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Clinical Commentary Review**Fatal Food Anaphylaxis: Distinguishing Fact From Fiction**

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Abstract

Although there is a general perception that the prevalence of food allergy is increasing, data supporting this are limited. Food is the least common cause of fatal anaphylaxis, and fortunately, is a very rare event; however, it is also unpredictable. There is widespread consensus that severe reactions cannot be predicted in a clinically-meaningful way. Certain food triggers are more frequently associated with fatal anaphylaxis than others. In observational studies peanut and tree nuts account for at least 30-50% of fatalities, with seafood and cow's milk also associated with fatal reactions. Fatal food-induced anaphylaxis is most likely to occur during adolescence and young adulthood, although the reasons for this are unclear. International guidelines agree that intramuscular (IM) epinephrine is the treatment of choice for managing food-triggered anaphylaxis, and has a good safety profile when given by the IM route. However, fatalities still occur despite the timely administration of epinephrine. Food-allergic individuals must navigate a world that requires daily vigilance for allergens and preparedness for allergic reactions. Although the actual risk of fatal reactions is minimal, it is not zero and severe reactions are unpredictable. Clinicians need to

help patients better understand the very low, but real risk of fatal reaction, and enable them to lead as normal a life as possible through appropriate education, safety-netting and risk reduction.

Key words: anaphylaxis; fatalities; risk factors; serum tryptase;

Abbreviations

EAI	Epinephrine auto-injector
ICU	Intensive care unit
IM	intramuscular
MCAS	mast cell activation syndrome
MCT	mast cell tryptase
NIAID	National Institutes of Allergy and Infectious Diseases
PAL	Precautionary Allergen Labelling
UKFAR	United Kingdom Fatal Anaphylaxis Registry

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Introduction:

Although there is a general perception that food allergy is increasing in prevalence, evidence supporting this is limited. In some countries, prevalence rates of up to 10% have been reported, although this may be limited to specific allergens (such as raw egg) in younger age-groups only (1). A more typical figure is around 3-5% confirmed by food challenge (2). The available data suggest that prevalence has been relatively stable over the last 10-20 years in the USA (3), United Kingdom (4) and Australia (5). However, what is less clear is whether individuals are presenting with a more severe phenotype of food allergy. Such a theory may be supported by data demonstrating an increase in hospital admissions for food-induced anaphylaxis in the UK, USA and elsewhere (6). In this article, we review the evidence surrounding the most severe presentations of food allergy – those causing fatal anaphylaxis – to try and distinguish evidence from perception so as to better inform individuals at risk of anaphylaxis and their families.

MYTH: “Fatal anaphylaxis is common and cases are on the rise”

Although hospital admissions for food-anaphylaxis have increased in the USA, Europe (Finland, Italy, Spain, UK) and Hong Kong (6), rates of fatal anaphylaxis have remained stable in the UK and USA. In Australia, a population-based epidemiological study reported an increase in anaphylaxis fatalities (including food-induced) between 1997-2013 (7). However, a subsequent analysis of the same data found that in all 3 regions, the case fatality rate (rate of fatal anaphylaxis expressed as a proportion of hospital admissions) has actually fallen (6). In the UK, where a national fatal anaphylaxis register has existed since 1992, the case fatality rate has more than halved in the last 20 years (8). Fortunately, fatal anaphylaxis is a

very rare event, and food is the least common cause of fatal anaphylaxis. A US study reported that 6.7% of 2458 anaphylaxis-related deaths from 1999-2010 were caused by food (compared to 59% attributed to medication).(9) These data are consistent with fatality data from France and Australia. (7) (10).

A systematic review and meta-analysis estimated the incidence of food-induced fatal anaphylaxis in the food-allergic population is 1.8 fatalities per million-person years across all ages (and 3.25 per million-person years in children), which is less common than the risk of accidental death in the general population(11). Fatal outcomes are so rare that currently, there are no evidence-based risk factors which can be used clinically to predict who might be more at risk of fatal reactions (12). Allergic individuals (or their parents) often perceive risk in a different way. Healthcare professionals might take an objective, more statistical approach to risk while patients and parents are more likely to understand risk in an emotion-led context, considering their child to be 'the one in a million' who might experience a fatal reaction (13). Clinicians need to take a supportive approach to discussing the very low rate of fatal anaphylaxis with food-allergic patients (and their families): just as everyday risks (such as driving or crossing a road) can be mitigated by following highway rules or crossing a road safely, we need to help food-allergic individuals live as normal a life as possible through appropriate safety-netting, risk avoidance, and facilitation of adaptive coping strategies.

MYTH: “Elevated mast cell tryptase (MCT) level is diagnostic of fatal, food-triggered anaphylaxis”

Mast cells can degranulate by the cross-linking of receptor bound IgE with allergen. The presence of mast cell tryptase (MCT) in serum can serve as a marker of mast cell activation but requires attention to the circumstance of sampling. Paired serum tryptase measured 1 to 2 hours after anaphylaxis may indicate the degree of mast cell activation (14) . However, it is not uncommon for MCT *not* to increase beyond the upper limit of normal of 11.4ng/ml during anaphylaxis. Data indicates that MCT does often increase in food-induced reactions (15,16), but the increase is small and insufficient to raise MCT beyond the normal range (defined as peak MCT >11.4 ng/mL and/or absolute delta-MCT $\geq$ 2 ng/mL (17,18). Furthermore, MCT was not discriminatory between anaphylaxis and non-anaphylaxis reactions. Sensitivity and specificity is only around 70% which is insufficient for clinical utility (19).

For fatal anaphylaxis, Mayer et al (19) reported that that MCT elevation was common in fatal anaphylaxis due to insect stings (18/21 cases), diagnostic agents (4/5), and perioperative reactions (4/6), but less so in fatal food anaphylaxis (7/19). In a case series from Australia (7), an increase in MCT beyond the normal range was not observed in 4/16 (25%) cases. Conversely, elevated MCT post mortem may not indicate anaphylaxis. MCT can also be mildly elevated following asphyxia (20) and acute fatal asthma (21) presumably due to local mast cell autolysis and/or degranulation. Edston et al (22) proposed a much higher cut-off of 45 μ g/ml for post-mortem diagnosis of anaphylaxis for these reasons. Therefore, elevated MCT alone cannot be used as indicative of anaphylaxis, but rather should prompt consideration of possible allergen exposure.

147

148 **MYTH: “Previous reaction severity predicts future risk”**

149 There is widespread consensus that severe reactions cannot be predicted in a clinically-
150 meaningful way (23). Arguably, this is the largest evidence gap in managing food-allergic
151 individuals. The interaction between host-factors (such as level of IgE sensitization) and co-
152 factors – such as intercurrent infections (24,25), age (7,9), ethnicity (26), menstruation
153 (27,28) sub-optimal asthma control (29), mastocytosis(30) ingestion of alcohol, proton
154 pump inhibitors, aspirin, NSAID and beta-blockers (31–33) all of which can have an impact
155 on reaction severity – is complex and inconsistent across patients. Some individuals appear
156 to be more at risk of co-factor related reactions than others. Data from food
157 immunotherapy studies indicate that even within the same individual, the impact of a co-
158 factor is inconsistent over time: someone may experience a more severe reaction associated
159 with exercise or infection on one occasion, but not another. Data from the European
160 Anaphylaxis Registry has identified cofactors as being suspected in food-dependent
161 anaphylaxis in 39% of adults and 14% of children (34) and may contribute to the risk of
162 biphasic reaction (35). However, in a prospective study (36) in 157 patients over a 1-year
163 period, while co-factors were potentially a factor in 74% of 153 food-related reactions, there
164 was no association between the presence of a co-factor and reaction severity. In UKFAR,
165 over half of fatalities reported to food were in individuals with only previous mild reactions
166 (29). The role of co-factors in severe anaphylaxis has not yet, to our knowledge, been
167 systematically evaluated.

168

169 Pouessel et al (37) recently reported follow-up of children admitted to intensive care units
170 (ICU) in France due to (non-fatal) food anaphylaxis. The report is limited by the inclusion of a

significant proportion of non-severe anaphylaxis cases. However, of the 39 children with food-induced anaphylaxis (of whom 28 (72%) had Ring grade 3/4 reactions), 30 had a further food reaction during follow-up. In 12 children, the subsequent reaction was anaphylaxis, and in 8 cases, the same allergen that was responsible for the original admission to the ICU. None had severe anaphylaxis, although 4 were admitted to ICU as a precautionary measure. Thus, a prior ICU admission does not necessarily mean that future reactions to the same allergen will be of the same severity.

FACT: “Certain foods seem to be more likely to trigger fatal reactions”

Certain food triggers seem to be more associated with fatal anaphylaxis than others. In 2001, Bock et al described 32 cases of fatal food anaphylaxis in the United States, with 94% attributed to peanut or tree nuts (38). More recent data have confirmed peanut and tree nuts are common triggers, but not the only ones. A recently published systematic review of common triggers for food-induced anaphylaxis including fatal anaphylaxis reported differences between regions (39). The main triggers in the USA, Australia, France and the UK were peanut and tree nuts, accounting for at least 30-50% of fatalities. Seafood caused 50% of fatal reactions in an Australian report, and 37% in a regional dataset from New York City. Cow’s milk is responsible for around one quarter of deaths in the UK and France, and around 10% in a US series (40). Milk has been identified as a leading cause of pediatric fatal anaphylaxis in the UK (39) perhaps due to its ubiquitous use as an ingredient.

193

194 POSSIBLE MYTH: “Asthma is a risk factor for fatal anaphylaxis”

195 Severe respiratory symptoms are frequent in fatal food anaphylaxis (41,42) an analysis of the
196 UK Fatal Anaphylaxis Register (UKFAR) reported that 86% of fatal food reactions were
197 primarily due to respiratory arrest (with cardiac arrest secondary to hypoxia) (41,42). Some
198 studies have reported an association between asthma (12) with a US series of 32 cases
199 showing that at least 24 (75%) had asthma (38). An association with asthma has been
200 reported in other fatal case series (43). However, a detailed analysis of 8055 cases in the
201 European Anaphylaxis Registry found an inverse association between asthma and severity of
202 food allergy (44). In UKFAR, although 78% of food anaphylaxis fatalities had a documented
203 diagnosis of asthma, the majority did not have evidence of recent exacerbation (45). A history
204 of asthma alone is a very poor predictor for severe outcomes, because asthma is common in
205 food-allergic individuals, and the vast majority of food-allergic patients will never have truly
206 life-threatening anaphylaxis. Therefore, asthma in itself is a poor predictor of severe
207 anaphylaxis. This, of course, does not negate the clinical need to optimise asthma control in
208 food-allergic individuals. It is likely that suboptimal asthma control and underlying airways
209 hyperreactivity is a risk factor for more severe reactions (30).

210

**211 FACT: “Teenagers and young adults appear to be more at risk for food-induced fatal
212 anaphylaxis”**

213 Fatal food-induced anaphylaxis is most likely to occur during adolescence and young
214 adulthood (38,40,46) . This pattern has been related to increased risk taking and sensitivity
215 to peer norms that occur at this age, coupled with decreased parental oversight and

supervision. Adolescents and young adults may not want to appear different from peers, may not have the required maturity to make safe choices, or may not have the necessary food allergy knowledge to engage in appropriate self-management. Strikingly, data from UKFAR has demonstrated that this increased risk persists through to the 4th decade of life (45). Although adolescence-related behaviors may contribute to the increase in fatal food anaphylaxis risk seen in this age group, it is unlikely that these factors apply to adults in their 30s and early-40s, displaying persistent higher risk of fatal reactions. These data suggest a specific vulnerability to severe outcomes from food-induced allergic reactions in the second and third decades of life, which may have a underlying physiological – rather than purely behavioral – basis.

Such an observation does not negate the need to focus on safety-netting in teenagers and young adults. Research in adolescents with food allergy consistently demonstrates difficulty with all aspects of food allergy self-management. Many adolescents cannot identify symptoms of anaphylaxis or when to use epinephrine (47–50). Several studies report that very few adolescents carry their epinephrine autoinjectors (EAI) with them at all times (38,46,51,52) , and this is affected by their perception of how “burdensome” (annoying/embarrassing) it is to carry EAI; adolescents may be particularly unlikely to have EAI when in the homes of friends, restaurants, and other locations such as the car (53).

Another food allergy self-management challenge is food allergen avoidance. Up to half of adolescents acknowledge they knowingly eat foods which can contain the allergen they are allergic to. Many rely on past experience with food to make decisions about food safety, which is not a reliable or recommended strategy (46,49,54). Management needs to be focused on increasing the food allergy knowledge and self-efficacy of this age-group to

achieve the right balance of safe and appropriate decisions, while avoiding overly cautious behaviours.

MYTH: “Prompt administration of intramuscular epinephrine alone may be sufficient to prevent a fatal outcome”

International guidelines agree that intramuscular (IM) epinephrine is the treatment of choice for managing food-triggered anaphylaxis, and has a good safety profile when given by the IM route (55–57). However, fatalities occur despite the timely administration of epinephrine. In UKFAR, at least one third of fatalities due to food-induced anaphylaxis occurred despite timely administration of adrenaline (29,42,58) . In a case series of 32 fatalities reported by Bock et al (38) at least 4 patients received epinephrine in a timely manner. A recent systematic review and metanalysis (of 36,557 anaphylaxis events) found that around 10% of reactions have a suboptimal response to a first dose of epinephrine (as assessed by a healthcare professional) and require further doses (59) . Typically, 2-3% are treated with more than 2 doses of epinephrine, and around 1 in 200 reactions with 4 or more doses (59) . The reasons for a suboptimal response to epinephrine are likely to be multifactorial: inadequate dose of epinephrine (which may be confounded by route of administration) (60) , delayed administration, presence of cofactors or augmentation factors which increase severity (61) or ongoing allergen absorption due to residual allergen in the gut. At least 80% of anaphylaxis events resolve spontaneously with little or no intervention (31,62). This implies that in many if not most individuals, compensatory mechanisms “kick in” during anaphylaxis which will often result in self-resolution. Whether a lack of ability to compensate is a factor in more severe reactions is unknown, but clearly some individuals

require epinephrine, and some have a suboptimal response to just a single dose and will require more than 1 dose(s). Multiple case series (including reports of fatal anaphylaxis) and case-control studies suggest that early epinephrine administration may be associated with improved outcomes in anaphylaxis (63). In reality, it is totally inappropriate to "play Russian roulette" and therefore all anaphylaxis reactions must be promptly treated with IM epinephrine dependant on adequate muscle perfusion for the dose to be transported to target organs. There is little doubt from observational studies (64,65) that anaphylaxis responds well to sufficient epinephrine dosing with sufficient circulatory support (intravenous fluids). However, some reactions require more epinephrine than can be delivered by one or two doses using an auto-injector device.

More controversial is whether administering epinephrine early in an allergic reaction, prior to the onset of symptoms of anaphylaxis, is protective. Such an approach seems to be based on an extrapolation of the data relating to adverse outcomes with delayed epinephrine. Due to ethical reasons, appropriate clinical trials evaluating the clinical benefit of early vs late administration of epinephrine in the prevention of fatal anaphylaxis are not possible. There is a single case report of note: a patient who was repeatedly administered epinephrine during an initially mild reaction to brazil nut, which did not prevent progression to fatal outcome (43).

Food-allergic individuals must be advised against over-reliance on epinephrine auto-injectors where symptoms do not respond to two doses of IM epinephrine, there is a need to rapidly escalate, obtain the necessary expert input and consider low-dose intravenous epinephrine infusion with intravenous fluid support to manage refractory reactions (31).

288

289

290 **FACT: “A clear chain of communication in food supply (labelling, restaurant staff etc.) is**

291 **key in preventing fatal outcomes”**

292 Food allergy information, especially regarding the presence of food allergens in food is

293 paramount to the prevention of unintended food reactions, and therefore fatal food-

294 induced anaphylaxis. Food-allergic individuals (and their caregivers) have to trust food

295 businesses to clearly communicate allergen presence in foods and facilitate their ability to

296 make safe food choices, as highlighted in a recent research prioritization exercise in the UK

297 (66). This requires food-allergic customers to be confident in their ability to clearly

298 communicate their dietary requirements to food establishments. A significant portion of

299 fatal food reactions occur outside the home. In UKFAR, 59% of fatalities were due to food

300 purchased from catering outlets, and only 27% occurred in the patient’s own home (45). A

301 recent study reported that over half of all allergic reactions in restaurants occur despite the

302 patient or caregiver informing restaurant staff about their allergy; a quarter occurred even

303 when allergens were declared on the menu, with 10% happening despite the allergens being

304 declared on the menu and restaurant staff being informed about the customer’s food

305 allergy (67). Allergic consumers prefer written allergen information, supplemented by

306 credible verbal communication from staff (68). Thus, restaurants would benefit from

307 providing more food allergy training to employees and/or designating a specific employee

308 as a food allergy point person (69). Communication needs to be bidirectional, with

309 customers also informing restaurant staff about food allergy needs (70). Alerting the

310 restaurant ahead of time of the food allergy, involving senior staff or the chef in the order,

and ensuring the table surface is adequately cleaned are simple, but key steps in minimizing risk (72).

SUMMARY

Patients with food allergy must navigate a world that requires daily vigilance for allergens and preparedness for allergic reactions. Although the actual risk of fatal reactions is minimal, it is not zero and severe reactions are unpredictable. Food-allergic individuals (and their caregivers) understandably perceive fatal anaphylaxis is far more common than the hard statistics indicate, and this has a significant adverse impact on quality of life. However, this burden may be eased by public health measures that distribute responsibility for safety and emergency treatment across multiple sectors.

There is a clear need for the communication of accurate food allergen information. Most countries have legislation informed by Codex Alimentus (for example, the 2004 Food Allergen Labelling and Consumer Protection Act (FALCPA) in the USA; the 2014 Food Information to Consumers (FIC) legislation in the European Union) which mandates priority allergens for disclosure when present as an ingredient (73). However, the legislation does not extend to allergens which may be present due to cross-contamination during food production, which has resulted in a proliferation of precautionary allergen labelling (PAL). The Codex standards are currently being reviewed, which may provide a regulatory basis for the use of PAL (66,73–75). Within catering (and school) settings, standardization of and requirements for food allergy training, clear plans for disclosing allergens in food/lunch menus, and clear plans for anaphylaxis management would also ensure that patients can make informed decisions about food safety and receive appropriate treatment (76,77).

Better management of anaphylaxis may also be supported by efforts to ensure that stock EAls are available in schools and other settings where someone may experience their first allergic reaction and/or not have their own EAI available (77–80). Equally important is ensuring that EAls are affordable for all families so that initial treatment is available when needed (82).

Even if such measures have minimal impact on the risk of fatal reactions (given the very low incidence of fatal food anaphylaxis), they will have a significant impact on the risk of any reaction and the quality of life and self-efficacy of patients with food allergies and their families. Specific research is needed to better understand the circumstances of near-fatal and fatal food anaphylaxis, in order to identify risk factors which can then be used to inform management at an individual patient and public health level. Until then, we need to help our patients to better understand the very low but real risk of fatal reaction, and help them lead as normal a life as possible through appropriate safety-netting and risk avoidance (Table 1).

Table 1. How to Communicate About Fatal Food-Induced Anaphylaxis with Patients and their Families

How to Communicate About Fatal Food-Induced Anaphylaxis with Patients and their Families	
Provide the Facts	
1. Fatal food anaphylaxis is rare. 2. Severity of previous reactions does not predict future risk. 3. Some foods are more likely triggers than others (peanut, tree nut, shellfish, milk). 4. Adolescents may have more difficulty with food allergy management than young children and may benefit from targeted education and problem solving. 5. Early epinephrine administration is associated with improved outcomes in anaphylaxis.	
Emphasize What Patients and Families Can Do To Prevent Fatal Anaphylaxis	
1. Allergen avoidance is of paramount importance because it prevents allergic reactions. a. Read food labels and ask about ingredients. b. Inform anyone preparing food for the allergic patient about their food allergy. This includes restaurant and school personnel. c. Teach children and adolescents how to manage and communicate about their food allergy. 2. Optimise asthma management because sub-optimal asthma control and underlying airways hyperreactivity is a risk factor for more severe reactions. a. Use asthma medications as prescribed. b. Follow the asthma management plan, and seek medical input if the need for reliever medication increases without an obvious infective trigger. c. Regular asthma reviews are essential. 3. When allergic reactions occur, prompt treatment with epinephrine is essential. a. Carry epinephrine auto-injectors when outside the home. b. Train all caregivers in how to detect an allergic reaction and when and how to use epinephrine. This includes school personnel. c. With anaphylaxis, use epinephrine early.	
Provide Support and Resources	
1. Listen to patients' and family members' fears and acknowledge them. 2. Offer additional resources (e.g., handouts, websites) that can give families the tools they need to successfully manage food allergy and boost their self-efficacy.	

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CME EXAM**MS# & Article title:** 21-00878, Fatal food anaphylaxis: dissecting fact from fiction**Author(s):** Aikaterini Anagnostou, Vibha Sharma, Linda Herbert, and Paul Turner**Issue:** January 2022 (Food Allergy theme)**Review series:** Clinical Commentary**Editor:** Scott H. Sicherer

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Learning objectives:

1. To describe the incidence and risk factors for fatal anaphylaxis.
2. To describe the most common reported food triggers associated with fatal reactions.
3. To discuss measures to reduce the risk of food -induced fatal anaphylaxis.
4. To interpret mast cell tryptase results in the context of anaphylaxis.

Questions:

1. Which of the following is true regarding fatal anaphylaxis?
 - A. The incidence has been increasing over the last decade.
 - B. Food is the most common trigger.
 - C. It is a frequent event.
 - D. There is an estimated 1.8 fatalities per million-person years in food allergic individuals

Answer: D

Explanation: Fatal anaphylaxis rates have remained stable and food is the least common trigger for fatalities (medications are the most common culprit). Food-induced fatal anaphylaxis is fortunately a rare event.

2. Which of the following is true regarding fatal food-induced anaphylaxis?
 - A. It is only due to peanut and tree nuts.
 - B. It does not occur in milk-allergic individuals.
 - C. It is caused by different food triggers in different regions of the world.
 - D. It always occurs in patients with asthma.

Answer: C

Explanation: Triggers for food-induced anaphylaxis fatalities include peanut, tree nuts, milk and shellfish. Triggers vary in different geographical regions. Fatal food anaphylaxis can occur both in asthmatic and non-asthmatic individuals, and asthma in itself is a poor predictor of severe anaphylaxis.

3. Which of the following statements is true when interpreting mast cell tryptase (MCT) levels in context of anaphylaxis?
- A. MCT levels are always within the normal range in those with food-induced anaphylaxis
 - B. MCT levels may be falsely low in post-mortem samples
 - C. Paired MCT samples taken 6 and 8 hours after anaphylaxis indicate mast cell degranulation
 - D. MCT levels alone, cannot be used as indicative of anaphylaxis

Answer D

Explanation: MCT should be interpreted within the clinical context. Levels may be within the normal range following food induced anaphylaxis (although not always) and can be elevated in clinical scenarios other than anaphylaxis such as hereditary alpha tryptasemia, renal failure, in infancy, and non-anaphylactic deaths from acute exacerbation of asthma and hemorrhage. Levels may be falsely elevated in post-mortem samples. Paired MCT samples should be taken 1 and 2 hours after anaphylaxis.

4. Which of the following is an important strategy to impart to adolescents and young adults with food allergies for navigating safe restaurant meals?
- A. Rely on having self-injectable epinephrine
 - B. Bidirectional communication with staff
 - C. Avoid restaurants
 - D. Rely on past experience to make decisions about food safety

Answer: B

Explanation: Patients may erroneously assume epinephrine is certain to rescue them in the event of errors in obtaining a safe meal but this is incorrect (option A is incorrect). Avoiding restaurants is not advised since this is impractical and a negative impact on quality of life (option C is incorrect). Adolescents and young adults are most likely to experience fatal food-induced anaphylaxis. Many adolescents rely on past experience with food to make decisions about food safety, which is not a reliable or recommended strategy (option D is incorrect). The best answer is B, to ensure bidirectional communication between restaurant staff when discussing the allergy and food preparation, ingredients, etc.