

Fatal Anaphylaxis to Foods: Epidemiology, Recognition, and Prevention

Dan Atkins, MD, and S. Allan Bock, MD

Corresponding author

Dan Atkins, MD
National Jewish Health, 1400 Jackson Street, J301,
Denver, CO 80206, USA.
E-mail: atkinsd@njhealth.org

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The inability to accurately predict the severity of future allergic reactions to foods in a given individual coupled with the real—although usually remote—risk of a fatal anaphylactic reaction complicates care and remains a constant source of concern to food-allergic patients, their family members, and health care providers. Current epidemiologic evidence suggests that the incidence of food-induced anaphylaxis is increasing, although confidently approximating the incidence of fatal allergic reactions to foods remains difficult. This article briefly reviews the epidemiology of fatal anaphylactic reactions to foods, discusses factors that may aid in identifying individuals at higher risk, emphasizes important aspects of patient education and prevention, and touches on the psychological impact of having a family member with food allergy.

Introduction

The incidence of food allergy is increasing in westernized countries around the world, stimulating debate about causality [1••]. A perplexing aspect of caring for food-allergic individuals is that exposure to a culprit food can result in a reaction ranging widely in severity from localized mild contact reactions to fatal anaphylaxis. In fact, allergic reactions to foods continue to be recognized as the most common cause of outpatient anaphylaxis [2,3,4••]. Fortunately, complete recovery from food-induced anaphylaxis is the norm, with fatal episodes the rare exception; however, even a single fatal outcome is excessive, and in the United States alone, an estimated 150 cases of fatal food-induced anaphylaxis occur annually [5]. Thus, the potential for fatal reactions remains a constant concern of patients with

food allergies, their families, and physicians, underscoring the need to accurately identify those at risk and raising the questions of whether and how this can be accomplished. The conundrum facing the treating physician is that over-emphasizing the risk can cause undue psychological stress, thereby decreasing quality of life (QOL) and increasing burden of illness. However, underemphasizing could have potentially fatal consequences. The following discussion reviews information concerning fatal allergic reactions to foods with a focus on the epidemiology of these reactions, characteristics that may aid in identifying those at greater risk, important aspects concerning education and prevention, and the often overlooked psychological burden associated with being at risk for fatal anaphylaxis.

Epidemiology

Several factors support attempts to determine the true epidemiology of fatal and nonfatal food-induced anaphylaxis. From a public health perspective, knowledge of the accurate incidence and prevalence could aid in defining the scope of the problem and documenting changes in prevalence and severity. This knowledge could aid governments in making more informed decisions about appropriate resource allocation to address financial issues encountered by patients and medical care providers and in providing adequate research funding to improve prevention and find a cure. From a care provider's perspective, realizing that population statistics cannot be directly applied to the individual patient, the information could still help to assuage irrational fears about death from food-induced anaphylaxis that plague some patients and their families.

Study of the epidemiology of fatal food-induced anaphylaxis has been hampered by the lack of centralized data collection or reporting organizations in most countries. Several studies are often quoted as providing a basis for estimating the number of individuals presenting to emergency departments with “anaphylaxis,” including severe allergic reactions to food and related fatalities. Although these studies provide rough estimates of the number of patients falling into these categories, prospective population-based statistics have not been collected.

In the United States, studies by Yocum et al. [2,6] have been widely quoted because they are based on data collected from a relatively well-defined and circumscribed population. Extrapolation of data from these studies is the basis of the previously estimated 29,000 food anaphylactic episodes in the United States each year that result in approximately 2000 hospitalizations and perhaps 150 deaths. In a more recent study, Decker et al. [4••] reported the results of a population-based analysis of the incidence and causes of anaphylaxis in Rochester, Minnesota, between 1990 and 2000. Allergic reactions to foods continued to be the most common cause of anaphylaxis, accounting for 33.2% of the cases. The overall incidence rate of 49.8 cases per 100,000 person-years was more than double the average annual incidence rate of 21 cases per 100,000 person-years reported by Yocum et al. [2] in their studies of Olmsted County residents from 1983 through 1987 [4••]. In addition, the annual incidence rate of anaphylaxis increased over the course of the study from 46.9 per 100,000 persons in 1990 to 58.9 per 100,000 persons in 2000 [4••]. No fatal cases of food-induced anaphylaxis were identified.

Pumphrey and Stanworth [7] reported findings similar to the initial studies by Yocum et al. [2,6] in another widely quoted study. The population under study was well described, and details on individual participants were available to the authors. In a review published in 2007, Pumphrey [8] reported that of 300 deaths from anaphylaxis in the United Kingdom that he had investigated since 1992, 90 were caused by allergic reactions to foods. He estimated the death rate from food-induced anaphylaxis in children less than 16 years of age in the United Kingdom to be approximately one per 20 million population per year. Based on information obtained from small series of fatal cases and personal communication with investigators in other countries, Pumphrey [8] estimated the death rate from food-induced anaphylaxis in children to be similar in Ontario (~ one child in 20 million population per year) and somewhat higher in Australia (~ one child per 6 million population per year). He noted that 12 fatal food reactions had been identified in Sweden (population, 9 million) from 1993 to 2003 and that none had been reported in Norway (population, 4.6 million) since the onset of data collection. Moneret-Vautrin et al. [9] identified and studied 107 cases of severe food anaphylaxis from the Allergy Vigilance Network in France. In this well-characterized group, there was apparently one death from shock and one from asthma. Although other foods have been implicated, in these and many other studies, the main offenders were peanuts, tree nuts, fish, and shellfish. These were also the major offending foods identified in reports from mortality surveys and registries [10–12,13•,14•].

A recent New York state administrative base analysis found that the anaphylaxis hospitalization rate for individuals younger than age 20 years had increased more than fourfold between 1990 and 2006 [15]. Four deaths

were documented in this population, all related to reactions to food. Although this may underestimate fatalities, the important points are the increased hospitalization rate and the high representation of young people.

Many other studies have been conducted on anaphylaxis in general (not limited to food anaphylaxis or mortality). Several of these studies were reviewed and superbly summarized by Lieberman et al. [16] in a working group report in 2006. All the studies and reviews on this subject raise the concern that cases of food anaphylaxis and fatalities are significantly underreported for many reasons. These reasons include, but are not limited to, poor recognition of initial anaphylactic events, improper diagnosis of asthma without a trigger when the trigger might have been an unrecognized food allergy, improper coding even when anaphylaxis is recognized, and lack of hospitalization (making coding errors impossible to detect or correct). These limitations were also well reviewed and discussed by Lieberman et al. [16] and in an editorial by Simons and Sampson [17].

What are some of the implications of these observations for practicing physicians? Realizing the limitations of the available epidemiologic data and the general agreement that episodes of food-induced anaphylaxis and related fatalities are probably underrecognized, the likelihood of dying from such an event remains low. However, if patients and health care providers, especially in emergency or urgent care settings, fail to recognize and diagnose food-induced anaphylaxis, then these episodes are not properly reported to the primary care physician, who is responsible for arranging for accurate diagnosis, implementation of proper precautionary measures, and follow-up. This can result in a missed opportunity to provide education and the possibility of another incident that could have been prevented or at least could have occurred with the patient better prepared and possessing an auto-injectable epinephrine device.

Recognition/Identification

Anaphylaxis has been defined as a serious allergic reaction that is rapid in onset and that may cause death [18]. A difficult but fortunate aspect of managing food-allergic patients is that although anyone with IgE-mediated food allergy could experience anaphylaxis, most never do, and only rarely does a patient succumb to a fatal episode. This raises the obvious questions of if and how those at higher risk can be accurately distinguished from those who are not. The difficulty of predicting the level of risk for a specific food-allergic individual is complicated by the myriad of factors—patient related and reaction related—that could impact the outcome of any specific episode of food allergen exposure. Yet another complicating aspect is that the level of risk for an individual patient is not static, but changes over time, underscoring the need for continued assessment and long-term follow-up. It is also recognized that many children react on the first known ingestion of the offend-

ing food. Obviously, identifying these individuals before the first reaction presents an almost impossible task until screening tools with better predictability are developed.

Patient characteristics that could impact the severity of a reaction include age, comorbid disease, implicated culprit foods, and the patient's level of sensitivity to those foods. Age has an impact on the foods commonly involved, the likelihood of accidental exposure, reaction symptoms, and the ability to recognize and communicate suspicion of a reaction. For example, foods most commonly implicated in anaphylaxis in young children are milk and egg, because in Western societies, nuts and fish generally are introduced into the diet at a later age. In adolescents and adults, anaphylaxis to peanuts, tree nuts, fish, and shellfish is more common because most milk- and egg-allergic patients either outgrow or experience a reduction in sensitivity to these foods. Infants and young children are at the relative mercy of their caretakers, as they lack the cognitive ability to avoid foods to which they are allergic and once exposed are limited in their ability to communicate the potential cause or nature of their discomfort. Nonetheless, many food-allergic youngsters effectively limit their intake of food allergens in response to unpleasant oropharyngeal symptoms that warn them of offending food exposure or by vomiting immediately. Thus, the absence of oropharyngeal warning signs or immediate vomiting places some children at higher risk for ingesting larger doses of food allergen, which, because of dose-response relationships, has been associated with more severe reactions. Behavioral responses such as irritability or vomiting may alarm the experienced caretaker but are common enough in the younger age group that they may not arouse immediate suspicion of an allergic reaction in the absence of other symptoms, such as flushing, urticaria, angioedema, or respiratory distress. Refractory anaphylactic shock occurs more commonly in fatal food-induced anaphylaxis in adults than in children, who die more frequently of anaphylaxis complicated by laryngeal edema with upper airway closure or severe bronchospasm [8].

In older children, adolescents, and adults, avoidance of culprit foods is enhanced by greater cognitive capacity but can still be hindered by inexperience, immaturity, and complicated social pressures. The overrepresentation of adolescents and young adults in case series of fatal anaphylaxis is attributed to the tendency of this population to participate in risk-taking behaviors such as failing to ask consistently about ingredients or to read labels [19]. Other problems in this age group include succumbing to peer pressure and failing to carry emergency medications for trivial reasons such as inconvenience or the mistaken belief that the offending food can be avoided successfully. Communication with others about the onset of an allergic reaction may be hindered by embarrassment, anxiety about expected medical intervention such as epinephrine injection, or (in rare instances) a language barrier. Alcohol consumption by adolescents and adults can facilitate

severe reactions by increasing risk-taking behavior, augmenting allergen absorption, and clouding judgment regarding recognition and assessment of reactions and seeking appropriate treatment.

Comorbid disease is a patient-related factor that can predispose an individual to fatal food-induced anaphylaxis as a result of direct involvement in the anaphylactic reaction or the requirement for medications (eg, β blockers) that significantly impair the response to recommended treatment. Asthma as a risk factor for fatal food-induced anaphylaxis has been documented clearly, as most patients in case series of fatal food-induced anaphylaxis in whom complete information was available were found to be asthmatic [5,13•]. Poorly controlled asthma and poor adherence to recommended asthma treatment present an even greater risk.

Because foods such as peanuts, tree nuts, fish, and shellfish are more often associated with fatal or severe anaphylaxis, sensitivities to these foods increase the risk of severe reactions. Unfortunately, awareness of the food allergy is not protective, as most patients experiencing fatal food-induced anaphylaxis died from accidentally ingesting a food to which they were known to be allergic. In many of these cases, unavailability of or delay in treatment with injected epinephrine was an identified contributing factor. The degree of sensitivity to the ingested food as estimated by previous reactions is an important clue, as a previous life-threatening or severe reaction after the ingestion of a small amount of the offending food is associated with increased risk. Unfortunately, a history of previous less severe reactions is not uncommon in those suffering from food-induced anaphylaxis. For example, Vander Leek et al. [20] reported that in a cohort of children with peanut allergy whose initial reactions consisted of cutaneous symptoms alone, more than half of those who experienced subsequent accidental exposures experienced potentially life-threatening reactions.

Aspects of an individual reaction that may play a role include the following: 1) the setting in which the reaction occurs; 2) the food involved (peanuts, tree nuts, fish, shellfish), including the route of exposure (contact, inhalation, injection, or ingestion), dose, and manner of preparation (uncooked vs cooked); 3) the target organ(s) (gastrointestinal, cutaneous, respiratory, circulatory, alone or in combination); 4) the severity and rate of symptom progression; 5) the timing and response to symptom recognition; 6) extraneous factors such as concomitant exercise or ingestion of NSAIDs; 7) the availability of rescue medications and their timely use; 8) the response to treatment; and 9) the availability of emergency medical care. Although first reactions to foods often occur at home, subsequent reactions often occur outside the home, such as in school, at restaurants, or in the homes of relatives. As previously mentioned, foods more often associated with severe reactions are peanuts, tree nuts, fish, and shellfish, although food-induced anaphylaxis and fatalities have been described with many other foods.

Most anaphylactic events are the result of food ingestion rather than cutaneous contact or inhalation. Although contact reactions to foods are quite common, they rarely progress to anaphylaxis. Fortunately, episodes of anaphylaxis resulting from the injection of food are extremely rare and are usually associated with medical procedures such as the injection of egg protein-like material contained in a vaccine. Thus, these episodes are more likely to occur in a medical setting.

Although severe anaphylaxis can occur as a result of minute exposure in an exquisitely sensitive patient, a dose-response relationship exists in regard to more severe reactions resulting from exposure to larger doses of the offending food. Involvement of the respiratory or circulatory system carries higher risk, as death in food-induced anaphylaxis is usually the result of upper and/or lower airway obstruction or refractory hypotension. Rapid onset and reaction progression are associated with more severe reactions. Interestingly, Pumphrey [8] reported a slower median time to first arrest (35 minutes) in food-induced fatal anaphylaxis compared with fatal iatrogenic-related (5 minutes) or insect sting-related (12 minutes) fatalities. Although food-induced anaphylaxis fatalities have occurred even after the timely injection of epinephrine, the unavailability of injectable epinephrine or delay in its administration has been identified as a significant risk factor. Simons [21] reviewed reasons for lack of a response to epinephrine treatment in detail; they include delay in administration, incorrect dose, the wrong route, and the use of medication past its expiration date. Obesity could have an impact if the degree of obesity encountered renders the needles of available auto-injectable epinephrine devices too short to deliver the medication intramuscularly. Pumphrey [22] also emphasized the importance of keeping the patient supine when possible to enhance venous return to the heart to maintain a positive cardiac output and optimize coronary artery perfusion. Thus, moving or encouraging the anaphylactic patient with poorly compensated shock to sit or stand could result in markedly decreased coronary artery perfusion with disastrous consequences. A poor response to appropriate medication during previous reactions is a concerning finding that suggests higher risk.

Unfortunately, the tools currently used to document sensitization to an offending food (eg, skin prick testing) and measure circulating food-specific IgE levels, although they are capable of predicting the likelihood of a reaction to certain common food allergens, are incapable of predicting reaction severity. Epitope mapping using microarray technology with determination of the number and location of epitopes recognized holds promise but is currently unavailable clinically and requires further investigation [23]. Thus, food challenges are the only means of prospectively documenting reaction severity. In addition to determining whether a patient has clinically relevant sensitization to a food, food challenges occasionally have been performed in an attempt to determine a threshold

dose. It is important to remember that threshold doses may vary over time and that exposure to the food in the “wild” may differ from the dose increments presented during a food challenge under observation in a medical setting [24–28].

Education/Prevention

Although the available literature regarding risk factors for fatal food-induced anaphylaxis is somewhat limited and retrospective, it supports measures to be incorporated in efforts aimed at education and prevention. Awareness of a particular food allergy is not uniformly protective. Most fatal reactions occur as a result of accidental exposures away from home with a lack of or delay in epinephrine administration. This underscores the necessity of consistently reading labels, heeding advisory labeling, and inquiring about ingredients in foods. It also reinforces the need to carry appropriate medications at all times in addition to having and, when necessary, executing an updated Food Allergy Action Plan. A recent review found no evidence that antihistamines were life saving when given in the absence of epinephrine [29]. Thus, it should be stressed that the only identified potentially life-saving medication is epinephrine [30]. Repetition of training about the use of the auto-injectable epinephrine device is important, as too many cases of accidental injection of the device into a digit have been reported [31]. Monitoring the expiration date on the device and discharging expired ones into an appropriate item such as an orange or another piece of fruit provide useful additional training. Reminding patients and caretakers about having individuals assume the supine position during an allergic reaction to reduce the likelihood of decreased ventricular filling and the provision of oxygen as soon as it is available would seem to be a wise recommendation.

The recognition that teenagers and young adults are at increased risk because of the factors outlined previously suggests that taking time to address these issues with this patient population is warranted. Aggressive monitoring and treatment of asthma in food-allergic individuals is indicated, particularly in those with histories of previous severe reactions with a respiratory component or sensitivity to foods commonly associated with severe reactions. The myth that every exposure to the culprit food leads to an increase in sensitization and a more severe subsequent reaction should be dispelled, but the unpredictable nature of reaction severity as a result of the many factors involved (as outlined previously) should be explained. Thus, the potential for severe reactions in patients who have experienced only minor reactions should be addressed. Considering individuals with histories of previous severe reactions to be at higher risk seems appropriate. In addition, it is important to inform patients that the results of skin testing and laboratory testing do not currently predict the severity of reactions, although active attempts are currently being made to develop such tests. Keeping a detailed log of all

reactions and reviewing them with a health care provider as soon as possible after any reaction is encouraged. Stressing that education regarding food allergy management and prevention is a continual process is key.

The importance of responding to questions raised by food-allergic patients and their families should not be underestimated. Questions about individual risk are usually difficult to address given that population statistics cannot be applied to individuals and that the data regarding fatal and near-fatal reactions are at best a gross estimation. Overemphasizing the risk of death should be avoided, as it is likely to engender undesired levels of anxiety. We suggest delivering the information in a manner designed to inform rather than alarm and acknowledging the gaps in our current level of knowledge.

Psychological Aspects

Food allergy is a chronic, potentially fatal disorder for which the only current treatment is avoidance of the offending food and rapid treatment of reactions caused by accidental exposures. Because of the potential for fatal reactions and the inability to guarantee the outcome of culprit food exposures, educational efforts by medical providers are sometimes presented with a worst-case scenario or “prepare for the worst and hope for the best” tone. These discussions often leave patients and parents wondering about their actual risk of death and how to apply the information learned to their daily lives. The food-allergic patient is usually well between exposures but experiences the rapid onset of unpleasant symptoms immediately or within minutes of accidental exposure to the offending food. These allergic reactions usually occur as the result of an unforeseen mistake, which evokes feelings of anxiety and guilt. In addition, the dietary measures required for avoidance can be time consuming and complex, requiring a certain degree of medical sophistication in regard to label reading and culinary awareness. Thus, it would seem reasonable that being food allergic or having a food-allergic family member could have a significant impact on the QOL and psychological well-being of the affected individual and his or her family.

The psychological impact of food allergy is an important topic that has begun to generate interest, as evidenced by an increasing number of studies over the past few years. Primeau et al. [32] compared children and adults with peanut allergy to children and adults with rheumatologic disease. The parents of children with peanut allergy believed that their children had more QOL impairment and that their family experienced more disruption in the familial/social dimension of relations than the parents of children with rheumatologic disease. The parents of peanut-allergic children attributed the disruption of their child's daily activities and impairment in familial/social interactions directly to their perception of their child's risk of death. The loss of parental mastery when others cared for their peanut-allergic child was a significant source of

concern for these parents. One potentially beneficial aspect of the higher levels of stress in the families of peanut-allergic children was that they were thought to provide the impetus for the development of better coping strategies.

Using a questionnaire, Sicherer et al. [33] evaluated a Food Allergy and Anaphylaxis Network cohort for QOL issues and identified significant disruption to daily living in families with a member with food allergy. One important observation was that being allergic to more than two foods significantly increased the negative impact on QOL beyond that identified in patients allergic to two foods or less. This observation emphasizes the importance of accurate diagnosis and, when possible, objective confirmation that each food suspected of causing symptoms truly must be eliminated from the diet.

The findings of these early studies on this topic have been confirmed and extended by additional and increasingly sophisticated survey instruments. Marklund et al. [34] used two questionnaires to evaluate 220 schoolchildren in Sweden whose parents reported them as being food allergic. Interestingly, they found that it was the risk or anticipation of food reactions and the efforts taken to avoid them rather than the reactions induced by food exposure that correlated with reduced QOL. Avery and colleagues [35] compared children with peanut allergy to those with insulin-dependent diabetes mellitus. They used a novel photographic method to allow the children to record areas of concern. The peanut-allergic group reported more anxiety about eating and fear of an adverse event and more concern about eating away from home. As noted in other studies, many of the peanut allergy group's concerns revolved around food, eating, and restrictions on issues of daily living. Although earlier studies have been helpful in generating information using general QOL questionnaires, it is encouraging that more recent studies are using specific and validated food allergy QOL questionnaires, especially from the child's perspective [36,37•]. In addition to identifying the psychological impact of food allergies on these patients and their families, these observations stress the importance of ongoing education about food avoidance, safety measures to take when eating away from home, and reinforcing the basic principles of treatment. Medical providers caring for food-allergic individuals and their families need to remain cognizant of the psychological issues encountered by these patients and their families. In addition to providing educational materials and resources addressing medical management, specific questioning about QOL issues and coping should be routinely included in regularly scheduled follow-ups and accompanied by appropriate psychosocial referral when indicated.

Conclusions

Much remains to be learned about fatal and near-fatal food-induced anaphylaxis. Whether the frequency has been exaggerated, as some have claimed, is not the impor-

tant issue. Any death from food-induced anaphylaxis is excessive because these reactions should be preventable. The information learned to date from available case series should be incorporated into current practice and shared with food-allergic patients and their families. Further research to improve diagnostic techniques and better identify those at risk is crucial. This would allow efforts to focus on those at highest risk and reduce the likelihood of causing undue alarm in those with negligible risk. The psychological impact of food allergies on patients and their families is being investigated and better characterized. The QOL data clearly demonstrate that imprecise diagnosis with attendant elimination of many foods from the diet is unacceptable because of the toll it takes on these patients and their families. The importance of monitoring the psychological impact of food allergy by questioning about QOL issues and coping styles is clear. Finally, it should be recognized that educating patients with food allergies and their families is a continual process until the food allergy is “outgrown” or a cure is found.

Disclosure

No potential conflicts of interest relevant to this article were reported.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance
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- 1.•• Sicherer SH, Sampson HA: **Peanut allergy: emerging concepts and approaches for an apparent epidemic.** *J Allergy Clin Immunol* 2007, 120:491–503; quiz 504–505.

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