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Fatal Anaphylaxis: Epidemiology and Risk Factors

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Abstract

Purpose of Review To provide clinicians with an understanding of risk factors associated with fatal anaphylaxis, and to promote individualized management plans with patients based upon key aspects of their clinical history.

Recent Findings While anaphylaxis can affect a significant percentage of the general population, death from anaphylaxis remains a rare outcome. The presence of asthma and peanut or tree nut allergy is associated with higher risk for severe or fatal anaphylaxis from foods. Specific triggers (medications, venom), underlying comorbid conditions, age, and use of some medications can also impact risk and warrant different counseling and management strategies.

Summary Anaphylaxis is a rapidly progressive systemic reaction with multiple different causes and encompasses a wide degree of severity in clinical presentation and risk for future episodes. Individualized management, discussion of risk, and shared decision making should occur with each patient and in consideration of their personal risk factors.

Keywords Anaphylaxis · Food allergy · Drug allergy · Venom allergy · Epinephrine · Shared decision making

Introduction

Patients with food, medication, and venom allergy live with the knowledge that they are at risk to experience anaphylaxis if they encounter their trigger at any time. This can negatively impact quality of life and impact their decision making. Their greatest fear is often death caused by their next allergic reaction. However, fatalities from anaphylaxis are rare, even among patients with prior history of anaphylaxis. As such, a patient's perceived risk of death from anaphylaxis is often discordant with their actual risk. Despite a lack of any biomarker or diagnostic test capable of reliably determining an individual's risk for future fatal anaphylaxis, the understanding of risk factors associated with fatalities has evolved in recent years. These risk factors need to be considered for each patient to allow for individualized counseling and management to occur. This review will highlight the current knowledge state regarding overall risk factors as well as variations related to food, medication, and venom allergies. Ideally, this information can be applied to clinical encounters in the form of anticipatory guidance and shared decision making.

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Diagnosis and Severity

Anaphylaxis is a sudden onset, potentially life-threatening condition that progresses rapidly and can affect many different organ systems. The consensus broad definition of anaphylaxis is "a serious allergic reaction that can lead to death", confirmed by the International Consensus on Anaphylaxis [1••, 2]. Anaphylaxis can be caused by many types of allergic triggers, or in some circumstances, without identifiable cause. The main effects at end organs are due to release of histamine and other mediators from tissue-based mast cells and circulating basophils, often in response to specific antigen triggers that cause Immunoglobulin E (IgE) cross-linking [3]. Diagnosis of anaphylaxis is based on clinical symptoms and descriptions of the acute event; anaphylaxis is a clinical diagnosis that requires adequate suspicion and prompt recognition. The presentation of anaphylaxis is variable, ranging in severity and symptomology but can include cutaneous, respiratory, gastrointestinal, neurological, and vascular symptoms (Fig. 1).

Diagnostic criteria have been established to assist in recognizing anaphylaxis. The first criterion relies upon the rapid onset of cutaneous or mucosal symptoms with respiratory compromise or signs of reduced blood pressure. The second criterion includes a combination of symptoms after likely exposure to an allergen. The final criterion involves the rapid onset of low blood pressure after known exposure to a known allergen. In addition to the variety of symptoms that may be present in anaphylaxis, the severity of anaphylaxis can vary widely (Table 1) [1••]. Currently, there are no biomarkers to predict severe anaphylaxis, although some have suggested the use of the basophil activation test. However, this finding has not been validated and as of this writing, the basophil activation test is not available clinically [4].

Epidemiology

Death is the most feared complication of anaphylaxis. Even though anaphylaxis is a relatively common event, affecting up to 5% of US citizens, fatal anaphylaxis is fortunately quite rare, with a mortality rate less than 1 death per million inhabitants per year [5–7]. For instance, in the USA, there are an estimated 220 fatalities from anaphylaxis each year [8]. Registries have shown a 2:1 male predominance in fatal anaphylaxis, which mirrors the generally increased risk for atopy among males [9]. Historically, drugs have been considered the most common cause of fatal anaphylaxis in several countries, including the USA [10]. However, one recent study suggested that food allergy may currently be the leading cause of fatal anaphylaxis [11]. In children and young adults, foods are universally the most common cause of fatal anaphylaxis, albeit still rare [6]. Estimates of anaphylaxis mortality are typically based on retrospective case series, postmortem studies, and population-based studies. Therefore, published rates may be an underrepresentation, as anaphylaxis is not always recognized or properly diagnosed, and registry data are likely incomplete.

Rates of fatal drug anaphylaxis may be increasing [7, 12, 13]. However, other types of fatal anaphylaxis such as food and venom do not appear to be increasing, even as the rates of non-fatal anaphylaxis increase [7, 10]. This stable rate of fatal anaphylaxis, in the presence of growing rates of allergy and anaphylaxis, is likely attributed to improved awareness and treatment.

Risk Factors

Age is a risk factor for a fatal reaction, with many more adults succumbing to anaphylaxis than children. Patients with advanced age are particularly vulnerable [7, 8, 14]. Although, in general, adults are more likely to experience fatal anaphylaxis, teenagers are most likely to experience a fatal food-related anaphylactic reaction and should be considered high risk [7].

A history of prior anaphylaxis is a significant risk factor for fatal anaphylaxis [15]. As mentioned above, fatal anaphylaxis is exceedingly rare and the vast majority of people who experience anaphylaxis will not have fatal anaphylaxis. However, most people who have experienced fatal anaphylaxis had a previous episode of anaphylaxis to the same or similar allergen [15, 16]. It is important to note that the severity of the previous anaphylactic reaction, in and of itself, is not a risk factor for fatal anaphylaxis.

In addition to age and history of anaphylaxis, there are medical conditions that increase the risk of fatal anaphylaxis, such as a complex medical history, conditions that require

Table 1 Severity of anaphylaxis

Mild	•Generalized erythema/flushing
-Cutaneous symptoms only	•Generalized urticaria
	•Pruritus
	•Angioedema of face/extremities
Moderate	•Dyspnea
-Respiratory, cardiovascular, or gastrointestinal involvement	•Wheezing
	•Chest or throat tightness
	•Nausea, vomiting
	•Abdominal cramping
Severe	•Cyanosis
-Hypoxemia, hypotension, neurological compromise	•Oxygen saturation < 92%
	•Systolic blood pressure < 90 mm Hg in adults
	•Confusion
	•Syncope

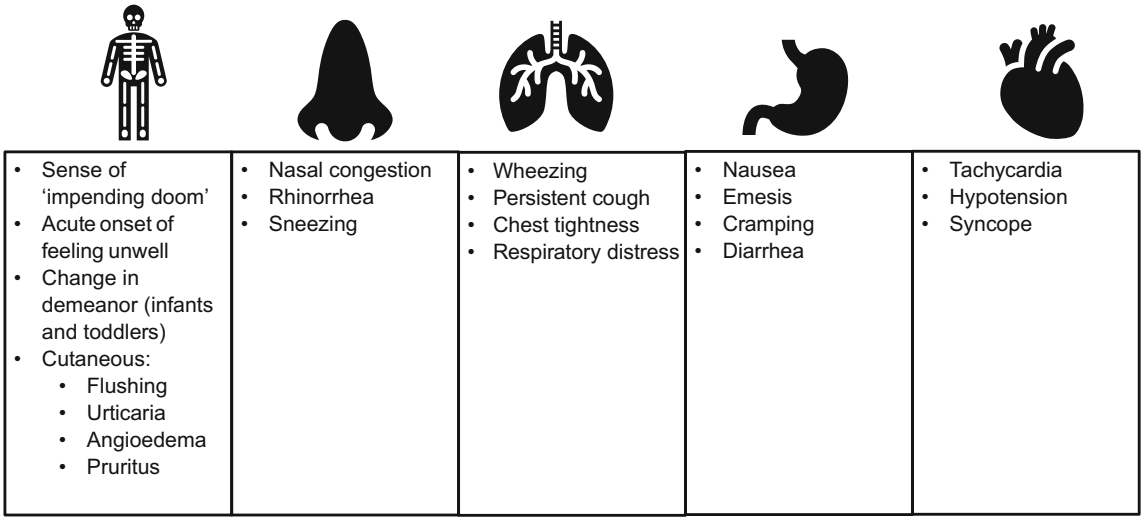

Fig. 1 Signs and symptoms of anaphylaxis

frequent use of antibiotics, asthma, cardiovascular disease, and mast cell disorders [7, 17–19]. Certain medications may also increase the risk of severe, non-fatal anaphylaxis, such as beta-blockers or angiotensin-converting enzyme inhibitors as these medications can interfere with the ability of epinephrine to exert its effects on adrenergic receptors [20, 21]. Interestingly, however, concurrent use of these medications has not consistently been associated with fatal anaphylaxis [7, 8, 17].

Fatal anaphylaxis has also been associated with lack of cutaneous findings during the allergic reaction [22]. It is likely that this is at least partially related to under recognition of anaphylaxis when the typical cutaneous findings of urticaria or angioedema are not present. It is important to note that cutaneous findings are not present in up to 20% of all anaphylactic reactions [3]. Upright posture has also been associated with fatal food-related anaphylaxis. It is suggested that patients experiencing anaphylaxis be put in the supine position to alleviate stress on the cardiovascular system, while also preventing complications should syncope occur [10].

Food-Related Fatal Anaphylaxis

There is a reported rate of 0.03–0.3 deaths per million person-years from food-related anaphylaxis in the general population, with an estimated number of 5–200 cases per year [9]. Fortunately, there has not been an increase in fatal anaphylaxis reported from foods in recent decades [10]. This is particularly reassuring as the rates of food allergies and food-related anaphylaxis do appear to be rising [6]. There also appear to be regional differences in the rates of fatal food-related anaphylaxis, with Australia and the UK reporting double the rate than the USA [10].

There are also regional differences in precise food triggers, with most countries reporting peanut and tree nut as the most frequent cause of fatal anaphylaxis, accounting for 55–87% of deaths attributed to food allergy reactions [17, 23–27]. However, recent data suggest that seafood is a common contributor in Australia [17]. Milk, particularly persistent milk allergy beyond childhood, is a common trigger in the UK and accounted for the majority of fatal food-related anaphylaxis in that country [7]. As sheep and goat milk are commonly consumed in France, they contribute to 13% of fatal anaphylaxis in this region [28]. Other foods are associated with a lower risk of leading to a fatal reaction. For instance, egg is a common cause of food allergy, but a rare cause of fatal anaphylaxis across several regions [10].

As with fatal anaphylaxis in general, age seems to be an important risk factor in fatal food-related anaphylaxis. Fatal food-related anaphylaxis is quite rare in infants and young children, even though this group comprises the highest proportion of food allergy, food-induced anaphylaxis, and hospitalizations related to food-induced anaphylaxis [23]. Adolescents and adults in the second and third decade of life seem to be at greatest risk for fatal anaphylaxis related to food [7]. Reasons behind this age association are unknown, but some suggest it may be attributed in part to increased risk-taking behavior and lack of available epinephrine at the time of anaphylaxis in adolescents and young adults. However, there may also be an age-dependent physiological predisposition to fatal food-related anaphylaxis in this age group [7, 29].

Fatal food anaphylaxis occurs more often in people with a known food allergy [7]. However, prior reactions are not usually severe, and severity of prior reactions does not appear to be a risk factor for, nor predict, fatal anaphylaxis [7]. Minimizing the risk of an accidental exposure to an allergen by reading food labels and communicating with food handlers is an important mitigation strategy to decrease the risk of food-

induced fatal anaphylaxis. Most fatal food anaphylactic reactions occur outside of the home. In the National Food Allergy Death registry maintained in the USA, 19% of fatal food anaphylactic reactions occurred in restaurants [9]. Despite the majority of fatal food-related anaphylaxis occurring in people with known food allergy, it is important to note (and communicate with patients) that the risk of mortality from food-related anaphylaxis remains very low [30].

Several case series have found that delayed use of epinephrine is a significant risk factor for food-induced fatal anaphylaxis [22, 25–27]. One case series found that epinephrine was only given in 14% of cases before cardiac arrest in fatal anaphylaxis. There are many reasons for the delayed use of epinephrine, including lack of knowledge (missed diagnosis, improper technique, etc.) and lack of access (epinephrine unavailable, epinephrine never obtained, etc.) or even lack of use despite availability [31]. In addition, patients with primarily respiratory symptoms occurring during anaphylaxis may confuse this with asthma, which can play an important role in delaying use of epinephrine. Prompt administration of epinephrine is the most practical intervention to decrease the rate of food-induced fatal anaphylaxis, and patients should be counseled on recognizing anaphylaxis and treating appropriately. There has also been international interest in increasing the availability of epinephrine. Many countries have legislation that allows (or mandates) for schools to have patient-independent (stock) epinephrine autoinjectors available to increase access to timely epinephrine administration in the school setting [6]. Despite the importance of rapid use of epinephrine, delayed use is not the only risk factor for fatal anaphylaxis from food allergies. Discouragingly up to 1/3 of cases of fatal anaphylaxis occurred despite timely administration of epinephrine [12, 27, 32].

The presence of asthma is a well-documented association with fatal anaphylaxis from food allergies and is reported as a comorbid condition in more than 2/3 of cases [25–27]. This may explain why fatal anaphylaxis is associated with severe respiratory symptoms, such as bronchospasm and laryngeal angioedema. One study noted acute dyspnea in 64% of cases of fatal anaphylaxis [17]. Interestingly, level of asthma control does not seem to be associated with risk for fatal anaphylaxis, and patients with poor asthma control do not have worse outcomes then those with good asthma control [10]. A history of asthma, in and of itself, would not be a reliable marker for risk of fatal anaphylaxis, as asthma is so common and heterogeneous in regard to level of control and severity among those with food allergies.

There are also situational associations with fatal anaphylaxis. Studies from Australia and UK have found the presence of alcohol and recreational drugs to be potential risk factors, but this risk is still debated [6, 17, 29]. It is unclear if this is due to disinhibition leading to increased risk for accidental ingestion, increased allergen absorption, masking of early signs of anaphylaxis, lack of recognition of early symptoms due to altered mental state, the suppression of physiological compensations for hypotension, or most likely a combination of factors [29]. There have been inconsistent findings of other risk factors for fatal food-induced anaphylaxis. Some studies suggest that African Americans and UK-resident South Asians have an increased risk of fatal anaphylaxis [7, 8]. Exercise and intercurrent illness have also been inconsistently associated with fatal food-related anaphylaxis [29].

It is well recognized that patients with food allergy and their families can suffer reduced quality of life due to their allergies [33]. Although there are several reasons to account for this, fear of anaphylaxis, specifically fear of fatal food anaphylaxis, significantly contributes to the reduction in quality of life and is often responsible for anxiety, social isolation, and other negative effects. It is important to empower patients with knowledge about risk in general, discuss the very low likelihood and associated risk factors of fatal anaphylaxis, and then equip them with proper mitigation strategies to lower risk and hopefully reduce anxiety. Simply asking about alterations in travel, social engagements, or dining at restaurants due to food allergy can be an easy way to start this important conversation.

Drug-Induced Fatal Anaphylaxis

As previously mentioned, drug-induced anaphylaxis is overall the most common cause of fatal anaphylaxis in countries where data are available, including the USA, Europe, and Australia [8, 17, 28, 32, 34]. A cross-sectional telephone survey within the USA estimated that medications were implicated in 35% of cases of anaphylaxis [5]. While the exact proportion of drug-induced anaphylaxis that results in death is unknown, the rate of fatal drug anaphylaxis has been estimated to be 0.5 per million population in the USA from 2008 to 2010 [8]. The data, however, are inconsistent on whether or not rates of fatal, drug-induced anaphylaxis are increasing. While studies performed in the USA and Australia have pointed to increasing rates, data from a national registry in the UK has shown stable rates from 1992 to 2012 [7, 8, 14]. One proposed reason for the increasing rate in the USA and Australian databases is the implementation of the International Classification of Diseases-10 (ICD-10) coding in 1999, which includes specific coding for drug anaphylaxis. This raises some concern that the increase may be the result of under or misreporting prior to ICD-10 implementation [10].

Not all drugs are associated with the same risk of severe anaphylaxis. The most common medication category implicated in fatal drug anaphylaxis is also variable depending on the country or region. A review of ICD-10 codes from death certificates in the USA from 1999 to 2010 found that when a drug was identified, antibiotics accounted for 40% of fatal,

drug-induced anaphylaxis, with beta-lactams being the most common type [8]. Antibiotics were also the most common identifiable cause of fatal, drug-induced anaphylaxis in a similar study performed in Australia [14]. In contrast, general anesthetics have been reported to be the most common cause of fatal drug-induced anaphylaxis in the UK, with neuromuscular blocking agents (NMBAs) being the leading trigger [32]. Radiocontrast agents are another common cause of fatal anaphylaxis in the UK, and this has been corroborated in studies from the USA, Canada, Australia, and New Zealand [8, 10, 14, 32]. A final medication category associated with a higher risk of fatality is chemotherapeutics. In the USA, chemotherapeutic drugs were found to be the third most common cause of fatal, drug-induced anaphylaxis [8]. While nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, local anesthetics, and proton pump inhibitors have been associated with both IgE-mediated and non-IgE-mediated hypersensitivity reactions, they are uncommon causes of fatal anaphylaxis [35••, 36, 37].

In addition to the medication category, other factors that increase the risk of fatal, drug-induced anaphylaxis have been identified. Increasing age has been consistently associated with both higher rates of drug-induced anaphylaxis and an increased risk of fatal anaphylaxis, particularly in patients older than 65 years of age [8, 10, 34, 36, 38]. While the reason for this increased risk among the elderly is unclear, two factors that have been proposed are increased drug exposure and increased cardiovascular vulnerability within this population [10]. Although one study identified male gender as an independent risk factor for fatal anaphylaxis, gender has not been found to be a risk factor for drug-induced anaphylaxis in most studies [10, 34]. Regarding ethnicity, African Americans had a higher risk of fatal, drug-induced anaphylaxis in one study within the USA, but this was not observed in other studies [8].

Medical comorbidities have also been associated with increased fatality risk in some studies. Known cardiovascular disease and pre-existing lung disease are two of the most commonly reported; however, these are not always found to be independent risk factors apart from age [3, 17, 18]. In contrast to food and Hymenoptera-induced anaphylaxis, most studies have not found atopy in general to be a significant risk factor for drug-induced anaphylaxis [21, 36]. A final notable risk factor associated with fatal, drug-induced anaphylaxis is a known drug allergy to the implicated drug or a closely related drug [17]. This emphasizes the importance of obtaining an accurate allergy history prior to prescribing or administering any medication.

A particular area of drug-induced anaphylaxis that warrants specific discussion is perioperative anaphylaxis, which is estimated to occur in 1 in 2000 to 1 in 20,000 surgical procedures [39]. In this setting, antibiotics and NMBAs have been identified to be the most common causes. Other important etiologies include latex, sugammadex, dyes, and disinfectants such as chlorhexidine. Less common causes include hypnotics, opioids, gelatin, and blood products [40]. Clinically, perioperative anaphylaxis typically presents within minutes of anesthesia induction, although reactions to latex and chlorhexidine can occur later. It is not uncommon for patients to develop hypotension and/or respiratory failure, which can present in the absence of other symptoms [39]. When present, cutaneous symptoms may go unnoticed secondary to surgical drapes obstructing visibility of large portions of the skin. All of these factors likely contribute to perioperative anaphylaxis having a higher mortality rate than other types of anaphylaxis. Early recognition of more subtle signs of anaphylaxis such as difficulty with ventilation, tachycardia, or hypotension is imperative.

Venom-Related Fatal Anaphylaxis

Venom is the second most common identifiable cause of fatal anaphylaxis in the USA, where it accounts for 20% of all cases of fatal anaphylaxis and at least 40 deaths annually [41••]. Similar to food and drug-induced anaphylaxis, emergency department visits and hospitalizations from venom anaphylaxis appear to be increasing over the last decade in both the USA and Europe [10, 42]. Fortunately, studies within North America, Europe, and Australia have not shown an increase in the rate of fatal anaphylaxis during this time, with the fatality rate from venom anaphylaxis universally being around 0.1 cases per million population [10]. One study within the USA did show some geographic variability of this rate with southern states having up to 0.17 fatalities per million [8]. Although the fatality rate among those with a known venom allergy is slightly higher, up to 60% of fatalities from insect stings occur in individuals who were not previously known to be allergic [43].

Stings from the order Hymenoptera, which include bees (honeybee and bumblebees), vespids (yellow jackets, hornets, and wasps), and stinging ants, are the most common cause of venom-related anaphylaxis. The most likely causal insect is related to exposure, which varies based on geographic, environmental, and ecologic factors [41••]. The cross-reactivity between different venoms is also variable with fire ant venom being the most antigenically unique and vespids having the highest rate of cross-reactivity [41••, 42]. Although there is some thought that vespid venom is more likely to cause severe reactions compared to bee venom, one study in Australia reported honeybee to be the most common cause of fatal venom anaphylaxis [17, 44, 45]. Honeybee venom has also been associated with more adverse effects and failures with venom immunotherapy, which overall has been shown to be highly effective in decreasing future risk of systemic reactions associated with insect stings [43]. In contrast to insect stings, allergic reactions to insect bites are less common causes of

anaphylaxis; however, very rare cases of fatal anaphylaxis associated with tick bites have been reported in Australia [17].

Several factors have been shown to increase the risk of fatal venom-related anaphylaxis. Delayed epinephrine administration has been associated with fatal anaphylaxis in venom allergy as it has in other causes of anaphylaxis [43]. Similar to drug-induced anaphylaxis, many studies have described older age as a significant risk factor for fatal anaphylaxis to venom [7, 8, 14, 17, 24, 46]. Unlike anaphylaxis secondary to drugs, venom anaphylaxis is notably more common in males, and both male sex and white race have been identified as independent risk factors for fatality [8, 14, 17, 24, 46]. Another factor associated with an increased incidence and severity of venom-induced anaphylaxis is the presence of an underlying mast cell disorder [47]. Specifically, patients with indolent macrocytosis have been shown to present with severe anaphylaxis to venom characterized by hypotension, a lack of cutaneous manifestations, and a normal baseline serum tryptase [48]. Despite this association of more frequent and severe anaphylaxis, there is very little evidence that underlying mastocytosis leads to an increased risk of fatal anaphylaxis [43, 49]. Underlying mast cell disorders have been associated with recurrent and severe reactions to insect stings despite desensitization with venom immunotherapy [47, 50]. For this reason, it is recommended that patients with mast cell disorders who have a diagnosis of IgE-mediated venom hypersensitivity and prior venom-induced anaphylaxis undergo lifelong immunotherapy [41••].

Several cardiovascular-related risk factors have also been implicated in fatal anaphylaxis to venom. One study performed in Australia showed an increased risk for fatal anaphylaxis in patients with underlying cardiovascular disease and upright posture following a sting [17]. There have also been long-standing concerns with associated antihypertensive use contributing to more severe anaphylaxis associated with venom allergy. While the debate is ongoing, more recent evidence has not consistently shown this increased risk and there is no evidence that they independently increase the risk of fatal anaphylaxis outside of having an underlying history of cardiovascular disease [10, 43].

While beyond the scope of this review, it is important to note that venom allergy is one of the few causes of anaphylaxis for which immunotherapy can significantly decrease the risk of future sting-associated systemic reactions. Studies have demonstrated that 30–60% of sensitized individuals with a history of a systemic allergic reaction to an insect sting will have a future systemic reaction when re-stung [41••]. In these individuals, 3–5 years of venom immunotherapy can reduce their risk of a subsequent reaction to less than 5%. While there is no clear evidence that venom immunotherapy results in a decreased risk of venom-associated fatality given that this is such a rare event, any patient with a history of anaphylaxis from venom should be referred to a specialist for further evaluation, and venom immunotherapy should be considered.

Rare Cases of Fatal Anaphylaxis

Although foods, drugs, and venom are by far the most common identifiable causes of fatal anaphylaxis, there are a few, more rare causes of anaphylaxis that are worth briefly reviewing. Routine childhood vaccination has resulted in the reduction and even eradication of many previously common communicable diseases associated with significant morbidity and mortality. While hypersensitivity reactions to vaccines can occur, they are typically mild and often not reproducible upon revaccination [51, 52]. In reviewing several post-vaccination studies within the USA, the rate of anaphylaxis associated with routine vaccination appears to be between 0.7 and 1.8 cases per million doses administered [52–55]. Vaccine-induced anaphylaxis can be caused by various components of the vaccine such as gelatin, antimicrobials, adjuvants, preservatives, and residual media. Extrinsic factors such as natural latex, present in multi-use vials, can also be implicated [51, 56]. Historically, egg allergy was thought to be a risk factor for adverse reactions to vaccines that could potentially contain small amounts of egg (influenza, yellow fever). However, dozens of studies evaluating the influenza vaccine have subsequently demonstrated that egg allergic children can receive this vaccine without any increased risk of anaphylaxis compared to the general population [57]. While it is important to recognize that systemic allergic reactions to vaccines can occur, vaccines overall have an excellent safety profile and risk for anaphylaxis is minimal.

Exercise-induced anaphylaxis (EIA) is an unpredictable syndrome whereby patients develop anaphylactic symptoms associated with vigorous exercise. Although a very rare cause of fatal anaphylaxis, EIA is thought to be the cause of 2 to 5% of anaphylaxis cases overall [58]. Syncope and laryngeal edema have been reported to occur in one-third and two-thirds of cases respectively, with individuals often having a personal or family history of atopic disease. In some cases, exposure to either a food or drug cofactor within 4–6 h of exercise is necessary to induce symptoms. Wheat is the most commonly implicated food in food-dependent, EIA; however, several other foods have also been described [59]. The most commonly implicated drugs in drug-dependent EIA are NSAIDs and antibiotics [58]. EIA is diagnosed with clinical history and if necessary, an exercise test where the patient is instructed to run on the treadmill for 30 min in an effort to reproduce symptoms. Management focuses on trigger avoidance, exercising with others in case symptoms occur, and the availability of an epinephrine autoinjector.

A final rare cause of life-threatening anaphylaxis occurs in individuals with acquired cold-induced urticaria after

extensive cold contact. Acquired cold-induced urticaria has an estimated incidence of 0.05% and is characterized by the development of cutaneous wheals after exposure to cold [60]. While most patients develop localized symptoms, up to 40% of individuals have been reported to have systemic reactions with cold exposure [61–63]. In patients with acquired cold-induced urticaria, swimming, particularly in unheated natural bodies of water, has been identified as a risk factor for severe reactions [60]. Several different sub-types of cold-induced urticaria have been described, and the clinical history along with cold provocation testing is often necessary for proper classification [64]. Management focuses on long-lasting, non-sedating antihistamine therapy for prevention and treatment as well as trigger avoidance. Patients should be cautioned not to swim alone and epinephrine autoinjectors should be considered for individuals with a history of systemic reactions.

Determination of Future Risk for Each Individual Patient

As highlighted throughout this review, fatal anaphylaxis is a very rare outcome associated with a variety of allergic triggers. Anaphylaxis, in and of itself, does not equate with death and can present with a wide range of symptoms and severity [1••]. Unfortunately, the potential for future episodes of anaphylaxis to cause life-threatening symptoms or fatality can negatively impact quality of life and lead to extreme anxiety in some patients. Given the variability in risk associated with each individual, which is based upon prior clinical history, trigger, age, and presence of comorbid conditions, discussion surrounding risk of potential fatality from anaphylaxis needs to occur on an individual basis.

For example, the parents of a 4-year-old child with a diagnosis of peanut allergy need to be educated about the risk for future reactions and counseled regarding recognition and treatment of anaphylaxis [6]. However, they also need to be informed that risk for fatal reaction is extremely low, especially when proper mitigation strategies are practiced. In addition, that specific child's history also needs to be considered. It is unfair for a family to make decisions impacting their dining habits, social engagements, travel, and school attendance if they are told their child could die if someone near them is eating peanut butter or if their child accidentally takes a bite of a cookie containing peanuts. There are many nuances to consider for each individual; if this hypothetical child was diagnosed with peanut based upon serum IgE testing but had never ingested peanut or was previously eating peanut but told to avoid based upon testing, that also impacts risk. It is equally important to interpret allergy test results properly and discuss that the size of the skin prick or serum IgE level does not correlate with severity of future reactions, including with newer component food and venom tests [65••].

Each patient diagnosed with anaphylaxis warrants discussion regarding their personal risk for future reactions, as well as potential for risk to wane over time. Young children with food allergies, particularly to egg, wheat, or soy, are not only at low risk for severe anaphylaxis (especially when avoidance strategies are practiced) but they also have a high likelihood of naturally developing tolerance to these foods as they age [66]. The conversation with a family whose young child has wheat allergy should be very different than with a family whose teenage child with asthma and known peanut allergy recently required hospitalization due to anaphylaxis from accidental ingestion of peanut and did not have their epinephrine autoinjector with them at the time of reaction.

In a similar fashion, patients with drug-induced anaphylaxis require counseling on future risk for severe reactions, the potential for IgE-mediated drug allergy to wane over time, and important details surrounding cross-reactivity with similar medications that could also pose risk [35••]. Likewise, patients receiving inhalant allergen subcutaneous immunotherapy are at risk for potential anaphylaxis, which should be discussed, but large studies show that risk is highest in those with active asthma symptoms or poorly controlled asthma at the time of injection, and within the first 30 min after injection. As such, there is debate whether every patient receiving subcutaneous immunotherapy warrants a prescription for an epinephrine autoinjector [67]. Given that risk for anaphylaxis in this scenario can be significantly lowered through administration of immunotherapy injections in a physician's office, screening questions and physical exam to evaluate for active asthma symptoms, and monitoring for 30 min after each injection, an argument has been made that it is not cost effective to prescribe epinephrine autoinjectors to every patient receiving subcutaneous immunotherapy [68].

While each scenario surrounding anaphylaxis cannot be reviewed in this article, the basic premise of taking an individualized approach towards each patient can be emphasized and practiced during clinical encounters. In addition, it is imperative that allergists or other medical professionals who diagnose and manage anaphylaxis understand the significant negative consequences that can occur when risk is overinflated. Helping patients live with informed understanding of realistic risk, including factors that both increase and lower risk, should not be associated with unnecessary fear mongering or lack of education. It is up to each clinician to anticipate concerns, address questions, and help each patient positively navigate their life on a daily basis. If these conversations are not held, including opportunities for questions and discussion, then patients will likely search for information on their own, with risk for finding incorrect information or details taken out of context [69].

Shared Decision Making

Shared decision making (SDM) is a process that includes joint involvement of the healthcare provider and patient in discussing evidence surrounding testing and treatment options, including potential benefits and harms, and incorporates patient preferences and values [70]. The SDM model has been employed for almost two decades and is becoming increasingly recognized as a useful tool for allergists to utilize given the numerous chronic conditions they specialize in diagnosing and managing [70]. Clinicians not versed in the elements and long-term evolving nature of SDM can find many resources available, including patient-centered decision support tools [71, 72].

SDM should not be thought of or employed as a one-time process, but instead should be utilized as a method for communication throughout the entire patient interaction. SDM is a collaboration between clinician and patient that allows for equal flow of information. Clinicians should discuss evidence surrounding testing and treatment options, then solicit feedback regarding patient preferences surrounding benefit and harm. This conversation should evolve over time and adapt to changes to health, evidence, options, or patient preferences. For instance, at the time of initial food allergy diagnosis, patients may not appreciate challenges associated with avoidance measures or cost associated with their epinephrine autoinjector. During follow-up visits, they may ask about other options surrounding risk from various exposures or different types of epinephrine devices. In addition, they may change their approach to risk after accidental ingestion of their food allergen at a restaurant caused anaphylaxis, despite communication with food handlers, or perhaps they had accidental ingestion that did not cause any symptoms and a newfound desire to expand dietary choices. Regardless of specifics, if SDM is employed consistently at each visit, it can change the dynamic between clinician and patient, allowing for more informed decision making [73].

Given the long-term management of anaphylaxis, potential for various levels of risk, and nuances associated with different options for avoidance measures and treatment, this is a perfect condition for SDM. For instance, a family whose child is diagnosed with soy allergy may opt to not obtain an epinephrine autoinjector if it is cost prohibitive for their financial situation after they understand that risk for severe or life-threatening anaphylaxis is very low, especially when mitigation strategies are put in place; whereas that same family may request six autoinjectors if their child had recent anaphylaxis to peanut and spends time at school, aftercare, and home. Likewise, a beekeeper with prior anaphylaxis to honeybee may decide to continue to work with honeybee colonies while receiving lifelong immunotherapy and having access to epinephrine autoinjectors because their love of beekeeping outweighs their perceived risk for future severe anaphylaxis. Regardless of the scenario, SDM for anaphylaxis should lead to management approaches that fall in line with patient preferences and their understanding of potential risks and benefits surrounding all aspects of care.

Conclusion

Fatal anaphylaxis is a tragic and thankfully rare outcome. While we lack any reliable biomarkers or diagnostic tests to determine which patients are at risk for fatal anaphylaxis, we have enough knowledge surrounding high-risk situations and risk factors to counsel patients and medical professionals. Education, patient involvement in medical decision making, and ongoing reassessment of management strategies over time can help individualize the approach to reducing risk and harm.

Abbreviations *EIA,* Exercise-induced anaphylaxis; *ICD-10,* International Classification of Diseases; *IgE,* Immunoglobulin E; *NMBAs,* Neuromuscular blocking agents; *NSAIDs,* Nonsteroidal anti-inflammatory drugs; *SDM,* Shared decision making

Declaration

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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