

Management of Food-Induced Anaphylaxis: Unsolved Challenges

Katherine Arias¹, Susan Waserman² and Manel Jordana^{1,*}

¹Department of Pathology and Molecular Medicine, Centre for Gene Therapeutics, McMaster University, ²Department of Medicine, McMaster University, Hamilton, Ontario, Canada

Abstract: Anaphylaxis is an acute and often severe systemic allergic reaction. The prevalence of food allergy has been increasing and is currently estimated at ~3.5%. Food allergic reactions account for one-third to one-half of anaphylaxis cases worldwide. It is estimated that approximately 30,000 food-related anaphylactic reactions are treated in United States emergency departments (ED) every year resulting in ~2000 hospitalizations and 150 deaths. The increasing rate of food-induced anaphylactic episodes in the last few decades underlines the existence of major challenges. This review will critically appraise current guidelines for the diagnosis as well as the acute and long-term management of food-induced anaphylaxis (FIA). Importantly, it will outline existing challenges and suggest measures to improve outcomes in patients with FIA. We propose that the discovery of novel diagnostic (i.e. biomarkers and predictors) and therapeutic approaches is a major challenge that may be overcome as the mechanisms underlying FIA are better delineated. We further propose that better dissemination, implementation and compliance with the consensus management guidelines are urgently needed. This will require education of ED personnel, patient empowerment as well as effective multilateral communication among patients, emergency and family physicians, allergists and specialized volunteer organizations.

Key Words: Food allergy, anaphylaxis, acute management, long-term management, measures.

INTRODUCTION

Anaphylaxis is an acute, often severe and potentially life-threatening systemic allergic reaction [1, 2]. It is a medical emergency that requires immediate intervention, yet paradoxically, a stepwise management approach with evidence-based guidelines is still to be in place. Indeed, most of the current anaphylaxis guidelines are based on “clinical experience” rather than randomized controlled trials. Similarly, the implementation of guideline recommendations represents a significant challenge in anaphylaxis.

This review will evaluate the latest literature on the epidemiology, clinical presentation and management of anaphylaxis, with particular emphasis on food-induced anaphylaxis (FIA). Importantly, it will highlight the suggested guidelines and existing challenges in the management of FIA. Since attention is often focused on managing the acute episode, this review will also appraise long-term management plans that may help improve outcomes in patients with FIA.

ANAPHYLAXIS

Definition and Epidemiology

Anaphylaxis is an old condition. The first documented evidence of anaphylaxis may have been in 2641 BC when the Egyptian pharaoh Menes suddenly died from a reaction to a wasp sting. However, it was not until 1902 that Portier and Richet formally coined the term “anaphylaxis” to describe a systemic shock reaction unexpectedly induced by immunization. The lack of a universally accepted definition of anaphylaxis has hampered research on the epidemiology,

pathophysiology and management of this disorder. In an effort to clarify these concepts, the Second National Institute of Allergy and Infectious Diseases (NIAID) and Food Allergy and Anaphylaxis Network (FAAN) Symposium recently recommended the following definition: “Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death” [1]. There are 3 proposed clinical diagnostic criteria (Box 1). Anaphylaxis is highly likely when any of the 3 criteria is fulfilled following exposure to an allergen. Note that as the majority of anaphylactic reactions include cutaneous manifestations [3-7], criterion 1 likely allows for the identification of most cases. However, such manifestations might be absent in up to 20% of anaphylactic reactions, particularly in children reacting to foods or insect stings [8-10]. In these cases, an allergic history and knowledge of probable exposure, along with symptoms consistent with criterion 2 would establish the diagnosis. Criterion 3 would identify the rare subset of patients experiencing acute hypotension following exposure to a known allergen [11]. The NIAID/FAAN Symposium acknowledged that no set of criteria will provide 100% sensitivity and specificity; however, there was agreement that the aforementioned criteria should accurately identify anaphylactic reactions in more than 95% of cases. Nonetheless, this proposal needs to be validated by a prospective multicenter clinical trial to determine if further refinements are needed.

Because anaphylaxis has been carefully defined only relatively recently, the “true occurrence rate” of anaphylaxis remains uncertain. Also since the symptoms of anaphylaxis mimic those of other conditions, anaphylaxis is felt to be underdiagnosed and/or underreported [12]. A recent review of available epidemiological data estimated the incidence of anaphylaxis to be approximately 50 to 2000 episodes per 100,000 persons, with a lifetime prevalence of 0.05 to 2% [13]. Of great concern, 600-800 deaths each year in the United

*Address correspondence to this author at the Department of Pathology and Molecular Medicine, Centre for Gene Therapeutics, MDCL 4013, McMaster University, 1200 Main Street West, Hamilton, Ontario, L8N 3Z5, Canada; Tel: 905-525-9140 (x22473); Fax: 905-522-6750; E-mail: jordanam@mcmaster.ca

Anaphylaxis is likely when any one criterion is fulfilled	
Criterion 1	Acute onset of an illness (minutes to several hours) with involvement of the skin and/or mucosal tissue (eg. generalized hives, pruritus, or flushing, swollen lips/tongue/uvula) and at least <u>one</u> of the following: ▪ Respiratory compromise (eg. dyspnea, wheeze/bronchospasm, stridor, reduced PEF, hypoxemia) ▪ Reduced BP or associated symptoms of end-organ dysfunction (eg. hypotonia [collapse], syncope, incontinence)
Criterion 2	Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours): ▪ Involvement of the skin/mucosal tissue (eg, generalized hives, itch/flush, swollen lips/tongue/uvula) ▪ Respiratory compromise (eg, dyspnea, wheeze/bronchospasm, stridor, reduced PEF, hypoxemia) ▪ Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence) ▪ Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
Criterion 3	Hypotension after exposure to a known allergen for that patient (minutes to several hours): ▪ Infants and children: systolic BP <70 mm from 1 month to 1 year, [$<70 \text{ mm} + (2 \times \text{age})$] from 1 to 10 years and <90 mm from 11 to 17 years. ▪ Adults: systolic BP <90 mm or greater than 30% decrease from that person's baseline BP.
A less common presentation includes sudden isolated hypotension without a known allergen exposure. Additional signs and symptoms that may occur during anaphylaxis are provided in Table 1. PEF: peak expiratory flow; BP: blood pressure Adapted from Sampson et al [1].	

Box 1. Clinical criteria for the diagnosis of anaphylaxis.

States are attributed to anaphylaxis [14, 15], the majority of which may be potentially preventable.

Pathogenesis

When originally described in 1902 [16], understanding of the events occurring between allergen contact and the manifestation of anaphylaxis was enigmatic. In recent years, studies in animal models have provided important insights into the underlying molecular mechanisms of anaphylaxis [17, 18]. It appears that both immunological and nonimmunological mechanisms are involved. The distinction between these basic mechanisms does not affect the clinical diagnosis and acute treatment of anaphylaxis, but it may be extremely relevant for long-term risk reducing measures.

A critical, and perhaps the most rigorously investigated, immunological mechanism involves the immunoglobulin E (IgE)/FcεRI pathway. IgE is synthesized in response to allergen exposure and binds to FcεRI, a receptor on the surface membrane of mast cells and basophils. Aggregation of receptor-bound IgE molecules on re-exposure to the allergen results in cell activation, mediator release, and the immediate hypersensitivity response. IgE may also contribute to anaphylaxis through mechanisms other than priming and activation; for example, it enhances expression of FcεRI on mast

cells and basophils [19, 20]. This may sensitize target cells with larger numbers of IgE molecules increasing cross-linking of FcεRI and, thus, responsiveness.

In addition to FcεRI, receptors such as G protein-coupled receptors [21, 22] and Toll-like receptors [23] have also been implicated in anaphylaxis. Additional immunological factors thought to be involved in anaphylaxis include immune aggregates, IgG, IgM and platelets; a shift in eicosanoid metabolism toward leukotriene formation; neuropeptidase release (substance P) and activation of the complement (C5a and C3a) or coagulation systems [24, 25]. However, the precise mechanisms by which these products may participate in the anaphylactic reaction remain to be largely elucidated. It is highly probable that more than one mechanism is involved in a given event [26]. In addition, in idiopathic anaphylaxis, FcεRI receptors may be aggregated through autoimmune mechanisms (i.e. presence of anti-IgE autoantibodies). Particularly, anti-IgE autoantibodies may act on mast cells to crosslink the FcεRI or IgE bound to this Fc receptor. Furthermore, an imbalance between histamine-releasing factors and histamine-releasing inhibitory factors, and a greater number of activated T and B cells have also been proposed as potential contributory mechanisms [27, 28]. However, there is poor evidence and understanding of the role of these

in the pathogenesis of idiopathic anaphylaxis. Nonimmunologic factors that can activate mast cells by mechanisms not yet fully understood include exercise, cold air or water exposure, radiation, ethanol, insect venom constituents, radiocontrast media, and medications such as COX-1 inhibitors, opioids and vancomycin [24].

Whether the triggering mechanisms are immunological or nonimmunological, mast cells and, likely, basophils play a central role in initiating and amplifying the acute allergic response. Once activated, the mast cell response is regulated by a balance of positive and negative intracellular molecular events involving Fc receptors and cell-associated tyrosine kinases and phosphatases. The role of these receptors as well as their potential as therapeutic targets has been comprehensively reviewed [29-31]. Differential activation of intracellular signals results in the release of several mediators, including vasoactive amines (e.g., histamine and serotonin), proteases such as tryptase, mast cell carboxypeptidase A3 and chymase, lipid-derived mediators such as platelet-activating factor (PAF), prostaglandins (PGD₂), and leukotrienes (LTC₄), as well as chemokines and cytokines. These mediators act on target cells to increase smooth muscle contraction, mucin secretion, vascular permeability and vasodilation, resulting in the cardinal clinical features of anaphylaxis including laryngeal edema, airway obstruction, hypotension, tachycardia, vascular leakage and hypothermia [24, 25]. Importantly, the extent of mediator release is thought to closely correlate with the severity and persistence of the anaphylactic reaction [24]. However, further basic and clinical research is needed to uncover the relative and specific contribution of individual mediators to the severity of the reaction. Clearly, this would be of great therapeutic utility.

While we now appreciate the role of IgE, Fc receptors and regulatory pathways upstream and downstream of IgE, we are not much further ahead than a century ago in uncovering the mediators and specific pathways that distinctively lead to anaphylaxis. Indeed, the basic processes involved in triggering mediator release from mast cells and basophils do not distinguish anaphylaxis from other allergic responses such as sneezing, itchy eyes or wheezing. A better understanding of the distinct mechanisms leading to anaphylaxis is evidently needed.

Clinical Presentation

Clinical Features

Anaphylaxis often affects several organ systems. Symptoms include, but are not limited to, pruritus, flushing, urticaria, angioedema, dyspnea (bronchospasm or upper airway swelling), gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea and abdominal cramps), syncope and hypotension (Table 1) [3]. Persistent gastrointestinal symptoms and/or hypotension have been associated with severe outcomes [5, 8]. Notably, markedly increased vascular permeability, a hallmark of anaphylaxis, may allow the transfer of 50% of the intravascular fluid into the extravascular space within 10 minutes in the absence of cutaneous or respiratory manifestations, hence leading to rapid hemodynamic collapse [32, 33]. Other determinants of severe outcomes will be discussed later. A number of differences have been documented be-

Table 1. Clinical Features of Anaphylaxis

Organ System	Signs and Symptoms
Skin/mucosal tissue	Urticaria, hives, angioedema, pruritus, flushing, morbilliform rash, swelling of lips, tongue or palate
Respiratory	Upper airway – sneezing, rhinorrhea, stridor Lower airway – cough, wheeze, dyspnea, chest cough, cyanosis
Cardiovascular	Tachycardia, arrhythmia, syncope, hypotension, shock
Gastrointestinal	Metallic taste in the mouth, nausea, vomiting, trouble swallowing, abdominal cramps, diarrhea
Neurologic	Anxiety, headache, seizure, syncope, loss of consciousness
Ocular	Pruritus, conjunctival injection, lacrimation
Hypotension	Systolic blood pressure < 100 mm Hg

tween children and adults. Anaphylaxis is most frequently caused by injected drugs and insects venom in adults. In contrast, foods are the most common triggers in children, likely due to the greater prevalence of food allergies in this age group [34]. Interestingly, although allergic reactions are more common in children, adults experience anaphylaxis more often [4]. Regarding the clinical expression, children often experience respiratory symptoms, whereas adults frequently have cardiovascular compromise [8]; the reasons for this are uncertain but a higher frequency of co-morbid conditions in adults may be a significant contributory factor.

Differential Diagnosis

Many signs and symptoms of anaphylaxis overlap with other diseases and conditions [35]; examples are provided in Table 2. Cutaneous manifestations may be a result of acute or chronic urticaria while respiratory symptoms are seen in asthma exacerbations, foreign body aspiration (especially in children) or vocal cord dysfunction. Other conditions to rule out include acute anxiety (e.g., panic attack or hyperventilation syndrome), myocardial dysfunction, pulmonary embolism, systemic mast cell disorders, food poisoning (in particular from scombroid fish), hypoglycaemia and seizure disorder [36]. A diagnosis of anaphylaxis should be considered in any patient presenting with unexplained syncope or shock.

Symptom Evolution and Biphasic Reactions

The onset of symptoms of anaphylaxis after exposure ranges from within seconds to a few hours, but the majority of reactions manifest within 1h of exposure to the causal allergen [37]. In general, the longer it takes for anaphylactic symptoms to develop, the less severe the overall reaction. Reactions to ingested allergens have a slower onset than in-

Table 2. Differential Diagnosis of Anaphylaxis

Presentation	Differential Diagnosis
Cutaneous symptoms	Acute generalized urticaria and/or angioedema
Hypotension	- Shock: septic, cardiogenic, hypovolemic - Vasovagal reaction
Respiratory distress with wheezing or stridor	- Airway foreign body - Asthma and COPD exacerbation - Bronchiolitis - Laryngospasm - Vocal chord dysfunction syndrome - Asphyxiation/suffocation
Postprandial collapse	- Airway foreign body - Monosodium glutamate, saurine or sulfite ingestion - Scombroid fish poisoning
Flush syndrome	- Carcinoid syndrome - Postmenopausal hot flushes - Red man syndrome [infusion of vancomycin] - Medullary carcinoma of the thyroid - Tumor secreting VIP or substance P
Miscellaneous	- Panic attacks - Increased intracranial pressure - Systemic mastocytosis - Leukemia with excess histamine production

COPD, chronic obstructive pulmonary disease; VIP, vasoactive intestinal peptide
Modified from Tang, AW [35].

jected allergens. In fact, while fatal reactions due to foods can occur within 25-35 min of ingestion, the median time interval for fatal anaphylaxis to injected drugs and insect venom ranges from 5 to 12 min [34]. A particular concern is that once initial symptoms have resolved, some patients may later experience a second phase of symptoms [38-40]. The occurrence of biphasic reactions has been reported to vary between 3 and 20% (Table 3). The interval between the initial and the second reaction is highly variable, from 1 to 78 h, although the majority occur within 8 h of the initial presentation. The severity of these secondary reactions is also highly variable, being either more or less severe than the initial reaction [41]. Currently, there is no consensus on what features of the primary response might predict the occurrence of a secondary reaction. However, it is thought that the severity of the initial reaction, the delayed onset of symptoms, the presence of hypotension or laryngeal edema, a history of a previous biphasic reaction and, most importantly,

delayed administration, inadequate dosing, or need for large doses of epinephrine may be risk factors for a secondary reaction [41-44]. Additionally, there is no agreement on the optimal observation time following the initial reaction. In this regard, the NIAID/FAAN Symposium recommended that observation periods be individualized according to the severity of the initial reaction, reliability of the patient and access to care [1]. For patients whose initial reaction is less severe, four to six hours of observation is reasonable, but extended observation times or hospital admission is advisable for patients with severe or refractory symptoms. Patients with asthma might also need extended care as most fatalities occur in this group of patients.

Risk Factors for Anaphylaxis

A detailed clinical history of any patient experiencing anaphylaxis is a crucial step in the determination of future anaphylactic reactions. Individuals with a history of anaphylaxis are at increased risk of a subsequent episode [11, 45, 46]. Similarly, it is thought that severe past reactions predispose to future severe reactions [47]. In contrast, there is evidence that children with mild reactions may suffer severe reactions later on [48]. A history of asthma is considered a major risk factor for life-threatening anaphylactic reactions to food [11, 37, 46, 49, 50]. Even though life-threatening anaphylaxis has been reported in children without asthma most fatal cases of anaphylaxis occur in patients with asthma [10, 34, 51]. Thus, a history of previous anaphylactic reactions or coexistent asthma can identify food-allergic individuals at higher risk of severe anaphylaxis.

A number of factors may increase, not necessarily the risk of anaphylaxis, but the severity of anaphylaxis or the efficacy of epinephrine. These include the use of aspirin, β -blockers, angiotensin converting enzyme inhibitors, monoamine oxidase inhibitors, tricyclic antidepressants and concurrent infection [34, 52]. Therefore, patients at high risk for anaphylaxis should, when possible, avoid these drugs.

FOOD ALLERGY

Food allergy is the most frequent cause of outpatient anaphylaxis [7, 37, 53, 54]. Despite the severity of the reactions that they elicit and the apparently rising prevalence over the past decades, the epidemiology of food allergies remains uncertain [4, 12, 55, 56]. This is likely due to the lack of standardized population-based methodologies that incorporate the gold-standard diagnostic method, a double-blind, placebo-controlled oral challenge. Recently, a meta-analysis of 51 studies examining the prevalence of food allergy, particularly to milk, egg, peanut and seafood showed a wide variation in prevalence estimates [57]. For instance, the prevalence of self-reported allergy to any food ranged from 3 to 35%. This variation likely reflects the shortcomings of self-reporting, dissimilar definitions of food allergy and true population heterogeneity. Similarly, approaches such as specific IgE levels and/or positive skin prick test (SPT) or self-reported food allergy along with specific IgE levels or positive SPT also showed broad ranges in prevalence. It is noteworthy that specific IgE levels and/or SPT cutoff values might not accurately predict clinical reactivity. Studies based on oral food challenges were few in this meta-analysis, but

Table 3. Biphasic Reactions

Study	No. of Patients with Biphasic Reactions/ Total No. of Patients	Frequency of Biphasic Reactions (%)	Time from Initial to Biphasic Reaction (h)
Brady <i>et al.</i> [38]	2/67	3	26-40
Brazil and MacNamara [39]	6/34	18	4.5-29.5
Ellis and Day [40]	20/103	19	2-38
Lee and Greenes [43]	6/105	6	1.3-28.4
Smit <i>et al.</i> [44]	15/282	5	1-23
Douglas <i>et al.</i> [99]	6/13	6	1-72
Stark and Suvillan [100]	5/25	20	1-8

Adapted from Lieberman, P [41].

prevalence estimates from 6 such studies that evaluated allergy to “any food” ranged from 1% to 10.8%, with a random-effects model showing a prevalence of ~3.5% [57]. The range of prevalence could reflect genuine variation between populations but it may have been influenced as well by differences in study design and/or methodology.

The prevalence of food allergy is greatest in the first 2 years of life and declines with age [58]. The most common food allergens causing reactions in children include milk, egg, wheat, soy peanuts, tree nuts, fish and shellfish [7, 49, 59, 60]. Milk and egg allergies are typically considered transient as they are thought to resolve by age 3 to 5 years. However, recent reports have prompted a reconsideration of this view. A retrospective chart review of 807 patients by Skripak *et al.* revealed that milk allergy resolved in 19% of patients by age 4, 42% by age 8, 64% by age 12, and 79% by age 16 [61]. A similar study that included 881 patients with egg allergy showed that resolution rates were 4% by age 4, 12% by age 6, 37% by age 10, and 68% by age 16 [62]. The latter study also reported that individuals with concomitant atopic diseases and higher levels of antigen-specific IgE were less likely to achieve tolerance to these foods. While the majority of children became tolerant, this relatively recent recognition that the acquisition of tolerance may be slow is disturbing. It is relevant to mention that both studies were carried out by the same center (Johns Hopkins University, Baltimore, MD). While the results may partly reflect a selection bias, they clearly underscore the need for continued attention and monitoring of egg and milk allergies well into the teenage years.

Peanut allergy often has an early onset but is typically life-long. Reports indicate that peanut allergy resolves in only ~20% of children by school age [63, 64]. A study on the natural history of peanut allergy in 35 subjects showed 25 with early onset at a median age of 3, and 10 with late onset, at a median age of 25 years with previous tolerance to peanut [65]. Patients with late onset had lower serum peanut-specific IgE levels than those with early onset. While anecdotal, the case of a 53-year-old subject with late-onset peanut allergy warrants attention because she had routinely tolerated peanut but had been instructed to avoid it after a positive

skin test response was detected. Three years after strict avoidance, a food challenge elicited lower airway symptoms, suggesting that *unnecessary* avoidance might have resulted in loss of tolerance.

Epidemiological studies suggest that environmental (i.e. diet, frequency and/or onset of food consumption, etc) and genetic factors might influence the epidemiology of food allergies [66-69]. There is geographic variability in the prevalence of food allergies across the globe. For instance, peanut, tree nut and shellfish allergies are common in North America and the United Kingdom [7, 49, 60, 70-72]. Seafood and royal jelly allergies are very frequent in Hong Kong [44], as is mustard allergy in France [67] and sesame allergy in Israel [73].

FOOD-RELATED ANAPHYLAXIS

Food allergic reactions are the leading cause of anaphylactic reactions treated in emergency departments (ED) [4, 37, 44]. They account for one-third to one-half of anaphylaxis cases in ED in North America, Europe, Asia and Australia. Estimates suggest that approximately 30000 food-related anaphylactic reactions are treated in US ED resulting in ~2000 hospitalizations and ~150 deaths [37, 56]. In the paediatric population, food reactions are responsible for a large proportion of anaphylaxis cases [74, 75]. In Lee and Greenes's report of 108 anaphylaxis episodes in children, almost half (n=51) were caused by food allergens; of these, 27% involved tree nuts, 24% peanuts, and 16% were due to seafood [43]. Other types of foods included fruit, eggs, and seeds.

Fatalities in FIA occur in <1% of cases; however, it has been described with first episodes. A study of 202 cases of fatal anaphylaxis in the United Kingdom reported that food allergens accounted for up to 30%, over half associated with nuts [76]. A US study of 32 patients with fatal anaphylaxis showed that peanuts and tree nuts were responsible for 94% of these fatalities, the majority involving adolescent and young adults [49]. Recent case series in the US [59] and the UK [71] indicated that 78% (25/32) and 38% (18/48) of fatal cases were caused by peanut and tree nuts, respectively. These case series also revealed that milk is an important cul-

prits, responsible for 10% of the deaths attributed to FIA. Consistent findings from most of these reports are that fatalities are associated with untimely use of epinephrine, co-existing asthma, and being a teenager/young adult. Distressingly, numerous studies in the US and Europe concur that most individuals who experienced food-related fatalities were aware of their food allergies and/or had a prior history of a reaction to the triggering food [49, 60, 77]. In this regard, accidental ingestion of the culprit food is not uncommon. For example, a study by Vander Leek *et al.* [48] reported that 58% (31/53) of children with peanut hypersensitivity experienced adverse reactions from accidental peanut exposure during a 5-year study period. In addition, Yu *et al.* [72] reported an annual incidence rate of accidental ingestion of 14.3% among schoolchildren in Montréal, Canada.

Diagnostic Tests for Food-Induced Anaphylaxis

A significant challenge in FIA is the lack of a readily available laboratory test to support the clinical diagnosis. It was initially thought that the measurement of mast cell-derived mediators, such as histamine and tryptase, would provide confirmatory evidence of an anaphylactic episode, including anaphylactic reactions triggered by food. In fact, Lin *et al.* [78] reported that increased levels of histamine (>10 nmol/L) correlated, to a great extent, with clinical signs (such as urticaria, extensive erythema, abdominal symptoms, and wheezing) of acute allergic reactions. Nonetheless, elevated levels of histamine were observed in less than 50% of the overall population (97 patients). Plasma histamine levels typically peak within 5 to 10 minutes from the onset of anaphylactic symptoms and, then, decline to baseline within 60 minutes as a result of rapid metabolism by N-methyltransferase and diamine oxidase [79]. This may limit the value of the test in many clinical circumstances as histamine levels may have returned to baseline by the time the patient arrives to the ED.

Similarly, there are concerns regarding the reliability and usefulness of tryptase measurements as evaluation of serum tryptase levels has both low sensitivity and specificity. For instance, Lin *et al.* [78] reported raised levels (>15 ng/mL) in only 20 of 97 patients with acute allergic reactions. Of particular importance, elevations in total tryptase are not commonly detected in individuals with FIA [10] or in those with positive food challenge tests [80]. A possible explanation for this finding is that in some individuals – for example, those whose primary symptom is laryngeal edema – localized rather than generalized mast cell degranulation may predominate, and, hence, the amount of tryptase entering the circulation may be insufficient to raise levels in serum.

It is evident that sensitive and specific biomarkers of anaphylaxis are needed, especially in cases where medical history is not available or symptoms are atypical. New proteomic and/or metabolomic approaches might prove valuable in identifying relevant biomarkers. Given the often fulminant nature of this disease, these biomarkers are unlikely to be useful to guide immediate interventions; yet, they may assist in the identification of patients at risk of persistent or late phase reactions. Recently, the usefulness of mediators such as carboxypeptidase A3 and PAF to support the diagnosis of anaphylaxis has been explored [79]. Of particular interest, a

study by Vadas *et al.* [81] highlighted PAF as a potential biomarker of anaphylaxis triggered by foods, medications and insect stings. They observed that circulating PAF levels were significantly greater among patients with anaphylactic reactions (n=41) than in control individuals (n=23) and correlated with the severity of the reaction. In fact, the proportion of subjects with elevated levels increased from 4% in the control group to 20% in the group with grade 1 (acute allergic reaction with cutaneous manifestations but no other organ system involvement) reactions, 71% in individuals with grade 2 (systolic blood pressure, >90 mm Hg; respiratory rate, <25 breaths per minute; and a normal score on the Glasgow Coma Scale) reactions, and 100% in patients with grade 3 (severe manifestations, with cutaneous, gastrointestinal, and potentially life-threatening respiratory or cardiovascular signs and symptoms) reactions.

The analysis of other biomarkers including leukotrienes may also be of value in the diagnosis of anaphylaxis. Recent data from our laboratory using a mouse model of peanut-induced anaphylaxis show that leukotrienes gradually increased following anaphylactic shock and remained elevated for a considerable period of time (manuscript under revision). Importantly, the presence of urinary leukotrienes and their metabolites, particularly leukotriene E4 and N-acetyl leukotriene E4, has been previously reported in patients for up to 11 days following recovery from anaphylaxis [82].

Management of Food-Induced Anaphylaxis

The available evidence for the recommended management of anaphylaxis is limited. This is due, at least in part, to the ethical and practical difficulties inherent in performing randomized clinical trials in medical emergencies. While adrenaline remains the mainstay of treatment, there is no clear worldwide agreement on the use and role of other commonly used first-line approaches and agents [83, 84]. Algorithms outlining key steps for the acute management of anaphylaxis have been published elsewhere [3, 85], and a summary of the most frequently recommended guidelines are provided below. It should be noted that these recommendations are also pertinent to the acute management of FIA.

Acute Management

Adrenaline

Patients fulfilling any of the 3 criteria for anaphylaxis outlined in Box 1 should receive adrenaline immediately. There are patients who present with symptoms not fulfilling these criteria, but in whom it would be appropriate to initiate therapy with epinephrine. For example, a patient with a history of anaphylaxis to peanut who suspects exposure to peanut and experiences urticaria and generalized flushing within minutes.

The α_1 -adrenergic effects of adrenaline increase peripheral vascular resistance, blood pressure and coronary artery perfusion, while reducing angioedema and urticaria [86]. The β_1 -adrenergic effects increase heart rate and contraction, whereas the β_2 -adrenergic effects mediate bronchodilation and reduce the release of inflammatory mediators [86].

No trials have been performed in humans to determine the optimal dosage of adrenaline; however, epinephrine [1

mg/ml] at a dose of 0.01 ml/kg body weight (maximum single dose 0.5 mg) is the recommended dosage for controlling symptoms and maintaining blood pressure [87]. This equates to 10 µg of adrenaline per kg body weight. This dosage can be repeated at short intervals (every 5–10 min) until the patient's condition stabilizes. A shorter interval between injections might be used if deemed necessary by the physician. Studies in children [88] and adults [89] *not* experiencing anaphylaxis have demonstrated that intramuscular injection leads to more rapid absorption and higher plasma concentrations than the subcutaneous route. In particular, peak plasma concentrations were attained more quickly following intramuscular injection into the mid-point of the anterolateral thigh (the bottom right of the right trouser pocket). In addition, these studies showed comparable results using both an ampule of epinephrine and a spring-loaded (e.g. EpiPen [Dey, Napa, Calif]) automatic epinephrine device. Currently, adult autoinjectors contain 300 µg of adrenaline, and junior/paediatric versions 150 µg. An adult autoinjector is recommended for children weighing >30 Kg [86]. The main limitations of currently available adrenaline autoinjectors include restricted range of premeasured doses, needle lengths and high cost. It should be noted that studies regarding the optimal route of administration have not been performed in patients experiencing anaphylaxis.

Intravenous epinephrine should be considered for patients with severe hypotension or cardiac arrest unresponsive to intramuscular doses of epinephrine and fluid resuscitation [90, 91]. There is no precise dosage for intravenous epinephrine in anaphylaxis; however, doses of 5 to 10 µg (0.2 µg/Kg) for hypotension and 0.1 to 0.5 mg for cardiovascular collapse have been suggested [92].

Adrenaline has a relatively narrow therapeutic window (benefit/risk ratio) which should be considered when planning treatment. Administration of adrenaline carries risks, including myocardial ischaemia and cardiac dysrhythmias; however, anaphylaxis itself can cause these problems. Since the potential for lethal arrhythmias following i.v. delivery of epinephrine exist, continuous cardiac monitoring is recommended.

Oxygen and Adrenergic Agonists

High-flow oxygen *via* a nonrebreathing mask or endotracheal tube should be administered to any patient experiencing respiratory symptoms, hypoxemia or hypotension associated with anaphylaxis [1, 3, 93]. Inhaled β_2 -agonists *via* a spacer device or nebulizer are a useful adjunct to treat associated airflow obstruction; however, drug delivery may be compromised by acute bronchospasm. At any rate, systemic adrenaline must still be considered the first line of therapy.

Fluid Resuscitation

Anaphylaxis often causes tachycardia and decreased arterial blood pressure. Patients who remain hypotensive despite epinephrine should receive fluid support [94]. A crystalloid solution or a colloid expander can be used, starting with a volume of 20 ml/Kg over 10–20 min. This can be repeated; however, the volume given must be tailored to the clinical situation; persistent hypotension may require an aggressive

approach with multiple fluid boluses including colloid, as well as crystalloid, whereas a largely respiratory reaction or one that responds promptly to initial treatment require less aggressive fluid management.

Vasopressors

Potent vasopressors such as noradrenaline, vasopressin or metaraminol might be required to overcome vasodilation if epinephrine and fluid resuscitation have failed to maintain a systolic blood pressure of greater than 90 mm Hg [90].

H₁- and H₂-Antihistamines

Most protocols recommend the use of antihistamines; however, evidence for their efficacy in anaphylaxis is weak [95]. They have a slow onset of action (1–2 h) and little effect on blood pressure and, thus, should be viewed as second-line treatment. Antihistamines are particularly useful for the treatment of associated urticaria-angioedema and pruritus. In these instances, treatment with a combination of H₁- and H₂-antagonists has been shown to be more effective in attenuating the cutaneous manifestations of anaphylaxis than treatment with H₁-antagonists alone [78, 96]. The ideal antihistamine should be in liquid form, rapid-in-onset, nonsedating and long-lasting. Diphenhydramine, administered intravenously or intramuscularly (or orally for mild symptoms), can be given at a dose of 25 to 50 mg for adults and 1 mg/kg (up to 50 mg) for children. Ranitidine and cimetidine have been most studied, but no controlled studies have demonstrated superiority of one H₂-antagonist over another.

Corticosteroids

The effectiveness of corticosteroids in anaphylaxis has never been determined in placebo-controlled trials. The action of corticosteroids requires *de-novo* protein synthesis. Thus, their biological activity is delayed by at least some hours and they are of no immediate benefit. It has been suggested that corticosteroids may be beneficial in preventing or ameliorating biphasic or protracted anaphylactic reactions. However, the evidence for this is weak. In some instances, failure to administer corticosteroids appeared to predispose patients to such a response [97], but this was not confirmed in other reports [98]. If given, the dosing of intravenous corticosteroids should be equivalent to 1 to 2 mg/kg per dose of methylprednisolone every 6 hours. Oral administration of prednisone, 1 mg/kg, up to 50 mg might be sufficient for milder reactions.

It is important to emphasize that a rigorous evaluation of most of the therapeutic measures and medications currently used is needed. To this end, systematic reviews of commonly utilized drugs are being conducted to document the existing evidence. It is noteworthy that the therapeutic strategies suggested by the NIAID/FAAN Symposium are largely based on "clinical experience and expert opinion". There is a virtually complete agreement that epinephrine should be the initial treatment of choice for acute anaphylaxis; yet, there are limited data on the appropriate dose, timing or frequency of administration. Similarly, there are practically no studies investigating either the functional role or effectiveness of H₁- and H₂-antihistamines as well as corticosteroids in the treatment of anaphylaxis. Prospective randomized controlled

multicenter trials to establish the appropriate dosing of these medications and the role of other therapeutic interventions, such as the optimal type and rate of fluid replacement, and the use of vasopressors, glucagon and nebulized albuterol or epinephrine are also desirable. Randomized controlled trials of any pharmacological intervention would be difficult to conduct in individuals in the ED as no baseline measurements would be available, symptoms and signs of anaphylaxis might be resolving as a result of first aid treatment, and patients may be too unstable for randomization. Nevertheless, such studies might be feasible in well equipped healthcare settings with appropriately trained personnel in which anaphylaxis can be elicited and readily controlled – for example, in selected patients undergoing a physician supervised controlled food challenge as part of their anaphylaxis risk assessment.

Long-Term Management

Emergency treatment must be followed by outpatient follow-up and a long-term management plan to prevent recurrences and help patients manage potential future reactions. The key elements of a long-term management plans should include education, a prescription for self-injectable epinephrine, and referral to an allergy specialist (Box 2). Importantly, the effectiveness and cost-effectiveness of management plans need to be formally evaluated [84, 99].

Education ▪ Instructions for food allergen avoidance ▪ Written emergency action plan ▪ Education resources
Prescription of self-injectable epinephrine ▪ Training for proper use ▪ Emphasis on carrying in-date autoinjector ▪ Encouragement for prescription refill
Referral to an allergist specialist ▪ Thorough evaluation ▪ Specialized follow-up care ▪ Intensive education on food allergic reactions

Box 2. Long-term management of food-induced anaphylaxis.

Education

Education should include instructions for relevant food allergen avoidance, a written emergency action plan, and a list of educational resources. Additional information on food labelling, approaches to restaurants and food service, and management of anaphylaxis of children in schools and other settings is critical to prevent reactions in food allergic individuals [100]. The importance of a thorough knowledge of all food ingredients before consumption cannot be overemphasized. Studies have shown that the majority of fatal reactions occurred in individuals who were aware of their al-

lergy, but felt that they were eating something safe. [34]. New food labelling laws in North America [101], requiring less complicated terminology, should facilitate food allergen awareness and avoidance. Patient educational resources (e.g. www.foodallergyalliance.org or www.foodallergens.info) are also recommended for better management of food allergy.

Prescription of Self-Injectable Epinephrine

Despite these measures, accidental exposure to food allergens still occurs [72]. Therefore, individuals with a known food allergy should be prescribed self-injectable epinephrine. The importance of carrying autoinjectors permanently is supported by a US report on fatal cases where ~ 90% of patients did not have epinephrine available at the time of the reaction [59]. Since retrospective studies indicate that 16 to 35% of reactions require a second dose of epinephrine [102, 103], carrying multiple doses is advisable. In addition to providing the prescription, it is imperative to instruct patients and their families on its proper use, reinforce the importance of carrying an up-to-date autoinjector at all times and encourage patients to refill the prescriptions. For instance, a study by Sicherer *et al.* showed that 86% of parents of food allergic children reported carrying self-injectable epinephrine at *all times*; however, only 71% had the device during the study visit, and, significantly only one-third were able to correctly demonstrate its use [104]. Of note, the same study reported that less than half of general paediatricians were knowledgeable on the use of the self-injectable epinephrine [104].

Epinephrine prescriptions should always be accompanied by a written, personalized, and regularly updated anaphylaxis emergency action plan (an example is provided in [2]). Such plan should list the most common symptoms and signs of anaphylaxis and emphasize prompt epinephrine injection, followed by transportation of the individual to the nearest hospital ED.

There are still limitations and concerns regarding self-injectable epinephrine. Autoinjectors are currently available only in 2 fixed doses, 0.15 and 0.3 mg. The recommendation for children with anaphylaxis is 0.01 mg/Kg up to 0.3 mg. Thus, a quandary exists with regard to dosing children who do not weigh approximately 15 Kg (33 lbs [for whom the 0.15 mg-dose is ideal]) or 30 Kg (66 pounds or more [for whom the 0.3 mg-dose is recommended]). This issue, along with some pertinent suggestions, is discussed in a comprehensive report by Sicherer *et al.* [86]. The length of the needle of currently available adrenaline autoinjectors is also a subject of concern, especially in obese or overweight adults, as it may not be long enough to penetrate the fat layer and reach the intramuscular space; this is further compounded in women who have more subcutaneous fat than men [105]. Another concern relates to the fears of patients and/or parents of using needles. This has created another barrier to autoinjector use, and therefore, alternatives to injectable epinephrine are now under investigation. The use of metered dose inhalers has been shown to be suboptimal because of the high number of inhalations required and the unpleasant taste of the drug [106]. More recently, sublingual epinephrine has shown some promising results. In fact, studies in rabbits showed that 40 mg of sublingual epinephrine resulted

in peak plasma concentrations, and time to peak levels, similar to the ones following i.m. administration of 0.34 mg of epinephrine [107].

Furthermore, there is a concern that individuals and caregivers are often reluctant to use self-injectable epinephrine [86]. Potential explanations for this include failure to recognize anaphylaxis, spontaneous recovery from a previous episode, reliance on oral H₁ antihistamines or asthma-relief inhalers and concerns about adverse effects of epinephrine [108].

Referral to an Allergy Specialist

Finally, confirmation of the diagnosis and anaphylaxis management plans must include referral to an allergy specialist. Allergy specialists will demonstrate sensitization to the suspected allergen with skin prick and/or blood tests, and educate patients how to self manage in the community. Comprehensive education should include education on early recognition of signs and symptoms and use of epinephrine autoinjectors.

Compliance with Recommended Management Guidelines

As with many medical conditions, compliance with established management guidelines by both patients and health care personnel is as or more important, than the guidelines themselves. A number of studies have documented that compliance by medical personnel with the emergency management of anaphylaxis remains poor. Low compliance appears to be pervasive as it occurs as much in North America as in Europe.

A 1996 British study in eight patients with severe allergic reactions to known causes reported that none of these patients had been given advice about avoidance of the offending allergen, prescribed self-injectable epinephrine, or referred to an allergy specialist [109]. Similarly, a 1995 US study evaluated 326 patients presenting to the ED with an allergic event; of these, 45 had a food-induced allergic reaction most often to seafood, peanuts, and nuts. None of these patients at discharge was given a prescription for self-injectable epinephrine or referred to an allergy specialist [110]. In 2003, Bellou *et al.* reviewed the charts of 324 patients in France admitted to the ED for an allergic event and found that 31 (9.5%) patients were diagnosed with food allergy. Six (19%) of these patients were observed to have a severe episode of anaphylaxis. Only 42 patients (12.9%) were referred for an allergy consultation after ED discharge [111].

A recent multicenter study conducted by the Emergency Medicine Network reviewed the ED charts of 678 patients who presented with a food-related allergic reaction in 21 North American hospitals [60]. Among this group of patients, 51% were identified as having a severe food-induced acute allergic reaction. Even among these patients, compliance with recommended guidelines for the emergency management of anaphylaxis was extremely low. For example, only 24% of patients with anaphylaxis were treated with epinephrine in the ED. At discharge, only 35% were given instructions to avoid the offending allergen, 22% a prescription for self-injectable epinephrine, and 13% were referred to

an allergy specialist. Only 2% of these severe cases received all three recommended preventive interventions [60].

Given recent estimates that FIA is the leading cause of anaphylactic reactions treated in the ED [54] it is evident that better dissemination and implementation of the consensus guidelines for the short- and long-term management of FIA are urgently needed.

Measures to Improve the Management of Food-Induced Anaphylaxis

The effective implementation of action plans will require education and participation of both ED personnel and patients. A number of initiatives have been proposed to improve short- and long-term management of FIA (Box 3).

Timely and accurate diagnosis ▪ Simulation-based training ▪ Electronic forms with algorithms in ED ▪ Specific and sensitive biomarkers
Patient empowerment ▪ Computerized ED discharge sheets
Medical identification ▪ Alert bracelet or necklace ▪ Folding wallet cards
Protective measures ▪ Sabrina's law ▪ Food Allergy Labeling Consumer Protection Act
Communication between ED personnel and primary care providers ▪ Automatic e-mail notification system
ED, emergency department

Box 3. Measures to improve the management of food-induced anaphylaxis.

1. Timely and Accurate Diagnosis

The evidence discussed above reveals the shortcomings of traditional continuing medical education practices in both the diagnosis and management of patients with anaphylaxis, in the ED and at discharge. Improvements in the management of anaphylaxis might benefit from methods that incorporate simulation-based training. This approach has been proven to significantly improve performance of healthcare professionals in the management of medical crises. In essence, simulation-based training involves highly realistic simulation scenarios requiring complex decision making and interaction with multiple personnel. Scenarios are followed by detailed debriefing sessions. This approach has been applied to a number of situations that involve complexity and dynamism, such as emergency and trauma medicine, intensive care, and cardiac arrest response teams and has been

adopted at major health care institutions around the world [112].

An independent and complementary strategy is the development of an emergency-management algorithm to help healthcare professionals in ED quickly recognize and treat anaphylactic reactions. As Clark *et al.* [113] propose, one approach to facilitate the implementation of this algorithm would be the development of electronic diagnosis and order forms that rapidly assess signs and symptoms if an allergic reaction is suspected, and to initiate treatment. The identification of multi-organ system involvement might be especially useful to recognize severe food-related allergic reactions and anaphylaxis. The aim would be not to create a definition with 100% sensitivity (with an inevitable number of false positives), but rather a definition that identifies most cases. The clinical criteria suggested by the NIAID/FAAN Symposium [1] as well as the severity grading system proposed by Brown *et al.* [5] might be useful in this regard. Since there is evidence that a delay in the initiation of treatment is associated with worse outcomes, the rapid recognition of food-related allergic reactions will not only ensure timely and appropriate treatment but also, particularly in severe episodes, prevent fatalities.

2. Patient Empowerment

Further improvements in patient management would greatly benefit from direct patient involvement. For instance, the distribution of computerized ED discharge sheets has been shown to improve compliance with ED referral recommendations [114] and modify patient behaviour [115]. These computerized discharge sheets could also include contact information from patient advocacy organizations (i.e. the Food Allergy and Anaphylaxis network (US) or Anaphylaxis Canada).

3. Accurate Medical Identification

All individuals at risk for anaphylaxis should be equipped with accurate medical identification listing their confirmed trigger(s) and their relevant comorbidities and medications. One available option includes MedicAlert® identification (i.e. bracelet, necklace, or keychain) [116]. Another approach is to carry folding wallet cards with embedded medical record (an example is provided in [2]). These devices should include personal identification, confirmed triggers, relevant comorbidities, concurrent medications, anaphylaxis symptoms flagging a life-threatening condition and the immediate management plan.

4. Protective Measures

The risk for anaphylactic reactions has been shown to negatively affect quality of life of both patients and their families [117-120]. As most episodes of anaphylaxis occur in the community, measures to ensure prompt and appropriate management of anaphylactic reactions would be exceedingly beneficial. Legislators appear to be receptive toward changing public policy and improving medical services for individuals with anaphylaxis. An inspiring example of such measures is the legislation that recently came into effect in Ontario, Canada, Sabrina's law, requiring school boards to include an anaphylaxis policy that provides training to staff,

plans for dealing with students at risk and emergency plans. In the future, legislations such as "Sabrina's Law" may serve as a model for other communities worldwide. An additional landmark legislation implemented in 2006 includes the National Food Allergy Labeling Consumer Protection Act in the United States, which mandates clear food labelling.

5. Communication Between Emergency Personnel and Primary Care Providers

Lastly, better communication between ED staff and primary care providers could also improve patient care following an ED visit for food-related allergic reactions or anaphylaxis. This might occur through automatic e-mail notification systems, which have been implemented in some hospitals. These e-mail alerts notify the primary care physician about the visit itself, the discharge diagnosis, and the management plan. Primary-care involvement would permit close follow-up and additional referral to specialist and augment the likelihood that self-injectable epinephrine prescriptions are refilled.

CONCLUDING REMARKS

Improving the management of anaphylaxis, in particular food-induced anaphylaxis, to reduce morbidity and mortality faces many challenges. We would propose that these can be aggregated into essentially two: *discovery* and *communication*.

The challenge of *discovery* embodies issues pertaining to diagnosis, prognosis (spectrum of severity) and management, acute as well as long term management. For example, there are no specific biomarkers of anaphylaxis, or its evolution, nor specific indicators that might inform about the risk and/or the severity of potential anaphylactic reactions. With respect to treatment, there are no proven therapeutics to date beyond epinephrine. There may not be better treatments than epinephrine for the acute and severe presentation of anaphylaxis. However, there is a need for therapies that could ameliorate the evolution of anaphylaxis or abort recurrent or protracted reactions. From a broader perspective, it may be argued that the greatest challenge might be the development of therapeutics, for food allergic patients, that could either prevent anaphylaxis or, at least, substantially limit the risk of severe reactions. Otherwise, patients will remain unprotected. This goal will only be achieved through a major commitment to research of the basic mechanisms underlying food allergy and, particularly, anaphylaxis.

The challenge of *communication* has been made, we believe, explicit in this review and is supported by extensive primary data. Even an improved pharmacological armamentarium may fail unless decisive efforts are implemented to substantially improve communication among all the participants involved in the process. The closest individual to the anaphylactic reaction is the patient itself. Unique to anaphylaxis is that patients live in an environment with abundant risks that can precipitate fulminant reactions. It thus seems intuitive that empowering patients and their families with knowledge about the disease, its risks, triggers and therapeutic tools is a direction that might yield obvious benefit. This will demand a much finer effort to institute effective multi-lateral communication among patients, families, emergency

and family physicians, allergists, specialized volunteer organizations, and the community at large. Paraphrasing Winston Churchill, *we should always trust the system, to do the right thing, once all the other possibilities have been exhausted*. The evidence of what has gone wrong is widely available.

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