



Food allergy guidelines and assessing allergic reaction risks: a regulatory perspective

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Purpose of review

To review information in food allergy guidelines and the literature on assessing and understanding food allergic reaction risks.

Recent findings

Current food allergy guidelines have focused on tools for better diagnosis of food allergy and treatment of reactions. These guidelines have not addressed the growing body of literature on risk assessment and diagnostic tools being used to assess dose–response relationships in relation to food-allergen exposures. The literature includes substantial data from food-allergen challenges performed in sensitive individuals, and probabilistic modeling of these data may help to elucidate the relationship between allergen dose exposures, including thresholds, and reaction risk in allergic individuals. Understanding this relationship has potential to improve the health-related quality of life of allergic consumers.

Summary

Recent findings in the literature have highlighted improved diagnostic tools and other information that can be used to assess risks for allergic reaction to low-dose allergen exposures (thresholds) and reaction severity in food allergic consumers. Recommendations to better define and stratify allergic reaction risks for consumers could be adopted into guidelines for the diagnosis and clinical management of food allergy.

Keywords

allergen hazard management, food allergic reaction, oral challenge, regulatory, risk assessment

INTRODUCTION

There are many uncertainties with regard to risks from food-allergen exposure [1,2^{***}]. Food allergens, when ingested by sensitive individuals, can cause acute and severe physical harm, including anaphylaxis and death. This harm is unpredictable and highly variable depending on the dose of allergen exposure and the degree of sensitivity of the affected individual. There are no current treatments for food allergies. Thus, preventive efforts to avoid causative allergens and prompt treatment of reactions resulting from untoward allergen exposure are the mainstays of food allergy management. Despite these efforts, accidental adverse exposures to food allergens occur and represent the number one cause of anaphylaxis cases presenting to emergency departments [3,4]. Fear of severe reactions, uncertainties with regard to risk for future reactions, the daily burden of strict allergen avoidance, and other psychosocial factors contribute to negatively impact the quality of life (QoL) of food allergic individuals and their families [5^{*},6].

Regulatory agencies such as the Center for Food Safety and Applied Nutrition (CFSAN) of

the US Food and Drug Administration (FDA) play an important role in the preventive management of food allergy by ensuring that major food allergens are properly identified on food labels and by assessing potential hazards posed by food allergens or allergenic ingredients in the food supply. In assessing these hazards, regulatory agencies rely on risk assessment-based methods to understand the known or potential adverse health effects from exposure to food allergens in sensitive individuals. As allergens cause acute serious harm, risk assessment considers information on the size of the population at risk for serious harm and, when available, data on dose–response relationships and

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Curr Opin Allergy Clin Immunol 2012, 12:000–000

DOI:10.1097/ACI.0b013e3283535aaf

KEY POINTS

- Current food-allergen management practices have not prevented all health hazards and risks to allergic consumers.
- Understanding risks to allergen exposures may assist consumers in coping with the burden of allergen avoidance and improve quality of life.
- Tools being used to assess population food allergenic risks may also be applied to address individual consumer concerns about risk for severe reactions and reactions to low-dose allergen exposures.
- Stratification of reaction risks for food allergic consumers provides a tool for the diagnosis and clinical management of food allergy.

severity of reaction in relation to any allergen exposure.

Recent national guidelines on food allergies in the USA and United Kingdom, respectively [7,8], have been developed to provide national consensus on the definition, clinical diagnosis and acute management of food allergies by clinicians. Although these guidelines help to better identify and treat individuals at risk for food allergic reactions and complications, there has been little focus on how to utilize information from food challenges and other methods or tools seeking to establish reaction thresholds and assess reaction risks posed by allergenic food hazards in sensitive individuals. This information is not only helping regulators and the food industry to better recognize and manage allergenic hazards in food but could also be useful for clinical management of food allergic individuals by providing a needed tool for communicating and stratifying [2nd] their risk of reaction to allergen dose exposures. Risk stratification of individuals at highest or lowest risk may ultimately help these individuals better cope with uncertainties about reaction risk, to low dose exposures in particular, in their food allergen avoidance practices. The purpose of this review, therefore, is to review the current state of food allergen hazard management and to highlight, from a clinical regulatory perspective, recent advances in characterization of key elements that address allergic reaction risks and diagnostic uncertainties surrounding these risks.

RISK AND ALLERGEN HAZARD CONSIDERATIONS

There are important diagnostic certainties and uncertainties in assessing allergic reaction risks (Table 1) [1,9–22,23rd,24]. In this context, risk is

defined as the likelihood of adverse outcome (e.g., allergic reaction) following exposure to a hazard, whereas hazard is the intrinsic capability of the food allergen to cause an adverse effect [25]. Although similar risks may result from other food allergic conditions, risks associated with immunoglobulin E (IgE)-mediated food allergy are the best studied and, because adverse exposure to hazards can lead to anaphylaxis and possible fatality, are the most important from a public health perspective. Given current risk information, allergen-labeling laws at the public health level have taken a conservative approach to risk management in which no level of major food allergen hazard can be deemed safe for consumers and presence of any amount of allergen intentionally added to food must be labeled (unless exempted by law). At the individual level, similar information about no safe level of allergen is communicated to consumers leading to recommendations of strict avoidance diets, including food products with allergen advisory statements and low likelihood of allergen presence [7,26]. Although these approaches may protect the most highly sensitive individuals from consuming and reacting to allergen hazards, they may also be limiting a number of nutritious food products that might be tolerated by the majority of the food allergic population. Moreover, diagnostic uncertainties about risk have also placed risk management decisions into the hands of consumers and their families [27] rather than those of healthcare providers, potentially driving food choices or avoidance practices that negatively impact health and QoL.

MANAGEMENT OF ALLERGEN HAZARDS

Management (and avoidance) of food allergen hazards is not a simple process. Over 170 different foods have been reported to cause IgE-mediated food allergies [7]. Food allergens are foods consumed daily and widely in the diet (e.g. at home, school, restaurants, social gatherings, etc.) and are ingredients routinely added to or found in a variety of food products. Communication of the presence of food allergens in these products may not always be clear [28,29]. Moreover, globalization of the food supply has introduced novel, potentially allergenic foods not previously encountered in the diet, and various processing methods may make some food proteins more or less allergenic [25,30,31]. Factors that promote or prevent allergic sensitization or development of food allergy are not currently known. Thus, regulatory and food industry efforts have focused on identifying and managing known food allergen hazards posing the greatest risk to sensitive consumers.

Table 1. Food allergic reaction risks	
Diagnostic certainties	Observations
Absolute elimination of risk is not possible	Allergenic hazards are encountered frequently and, despite strict avoidance, accidental reactions can and do occur Although some food allergies are outgrown, factors that prevent allergic sensitization are not known and there are no known treatments to prevent risk for reaction in sensitized individuals
Greatest risk is associated with oral route of exposure	Casual food allergen contact by skin and inhalant routes can frequently elicit mild reactions Severe reactions have been demonstrated to only occur with oral consumption of allergen [9–11]
The magnitude of risk (eliciting dose, severity) to a given allergen exposure varies:	Within a given allergic population, food challenge MED data show a wide range in individual reactivity to allergen threshold exposures, from doses as low as micrograms to as high as grams of allergenic protein [1,12–14]
Among individuals within the allergic population	Allergic reaction type and severity to allergen challenge doses vary among individuals in a food allergic population [15,16]
Within a given allergic individual	Eliciting challenge doses have been shown to vary by as much as a 100-fold magnitude within the same individuals on different challenge days [17] Concomitant factors during/after the meal such as alcohol consumption, medications, exercise, fatty food matrix may delay or potentiate risk [13]
Skin test wheal size/serum IgE levels predict who will fail food challenge	Changes in individual sensitivities, such as concurrent development of asthma and/or acute febrile illness, may potentiate severe reactions and/or lower individual MEDs, respectively [18] Skin test wheal size/serum IgE levels are generally considered poorly predictive of magnitude of risk to future allergen exposures
History of prior anaphylaxis predicts greater risk for severe reaction	Prior history of mild reaction is poorly predictive of mild severity and does not preclude risk for severe or fatal reaction [7]
Diagnostic uncertainties	
Who is at risk for severe reactions?	Not all individuals with IgE-mediated food allergy exhibit severe allergic reaction after allergen exposure Prevalence data on severe reactors within the food allergic population are lacking General risk factors include: type of food, e.g. peanut and tree nut, dose of food, and history of asthma Potential anaphylaxis biomarkers [20]: PAF hydrolase deficiency, reduced ACE levels (severe angioedema), multiple food allergen epitope specificity, basophil activation markers
Who is at risk to minute allergen exposures?	Reactions to trivial or minute amounts of allergen contact or exposure are reported to occur in individuals; analytical confirmation of low eliciting doses cannot be verified in most cases Probabilistic modeling of food challenge MED distributions in a population of allergic individuals can help identify size of population at risk for reaction to certain allergen dose exposures; these data show that a minority of allergic individuals react to very low allergen dose exposures [1] Data are lacking on actual allergen dose/amounts in products causing adverse consumer reactions in the community to corroborate experimental low-dose MED data from challenge studies Some tolerizing treatments (e.g., oral allergen immunotherapy/desensitization, [21] anti-IgE therapy [17]) have been shown to increase individual reaction thresholds to low-dose exposures Recent findings suggest that elevated food-specific IgE levels may be predictive of risk [22,23 ^{***}]
Does sensitivity to low-dose allergen exposures predict more severe reactions, or vice versa?	Studies have shown conflicting results with regard to evidence of a direct relationship between low MED and risk for severe reaction

Diagnostic certainties	Observations
	Data are needed on the interrelationship between low MEDs and individuals with severity (anaphylaxis) biomarkers
Is same risk reproducible on subsequent exposures?	There are limited data on repeat oral challenges to assess reaction reproducibility; one study found good correlation between reaction type and severity experienced in community and that elicited by challenge; however, repeat challenge of certain foods (i.e. egg) resulted in different reaction type in nearly half of cases [24]
What is an allergic response that poses risk to human health?	Anaphylaxis is a response that poses significant risk to health; however, there are few biological or symptom endpoints, predictive of responses that will progress to anaphylaxis or be mild and self-limiting

ACE, angiotensin converting enzyme; IgE, immunoglobulin E; MED, minimal eliciting dose; PAF, platelet-activating factor.

CFSAN has multifaceted programs to assess the various hazards posed by food allergens in food products. CFSAN is responsible for ensuring proper labeling in most regulated food products of all ingredients containing protein from ‘major food allergens’: peanut, tree nuts, egg, milk, Crustacean shellfish, fish, soy, and wheat – representing 90% or more of foods causing severe reactions or anaphylaxis [32] – in compliance with the Food Allergen Labeling and Consumer Protection Act of 2004 (FALCPA). The one current labeling exemption is ‘highly refined oils’ derived from a major food allergen. FALCPA also defines two processes for granting additional exemptions based on scientific evidence demonstrating that an ingredient ‘does not contain allergenic protein’ or ‘does not cause an allergic response that poses risk to human health’. It is important to recognize that FALCPA does not apply to allergenic ingredients that can result in food products due to cross-contact during manufacturing. Management of these hazards focuses on enforcement of good manufacturing practices (e.g. allergen clean-up and control measures). In cases in which it deems allergen cross-contact to be unavoidable, the food manufacturer may choose a voluntary advisory statement (e.g. ‘may contain’ or ‘produced in a factory’) to convey risk of allergen hazard to consumers. Other allergen risk mitigation measures include inspections at food manufacturing facilities and recalls of adulterated products with undeclared allergens. Since 2009, FDA has established the Reportable Food Registry, an electronic portal for the food industry to report food hazards, including allergens, with serious adverse health consequences or death to humans or animals.

CFSAN also conducts various assessments of allergenic risks and hazards in the food supply. These include premarket evaluations of potential allergenicity of novel proteins, characterization of health hazard posed by undeclared allergenic

substances in food products subject to recall, and postmarket surveillance of food allergic events to FDA-regulated food products reported to the CFSAN Adverse Event Reporting System through *Medwatch* at www.accessdata.fda.gov/scripts/medwatch/ or through FDA district offices. Safety data on treatment modalities for anaphylaxis and on oral desensitization studies to food allergens are assessed by FDA’s Center of Drug Evaluation and Research and Center of Biologics Evaluation and Research, respectively. Within CFSAN, implementation of FALCPA labeling exemptions and other scientific labeling issues has led to consideration of approaches to determine the existence of ‘threshold’ levels below which it is unlikely that a food allergic individual would experience an adverse effect [32]. Thresholds can apply to individuals and to populations and establishment of thresholds depends on understanding the dose–response relationship between allergen ingestion and elicitation of an allergic response and characterization of any exposure levels below which all, or part, of the allergic population does not respond. To date, CFSAN has not set a threshold for any major food allergen.

Despite these efforts, mismanagement of allergen hazards in the food supply can occur and pose risks to consumers. Undeclared allergens have historically represented 30–40% of all US food recalls [33]. A more recent review of the FDA recall database has found that 15% of allergen-related recalls are associated with consumer reactions, milk allergen being the most common culprit [34]. Also, various studies have identified potentially hazardous levels of unlabeled allergens in products currently on the market, [26,28,35] in particular chocolate [36,37]. The impact of exposure to undeclared allergens in food is difficult to quantify, as anecdotal observations and studies on accidental reactions to allergens in consumers consistently

demonstrate that most reactions occur to non pre-packaged food consumed at home or restaurants and other retail establishments [9,38,39].

CONSUMER RISKS

There is no inherent harm to food allergic consumers if allergen hazard is avoided. However, constant vigilance of food labels and creating an environment free of food allergen exposure is both challenging and burdensome, and multiple studies using either QoL measures or generic health-related scales consistently demonstrate that food allergy has a significant impact on the psychosocial well-being of allergic consumers and their families [5[■],6]. Despite improved understanding and clarity of food labels, FALCPA requirements that any level of major food allergen, including those found in processing aids, must be declared in food products has led to a notable number of US food products carrying allergen labels or advisory statements [29]. As most allergen avoidance practices advocate avoidance of all products with relevant allergen labels or advisory statements [7,26], this has led to fewer overall food choices for allergic consumers. Another consequence is that consumers are increasingly admitting to consuming products based on perceptions of risk conveyed by certain advisory statements [28]. As it is possible that some products would contain significant levels of allergen hazard, this behavior could eventually lead to adverse health consequences.

The fear and uncertainty of accidental, severe reactions also negatively impact QoL and lead to coping strategies that often limit daily family or social activities to minimize this risk. Conversely, there is increasing evidence that better understanding of risks posed by allergen exposures may indeed improve QoL or other health measures. Studies have demonstrated that diagnostic food challenge, whether positive or negative, results in overall improved QoL measures [40[■],41[■]], parental anxiety [42], and parental perception [43]. Of particular interest, QoL improvement for the positive challenge group was greater than for a control group receiving no challenge at all [41[■]]. Thus, diagnostic confirmation and understanding of risks to allergen challenge, even when this information may suggest that someone is severely allergic, appear to have a better health-related outcome than the uncertainty of not knowing these risks. In practice, comprehensive allergen avoidance education and management plans addressing risk based on reaction severity have been shown to reduce frequency of reactions in consumers [9,44].

The health impact of understanding risks associated with individual reaction thresholds has not

been systematically studied nor addressed in current guidelines. Recognizing that thresholds may still vary within individuals [15,17], it is possible that this information would provide more clarity on (and stratification of) risks, in particular when consumers react to high challenge doses and are thus likely to tolerate low-level allergen exposures. These data may help consumers make better informed choices when confronted with trivial allergen exposures in their avoidance practices as well as help introduce a greater number of previously avoided products into their diet.

SIZE OF POPULATION AT RISK FOR SEVERE HARM

IgE-mediated food allergy places individuals at risk for anaphylaxis and serious harm. However, not all individuals with allergy will experience anaphylaxis and there remain relatively little data to estimate the number of individuals truly at risk for severe harm from allergen hazards encountered in food. Data from anaphylaxis cases in the community or allergic reactions presenting to emergency departments and/or associated with epinephrine use have been employed to estimate the number of annual serious adverse events due to food allergy [3,45,46]. According to these data, food anaphylaxis represents the most prevalent cause of anaphylaxis presenting to emergency departments [3,4] with estimates of 150 deaths per year due to food allergic reactions in the USA alone [47]. However, these annual rates do not fully capture the size of the population at risk for severe reactions. Some individuals with severe reaction may self-administer epinephrine and, after symptoms resolve, not go to the emergency department or to their physician [13]. Moreover, reactions that take individuals to the emergency department may not always be severe or life threatening, as shown by the wide variability (13–65%) in proportion of cases judged to be anaphylaxis among studies [7]. Also, estimations of reported fatality rates have been extrapolated from data from small community studies. These estimated rates have not been validated by national International Classification of Diseases review of death certificates or by number of deaths reported in US fatality registries [19].

Data on the number and percentages of severe allergic reactions from accidental exposure to food allergens reported by consumers from specialist clinics or the general population have also been used to estimate size of population at risk for severe reaction. Use of these data are hampered by differences in diagnostic criteria as well as choice of population studied and show a wide variability in frequency of

yearly reactions and percentage of severe responders, from 1 to 26% [9,48,49]. Moreover, these data involve retrospective review of clinical charts or patient interview, which may be subject to recall bias.

Within each allergenic food, there are multiple proteins with diverse epitopes to which individuals can become sensitized and/or react. The relative concentration of these epitopes may vary from product to product depending on the type of allergenic ingredient and degree of preparation or processing of the ingredient. Thus, diagnostic (e.g. 'component resolved') information on IgE sensitization patterns to specific allergenic proteins may provide more correlative information and answers regarding individual risk to allergen hazard exposures [50]. To this end, analyses have confirmed a remarkable heterogeneity in patterns of protein or epitope recognition between individuals, and individuals with a history of more severe allergic reactions to peanut were more likely to have IgE to multiple epitopes to Ara h 1-3 [51]. Protein component diagnostic information has also been used to characterize risk in populations of allergic individuals. A study [52²²] of peanut allergic individuals from different geographical areas, Spain, USA, and Sweden, found striking differences in onset of allergies, types of sensitizing proteins and severity of reactions among the three populations, with US consumers primarily sensitized to Ara h 1-3, developing allergy earlier in life and having more severe presenting symptoms. These findings highlight the promise of allergenic protein-specific diagnostics as a potential biological tool or marker for characterizing individual and population hazard or risk questions.

RISK IN RELATION TO MINIMAL ALLERGEN EXPOSURES

Establishing safe levels of exposure to food chemicals has historically relied on assessing minimum levels of toxicity found during feeding studies in rodent animals [32]. For food allergy, however, there are no validated animal models and no known biological markers to predict how much allergen exposure will cause an allergic reaction and/or pose risk to health. The best tool available to clinicians and scientists who look to understand reaction risks to a level of allergen exposure remains the double-blinded and placebo-controlled food challenge (DBPCFC) [1,12,13]. Over the past 15 years, low-dose DBPCFCs have been employed to determine minimal eliciting doses (MEDs) both for individual consumers as well as populations of individuals. These MEDs have been determined mostly to estimate thresholds [13,14,53²²]. However, DBPCFCs have also been undertaken to understand severity

of MEDs [15,53²²] as well as to identify eligible individuals, determine individual starting dose(s), and assess tolerance in therapeutic trials [17,21]. Numerous studies [16,54,55] have reported food allergen challenges to be relatively well tolerated procedures.

MED distribution data from a single individual or combined population(s) of allergic consumers receiving similar allergen dose challenges have been used to generate probabilistic risk assessment models [14,53²²,56]. Information from these models, such as the estimated dose of allergen eliciting a reaction in a 10% of the population and the proportion of population reacting to a given dose, has been proposed to address various questions on threshold dose estimations or to assess the potential risk to certain allergen levels in products. Currently, the most complete dataset is for peanut, which now includes over 600 consumers, mostly from Europe [14,53²²]. Although uncertainties remain with regard to exclusion of sensitive populations (e.g. those with history of anaphylaxis), geographic food allergy differences between populations, and lack of understanding of severity in relation to MEDs, MED distribution data corroborate the wide variability in responses among individuals to low-dose challenge and have begun to suggest that the majority of responders in a population would tolerate doses of peanut protein in the low milligram range (peanut size equivalent to 1 of 40 peanuts). A clinician might view these findings and conclude that more routine use of food challenge could be used to inform allergic individuals where their risk lies on this MED distribution. Also, although therapeutic trials are outside the scope of this review, as MED data help inform oral desensitization starting doses [21] and more individuals partake in desensitization trials, it will become interesting to observe how daily exposures to potentially tolerizing, low doses of allergen will impact population MED distributions in the future.

REACTION SEVERITY RISK

Biological or historical markers or endpoints to predict reaction severity of future allergen exposures are still lacking. Allergen-specific IgE levels may predict who is likely to fail allergen food challenge; however, these levels do not identify or distinguish who is at risk for severe reaction [16,20]. Likewise, prior history of anaphylaxis may predict someone with a greater risk for future anaphylaxis (71% risk in subsequent reactions); however, 44–80% of subsequent reactions in individuals with prior history of mild reactions were severe [48,57]. Also, use of specific clinical symptoms as predictive endpoints of severe

reaction or anaphylaxis may be problematic because the severity of the allergic response is progressive and not well defined, with no criteria for which one of the many symptom endpoints is most consistent for anaphylaxis [4,20].

DBPCFC data can be used to predict risk for severe reactions [15,16]. However, these data may be limited in that DBPCFC often are stopped at the earliest signs of reaction (MED) to minimize harm to subjects. As a result, only MED severity endpoints are achieved, and the dose–response relationship between MED severity and severity endpoints at higher doses remains uncertain [12,22]. Nonetheless, MED severity may be used as a tool to understand reaction severity risk at threshold doses or to assess responses that pose risk to human health. Clinical evidence suggests that most MEDs resolve without need of rescue medication [16,54,55]. However, 28% of MED responses in one clinic population were classified as severe [15]. In this study, challenge doses began in the high (100+) milligram range and may not have represented true MEDs for some severe responders. Studies comparing MEDs and reaction severity (i.e. prior history of anaphylaxis) have found conflicting results with some studies suggesting a correlation [14,15] and others not [16,17]. Other studies have found that elevated allergen-specific IgE levels predicted higher challenge scores [55] and risk for reaction to lower MEDs [22,23[■]]; this risk was found to be greater for individuals without concomitant asthma [22], without eczema [23[■]], and with increasing age (greater in adults than children) [23[■]].

Promising biological markers that may identify and differentiate severe responders from nonsevere responders include platelet activating factor (PAF) acetylhydrolase deficiency, which leads to inefficient breakdown of PAF, a mediator that may potentiate anaphylaxis [58]. Also, individuals with life-threatening angioedema were found to have reduced levels of angiotension converting enzyme, suggesting an abnormality of the bradykinin pathway in this response [59]. There is a need for identification and inclusion of sensitive individuals with known severity markers in future challenge studies, and correlation of MED response and severity in this severe responder population may add value to interpretation and understanding of reaction severity endpoints.

CONCLUSION

Allergen hazards are everywhere and cannot be effectively managed without some understanding of allergic reaction risks. Diagnostic uncertainties about reaction risk and burdensome restrictive diets

are likely contributing to decreased QoL in food allergic consumers. Recent data from studies using food challenges and other biological endpoint data to understand dose–response relationships to allergen exposures, severity of reaction and impact on QoL measures have highlighted the need to introduce risk stratification into the clinical management of consumers and to advance diagnostic tools, such as food challenge, to better characterize risk and reaction severity. Addressing consumer reaction risks may inform allergen management not only from the public health and regulatory viewpoint but from the physician–patient viewpoint as well.

Acknowledgements

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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