agonists either alone or in combination do not substitute for epinephrine's lifesaving role in the treatment of anaphylaxis. Although, for obvious ethical reasons, prospective controlled studies of its use in human anaphylaxis have not been conducted, the evidence for its utility is persuasive. Epinephrine is an α -1 agonist, causing vasoconstriction leading to increased blood pressure and decreased mucosal edema; a β -1 agonist, causing increased cardiac contractility; and a β -2 agonist, reversing bronchoconstriction and inflammatory mediator release.^{13, 59} In controlled animal models and in human clinical experience, injected epinephrine rapidly reverses anaphylaxis. In humans, retrospective studies have shown that lack of prompt treatment with epinephrine is one of the major risk factors for death from anaphylaxis.^{25–29, 40, 54}

The optimal method of administration of epinephrine is by intramuscular (IM) injection. Subcutaneous injection is not preferred, as administration via this method can lead to local vasoconstriction, delayed absorption and decreased peak levels of epinephrine.⁶⁰ Injection into the vastus lateralis muscle (lateral thigh) leads to a faster peak blood level compared to deltoid injection⁶⁰, although the clinical relevance of this has not been established.¹⁶ IM administration is considerably less complicated than intravenous (IV) dosing, which lacks an established dosing regimen, and is prone to dosing errors.^{16, 59} Moreover, IV epinephrine can lead to lethal arrhythmias.¹⁶ The most recent practice parameter recommends restricting use of IV epinephrine to patients with profound hypotension or failure to respond to IM epinephrine. In addition, patients that receive IV epinephrine should have continuous cardiac monitoring in place.¹⁶

The recommended dose for IM injection is 0.01 mg/kg to a maximum of 0.3 mg in children, given as a 1:1000 solution (1mg/1ml). In adults, the dose is 0.2 to 0.5 mg.¹⁶ Commercially available prefilled syringes for auto-injection (EpiPen, Twinject, Adrenaclick) are available in strengths of 0.15 mg and 0.3 mg. They should be administered in the lateral thigh. The package insert for both commercially available auto-injectors suggests the 0.15 mg dose for those who weigh 15–30 kg and the 0.3 mg dose for those weighing more than 30 kg, but the most recent guidelines from the National Institutes of Health recommend switching to the 0.3mg dose at approximately 25 kg because of the risk of under-dosing above this weight if the smaller dosage is used. [Article in Press at the Journal of Allergy and Clinical Immunology]. Because the risks of overdose if the auto-injector is given must be weighed against the demonstrated difficulty that non-professionals have with correctly and promptly drawing up epinephrine into a syringe⁵⁹, the same guidelines recommend the use of the 0.15 mg auto-injector for patients down to 10 kg. In practice, self-injected epinephrine is prescribed to even smaller infants.⁶¹ The dose may be repeated at intervals of at least 5 minutes if necessary. Ideally, epinephrine auto-injectors are prescribed on discharge from the emergency room (ER) after management of anaphylaxis, or following consultation with a pediatric allergist for suspected food allergy.

Despite universal recommendations for the use of epinephrine in anaphylaxis, it is actually uncommonly used in either home or emergency room treatment of food-induced anaphylaxis.¹¹ This may be due to patients perceiving epinephrine as a dangerous medication, or because patients and practitioners do not think their symptoms are severe enough to merit epinephrine.⁹ One review of patients presenting with food allergy to 21 emergency rooms in North America found that while 33% were treated for respiratory symptoms with albuterol or other inhaled treatments, only 16% received epinephrine in the emergency room, and only 16% were prescribed it at discharge.⁸ How to improve translation of practice parameters into the actual emergency treatment of anaphylaxis is an area ripe for examination. Individual action plans, which are reviewed elsewhere in this issue, are one method to improve community treatment of anaphylaxis. In general, we recommend that epinephrine be given to food-allergic children at the first signs of a systemic reaction, before full blown respiratory systems or hypotension develop.

Beta-blockers are infrequently used in children, but are associated with anaphylaxis that is difficult to treat in adults. If the patient is taking beta-blockers, glucagon can be useful. Additional potentially lifesaving supportive measures include putting the patient in a supine position in order to maximize cardiac return, administering oxygen if needed, and giving IV fluids if hypotension develops.¹⁶

H1 Anti-histamines

H1 antihistamines are the most commonly used medications in the treatment of anaphylactic episodes. In one multicenter sample they were used in 72% of emergency visits for food

allergy⁸, and others have reported rates of use consistently exceeding 50% for anaphylaxis.¹³ H1 antihistamines are inverse agonists at the H1 histamine receptor, in that they bind the receptor in its inactive state, preventing signaling through the receptor. First-generation H1 antihistamines are lipophilic, and can readily cross the blood brain barrier, resulting in sedation. Second-generation antihistamines are modified so that they cannot enter the central nervous system, effectively eliminating sedation and other neurologic effects. In addition, they lack the cholinergic, α -adrenergic and serotonergic effects of the first-generation antihistamines, ameliorating some of the most troublesome adverse effects, including dry mouth, urinary retention, prolonged QT interval and increased appetite.⁶² While H1 antihistamines decrease skin symptoms (itch, flush, urticaria) and nasal symptoms (rhinorrhea, congestion), they do not prevent or treat airway obstruction, wheeze or hypotension. Suppression of wheal and flare response to allergen takes 0.7 to 2.6 hours after oral administration.¹³ Because they do not prevent the serious manifestations of anaphylaxis, they are considered secondary medications for the treatment of anaphylaxis. The most recent practice parameter suggests that they may have utility for “control of cutaneous and cardiovascular manifestations” of anaphylaxis,¹⁶ although others recommend against their use because of their potential for both delaying life-saving therapy and causing dangerous side effects.⁶³ Complications of H1-antihistamines include sedation, as mentioned above, other neurotoxicities such as seizure, and potentially fatal QT prolongation.

If the decision is made to use them, antihistamines can be given by mouth (po), intravenously or intramuscularly. For children, the dose should be 1mg/kg up to 50 mg, while for adults, the dose is 25–50mg, whether given IM, IV or PO.¹⁶

H2 Antihistamines

As outlined above, the H2 receptor participates in the anaphylactic response, and, theoretically, blockade of this receptor may interfere with cardiac, vascular and skin symptoms by distinct pathways from the H1 receptor. Like H1 antihistamines, H2 antihistamines are inverse agonists that preferentially bind to the inactive state of the receptor. They are generally safe, although infusion of cimetidine should be done slowly to prevent hypotension.¹⁶ Two randomized controlled trials of H2 antihistamines added to H1 antihistamines for treatment of acute allergic events showed improved efficacy with both agents compared to H1 antihistamines alone for treatment of urticaria, but not for itching, angioedema or erythema.^{64–65} One of the studies also showed less tachycardia after treatment with the H2 blocker than placebo. Of note, although the difference was not statistically significant, almost twice as many subjects in the H2 antihistamine group in the study received epinephrine.⁶⁴ Several additional single case reports suggest utility for H2 antihistamines in treatment of anaphylaxis refractory to other therapies, but their utility in anaphylaxis has not been carefully examined.¹³ The most recent U.S. practice parameter for anaphylaxis states that “an H2 antagonist added to the H1 antagonist may be helpful in the management of anaphylaxis.” If used, ranitidine can be given IV or IM at 1mg/kg in adults and 12.5 mg to 50mg in children.¹⁶

Glucocorticoids

Like H1 antihistamines, glucocorticoids have not been subjected to randomized controlled trials for anaphylaxis, but are widely used in the emergency room setting. The onset of action of glucocorticoids is even slower than oral H1 blockers, occurring hours after administration.¹³ Steroids are lipophilic, crossing the cell membrane to bind the glucocorticoid receptor, causing heat shock proteins to dissociate and the receptor to be phosphorylated and then transported to the nucleus. There they bind to glucocorticoid receptor elements and cause altered expression of a wide range of genes. Although

pretreatment for 48 hours with glucocorticoids prevents the late phase response to allergen challenge, it does not affect the acute-phase response.⁶² Glucocorticoids can cause significant adverse events, including effects on bone metabolism, glucose metabolism, muscle wasting, cataracts, hypertension, and skin thinning, although short-term administration is generally much safer. Mood changes and effects on glucose metabolism can occur with even very shorter term use.⁶⁶ Glucocorticoids are commonly used in acute anaphylaxis to prevent biphasic reactions, although their utility for this purpose has not been conclusively demonstrated.

β-agonists

β-agonists may be used as an adjunct to epinephrine for the treatment of wheeze, but should not replace epinephrine because they lack the widespread effects of epinephrine and do not effectively treat angioedema.¹⁶

Conclusions

Even though anaphylaxis was first described centuries ago, ensuring high quality emergency treatment of food-allergen induced anaphylaxis and appropriate follow-up, still remains a challenge in many instances. Although they are commonly used instead of epinephrine, antihistamines, β-agonists and glucocorticoids do not reverse the life-threatening symptoms that are characteristic of anaphylaxis. Because almost all food-induced anaphylactic events occur in the community, provision of self-injectable epinephrine to patients at risk is essential. Patients should be referred to allergists to ensure that diagnosis of the underlying food allergy is correct and that the patients and their families receive appropriate education. Although new discoveries relating to the pathophysiology of anaphylaxis and its causes may ultimately alter how we treat and prevent it, we already have the tools to prevent deaths from anaphylaxis. We just need to use them.

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