**Can we identify patients at risk of life-threatening allergic reactions to food?**

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Anaphylaxis has been defined as a “severe, life-threatening generalized or systemic hypersensitivity reaction”. However, data indicate that the vast majority of food-triggered anaphylactic reactions are not life-threatening. Nonetheless, severe life-threatening reactions do occur, and are unpredictable. We discuss the concepts surrounding perceptions of severe, life-threatening allergic reactions to food by different stakeholders, with particular reference to the inclusion of clinical severity as a factor in allergy and allergen risk management. We review the evidence regarding factors which might be used to identify those at most risk of severe allergic reactions to food, and the consequences of misinformation in this regard. For example, a significant proportion of food-allergic children also have asthma, yet almost none will experience a fatal food-allergic reaction; asthma is not, in itself, a strong predictor for fatal anaphylaxis. The relationship between dose of allergen exposure and symptom severity is unclear. While dose appears to be a risk factor in at least a subgroup of patients, studies report that individuals with prior anaphylaxis do not have a lower eliciting dose than those reporting previous mild reactions. It is therefore important to consider severity and sensitivity as separate factors, as a highly sensitive individual will not necessarily experience severe symptoms during an allergic reaction. We identify the knowledge gaps which need to be addressed to improve our ability to better identify those most at risk of severe food-induced allergic reactions.

**Introduction**

Anaphylaxis has been defined as a “severe, life-threatening generalized or systemic hypersensitivity reaction” (1,2). However, evidence suggests that the majority of food-triggered anaphylactic reactions are not life-threatening (3): 80% of young adults recover spontaneously from food-induced anaphylaxis, despite not receiving adrenaline (epinephrine) or medical attention (4). Other definitions (e.g. “an acute, potentially fatal, multi-organ system, allergic reaction” (5)) may therefore be more appropriate. Nonetheless, severe life-threatening reactions do occur. These are unpredictable, resulting in a perception of risk which adversely affects health-related quality of life (HRQoL) to a degree comparable to chronic illnesses such as diabetes (6). Attempts to reduce this is hampered by our inability to identify those at greatest risk. It is for this reason that all anaphylaxis should be considered as potentially fatal, justifying the need for patient education and provision of appropriate rescue medication including adrenaline autoinjector devices (AAI).

The EU-funded iFAAM (Integrated Approaches to Food Allergen and Allergy Risk Management) collaboration is developing evidence-based approaches and tools for the management of food allergens and their integration into patient management. A major aspect of the collaboration is to investigate the role of factors, such as the food matrix and medication (e.g. proton pump inhibitors), in severity of food-allergic reactions. In a parallel activity, the TRACE Peanut Study (funded by the UK Food Standards Agency) is assessing the effect of exercise and sleep deprivation on severity. In a joint workshop, perceptions regarding severity and the need for a harmonised approach to classifying severity of food-allergic reactions were explored. This paper discusses the concepts and misinformation surrounding the perception of severe i.e. life-threatening anaphylaxis to food (in contrast to anaphylactic reactions of lesser severity, which we propose are *potentially* life-threatening), and identify the knowledge gaps which need to be addressed to predict those most at risk of such reactions.

**Epidemiology of life-threatening anaphylaxis**

Determining an accurate incidence for food-triggered anaphylaxis is difficult, due to study heterogeneity, differences in definitions of anaphylaxis, and method of data collection (e.g. hospital coding, self-report). Consequently, estimates of the proportion of food-triggered allergic reactions that result in anaphylaxis (of any severity) vary widely, between 0.4% and 39.9% (5). A systematic review, incorporating a sensitivity analysis based on different estimated food allergy prevalences, reported an incidence for medically-coded, food-induced anaphylaxis in food-allergic individuals of 110 to 210 per 100,000 person-years (7).

The frequency of *life-threatening* anaphylaxis (e.g. requiring hospitalisation or fatal outcome) is more difficult to determine. Prospective case collection in a population-based cohort using a pre-defined diagnostic algorithm has never been attempted, due to the need for a large sample size given the very low expected incidence (5). Disease-specific registries – an alternative for rare disorders – are unlikely to include all cases (8). Retrospective evaluations are hampered by the heterogeneous clinical presentation, variable appreciation of severity by patients and healthcare professionals (HCPs), and recall bias. Data relating to fatal anaphylaxis may be more reliable given the unambiguous outcome, although causality can be difficult to ascertain. Case fatality rates are very low at <0.0001% (9,10). The UK Fatal Anaphylaxis Registry (UKFAR) reported a doubling in hospitalisations for food anaphylaxis from 1998-2012, but no increase in fatalities (0.011 (95%CI 0.009-0.013) cases per 100,000 per annum) (11). Fatalities were most common in the second and third decades of life, consistent with US and Australian datasets (10,12). A recent systematic review estimated the incidence of fatal anaphylaxis in food-allergic individuals at 1.81 per million person-years (95%CI 0.94-3.45); in comparison to other significant events, fatal anaphylaxis remains a rare – but unpredictable – event (Figure 1) (13).

***The impact of severity on food allergy***

Food allergy, of any severity, impacts significantly on HRQoL. We do not know how HRQoL is affected by specific subjective and objective measures of severity (14-16). There is a certain opacity in terms of operational definitions of “severity” in the context of food allergy: many studies rely on self-reporting of symptoms or group moderate/severe cases together, leading to difficulties in interpretation (17). “Food allergy severity status” is currently a tentative construct and cannot be reliably used as a predictor of outcomes. However, subjective perceptions of severity and risk can be important prognostic factors for long-term HRQoL outcomes (18).

Reactions are unpredictable in relation to occurrence, severity and outcome, and occur despite appropriate allergen avoidance (19). Uncertainty has a direct effect on perception of control and trust, and indirect effects on emotional adjustment, social interaction, HRQoL and coping/management strategies (16). Severity is a contextual phenomenon: an allergic reaction may not be perceived as severe, if treated in familiar surroundings with a heightened perception of control. However, the same reaction in the public domain, often to an unknown degree of allergen exposure, will cause considerable fear, anxiety and possible embarrassment (20). Children, in general, have less comprehension of the meaning of “severity”, while teenagers are reported to ignore symptoms. Parents may be prone to anxiety and over-interpretation of symptoms, independent of their actual experience of severe reactions (21). These will all impact on the ‘accuracy’ of reported severity, with implications in terms of competency in future self-care.

**Can we predict those at risk of life-threatening reactions?**

A variety of factors might contribute to reaction severity (Figure 2), some of which have been termed augmentation or co-factors, although different terminologies exist (22,23). These are frequently used to risk-stratify allergic individuals, but are of limited clinical utility. A history of prior anaphylaxis *is* a risk factor for future anaphylaxis, but many such patients only experience mild symptoms at subsequent allergen exposures (24,25). Over half of the food allergy-related deaths in UKFAR were in subjects with only previous mild reactions (26), consistent with previous reports (24,27,28).

*1. Food and allergen-related factors* (Figure 3)

**Type of food:** Peanut and tree nuts are the most common causes of food-induced anaphylaxis, but this is likely to be related to the higher prevalence of nut allergies (11,29,30). Seafood is increasingly seen as a frequent trigger (31-33). Peanut and tree nuts are the commonest triggers for fatal anaphylaxis in the UK and USA, but in children, cow’s milk is the most common cause in UK and Israel (after taking prevalence into consideration) (11,34). This may be related to the ubiquitous role of milk in the diet, and high rates of cross-contamination, at least within certain sectors of industry (35). Persistent cow’s milk allergy is associated with a more severe allergic phenotype (36). Milk-allergic individuals who do not tolerate extensively-heated cow’s milk may be at greater risk of severe reactions (37). Although a common cause of anaphylaxis, egg rarely appears to cause life-threatening reactions, at least in children (11,38).

**Dose of allergen:** Dose is considered to be an important determinant of severity (39) but there is little data to substantiate this. Severe reactions have been observed down to milligram levels of allergen exposure (40). Estimating the amount of allergen consumed during reactions occurring in the community is unreliable. Threshold studies provide more accurate information, but may exclude those with prior anaphylaxis. Furthermore, challenges are usually terminated at the onset of objective and generally mild symptoms, so the relationship between dose and severity is poorly described. The available data (from studies which have included those with previous anaphylaxis) suggest that peanut-allergic individuals with a history of anaphylaxis are not more sensitive to low doses than those without (29,41-43). In a unique study, Wainstein *et al.* performed food challenges in 27 peanut-allergic children; in contrast to other studies, challenges were not stopped following onset of mild symptoms but allowed to progress (44). Anaphylaxis was provoked in 21 children; in 13/21 (62%) cases, this was attributed to further allergen exposure following initial non-anaphylactic symptoms; the eliciting dose itself did not predict anaphylaxis. Thus, the dose of allergen may be important in determining the occurrence of anaphylaxis for a specific individual, but not in determining the *severity* or outcome of anaphylaxis. Little attention has been given to distinguishing between the amount and “dose” (amount/kilogram body weight), which will differ significantly between young children and adults.

It is therefore important to consider severity and sensitivity as separate factors: a highly sensitive individual will not necessarily experience severe symptoms during an allergic reaction. Although fatal reactions are reported to have occurred to low exposures (34,45), most fatalities in UKFAR are thought to have occurred to substantial levels of allergen exposure (11).

**Food processing and the food matrix**: The three dimensional structure of any protein determines its physicochemical properties and biological activity. This includes its allergenic activity, a property which may be influenced by the stability of the protein to food processing (e.g. heat treatment) (46,47) and its resistance to gastric digestion (48). Allergenicity is also affected by other components within the food, referred to as the food matrix. Wheat incorporated into a matrix containing cow’s milk or egg reduced *in vitro* IgE binding to these allergens, independent of the effect of heating (49,50). Gastric emptying is affected by fat (51) and high fat matrices may inhibit binding of IgE to allergen (52), impacting upon reaction severity. This effect has been observed for peanut, which itself has a relatively high fat content (52,53), but not hen’s egg (54).

**Sensitisation status:** Individuals with more severe reactions may have IgE to specific epitopes which are more resistant to modification through food processing (46), something proposed for lipid transfer proteins (LTPs) (55). However, this may not be true for all food allergens: sensitisation to ovomucoid, an egg protein considered to be more resistant to heat-modification than ovalbumin (56), does not discriminate between tolerance or clinical reactivity to extensively-heated egg in clinical studies (57,58).

Skin prick testing (SPT) and/or specific IgE (spIgE) are predictive of the likelihood of a clinical reaction to food, but do not predict severity with sufficient discrimination to be of clinical use (59). Most of the available literature relates to peanut: associations between the degree of sensitization (SPT wheal size, spIgE level) and severity have been reported in some studies (27,44,60,61) but not others (62-66).

More recently, the predictive value of component resolved diagnostics, where spIgE to single allergen components from the same food source are measured, has been investigated (67). For example, sensitisation to food proteins homologous with Bet v 1 and profilins are associated with mild symptoms, mostly restricted to the oral cavity. These allergens are highly susceptible to gastric proteolysis, which may limit their ability to trigger a systemic reaction (68), a situation often referred to as Pollen Food Allergy Syndrome (PFAS). Food-allergic individuals frequently experience oropharyngeal pruritus as an initial symptom, the so-called “Oral Allergy Syndrome” (OAS). However, PFAS and OAS are not synonymous (69). The term “OAS” was first proposed by Amlot *et al* to describe symptoms in a cohort of food-allergic patients, 50% of whom went on to experience systemic symptoms (70). In a more recent study, 49% of adults with objective symptoms to hazelnut (not limited to oral symptoms) were sensitized to no other component other than the Bet v 1 homologue Cor a 1, possibly due to the presence of spIgE to other, non-detected components (71). Thus, monosensitisation to Bet v 1 homologues cannot, with current testing, always be assumed to imply a low risk of anaphylaxis. Individuals may be misclassified as being at no risk of systemic reactions, and not provided with appropriate education and rescue medication.

Significant geographical variations in sensitisation have been reported, particularly for hazelnut (72,73) and apple (74). An association between LTP-sensitization and severity has been reported particularly in the Mediterranean region (55). However, LTP sensitization does not always predict a clinical reactivity nor severity: peanut LTP rAra h 9 did not discriminate between clinical allergy and sensitization in two recent studies (75,76). Similar findings have been reported for Spanish patients sensitized to peach LTP (77). These data imply that in unselected populations, LTP sensitization may not useful in identifying patients at increased risk for severe reactions.

Some studies have reported an association between sensitisation to peanut Ara h 2 and severity (78-82), but not others (43,76). In EuroPrevall, spIgE to Ara h2 ≥1.0 kUA/L conferred a 97% probability for *any* systemic reaction, but did not differentiate between anaphylaxis and *non-anaphylactic* systemic skin reactions (76). This supports the assertion that the presence (or absence) of binding to Ara h2 (or Ara h1-3) does not predict risk of severity (83). Individuals with increased diversity of IgE against multiple components (78,80,81) or epitopes (84-86) may be more likely to experience severe reactions, but such diagnostic tools are not routinely available. IgE binding may be affected by other factors: allergen-specific IgG can neutralize IgE binding (85) which may reduce reaction severity. Data from a study assessing anti-IgE as an adjuvant for cow’s milk oral immunotherapy imply that IgE neutralization may be an important factor governing symptom severity (87). However, the data are contradictory (88), perhaps due to differences in the ratio of IgG4 and IgE competing for the same epitope. Avidity of IgE and IgG for peanut correlates weakly with symptom severity at food challenge (89), suggesting a more complex integration of different allergen-antibody-effector cell interactions are involved in determining severity.

**Variations in host cellular responses:** In addition to distinguishing between sensitization and true clinical reactivity, the basophil activation test may also correlate with symptom severity (88,90). However, baseline basophil responsiveness varies from day-to-day within the same subject, and so may not predict reaction severity on a different occasion (91). Understanding the intra- and inter-person variability in allergen-induced basophil reactivity may help to predict reaction severity in the future.

*2. Host behaviours*

**Risk taking:** Health-risk behaviours play an important role in disease management (92). In food allergy, risk-taking is a relevant factor in the context of predicting severity. Studies identify adolescents as being particularly prone to risk-taking, such as playing ‘tough’ by deliberately eating risky food or not carrying AAIs (93,94). Given this, one might expect fatal anaphylaxis to be greatest in teenagers and young adults. However, UKFAR reported that the increased incidence of hospitalisations (perhaps an indicator of severity) and fatalities due to food-triggered anaphylaxis persisted well into the fourth decade of life (11). Determinants of severity are likely to be multi-factorial. A recent review suggested that adolescents use many behavioural strategies when managing risk, with risk-taking dependent on the context (e.g. if help is more likely to come quickly, more risk is taken), and most teenagers manage their food allergies well (94). For parents of food-allergic children, risk-taking can be a deliberate strategy in an attempt to manage the disease and its psychosocial impact. Feeling ‘in control’ or reducing ‘uncertainty’ is a central part of ‘voluntary risk-taking’, where possible costs and benefits are sometimes planned rationally (95). Risk avoidance and risk-taking cannot be understood as uniform strategies but vary by situation and time. More research needs to be undertaken, as clinical studies do not include measures evaluating risk propensity, and our current knowledge is based mostly on qualitative data (96).

**Alcohol:** Data from the European NORA anaphylaxis registry has identified alcohol as a suspected co-factor in 3% (142/4783) cases (97), often in combination with other co-factors such as exercise, medication and additives (summative anaphylaxis) (98). Alcohol impacts upon risk-taking, potentially impairing allergen avoidance and affecting the ability of an individual to respond to symptoms. Alcohol can activate mast cells and basophils, either directly (99) or very occasionally via an IgE-dependent mechanism (100). Individuals with chronic alcohol exposure may also be at risk of more severe reactions (101) through effects on IgE generation and a pro-Th2-immune milieu (102).

**Medication:** Medication can induce or aggravate allergic reactions (103,104). This is seen more frequently in adults than children due to age-related differences in medication use (38). The most commonly implicated medicines are non-steroidal, anti-inflammatory drugs (NSAIDs), which are thought to enhance the absorption of food allergens (105), as well as acting directly on effector cells (106). In NORA, NSAIDs were a suspected co-factor in 4.9% (243/4917) reactions, almost all in adults (data to March 2014). Medicines used to treat cardiovascular disease have also been implicated: combined use of β-blockers and angiotensin-converting enzyme inhibitors increases the risk of severe reactions, possibly due to a synergistic effect resulting in mast cell priming (97). These medications taken in isolation can also increase risk, albeit to a lesser extent (97).

**Exercise:** Exercise is the most common co-factor implicated in anaphylaxis, present in almost 20% of cases in NORA (38,97) and a co-factor for reactions during OIT (107,108). There are two entities: exacerbation of classical IgE-mediated reactions, and food-dependent, exercise-induced anaphylaxis (FDEIA) where reactions are triggered by exercise. Whether the same mechanisms are involved is unclear. Wheat is the most frequent eliciting allergen in FDEIA (109) but other food allergens have also been implicated (98,110-112). Potential mechanisms are thought to include changes on gastrointestinal perfusion and absorption, and direct effects on mast cells and other effector cells, as reviewed elsewhere (111). One discrepancy is that many of the physiological changes seen during exercise require significant exertion, whereas FDEIA can occur following mild-moderate activity (112).

*3. Intrinsic and extrinsic factors not related to host behaviours*

**Immune-activation:** Data from NORA (98), case reports (113) and studies of oral immunotherapy (107,108) have highlighted the relevance of intercurrent infections, typically upper respiratory viral infections, in triggering allergic symptoms. Within UKFAR, there are cases of fatal anaphylaxis associated with flares in eczema (26), which might imply an underlying state of immune-activation contributing to severity. The reported effect of menstruation on allergic symptoms during OIT (107,108) suggests that oestrogens might promote effector cell degranulation (114,115), although recent findings from a murine model reported no effect on mast cell responsiveness but promotion of vascular leakage during anaphylaxis (116).

**Asthma:** Retrospective studies report an association between asthma and severity of anaphylaxis (117-119), an observation seen in studies of fatal anaphylaxis (11,26,120). Life-threatening manifestations in food anaphylaxis are generally caused by respiratory compromise, so asthma and/or underlying bronchial hyperactivity are likely to be significant risk factors (121,122). However, in UKFAR, many cases of food-triggered fatal anaphylaxis do not have a history of asthma *exacerbation* prior to the terminal episode (26), suggesting that other factors are also involved. Food anaphylaxis also frequently occurs in patients without coexistent asthma. Up to 50% of food-allergic children have asthma (24,123), yet almost none will experience a fatal food-allergic reaction; asthma is not, in itself, a strong predictor for fatal anaphylaxis. This does not, of course, diminish the need to achieve optimal control of asthma symptoms to manage risk in food-allergic individuals.

**Allergic rhinitis**: Severe rhinitis has been reported as a risk factor for pharyngeal oedema in nut-allergic individuals (65). Vetander et al reported a cohort of 35 children with both food allergy and hay fever, in whom admissions due to food-anaphylaxis were increased during the tree pollen season compared with the rest of the year (124). No seasonal distribution has been observed for fatal food anaphylaxis in UKFAR (unpublished data).

**Cardiovascular disease:** Recent data from the US suggest that patients on antihypertensive medication experience greater reaction severity (125). Pre-existing cardiovascular disease was associated with the most severe allergic reactions in NORA (97). In contrast, in a prospective Australian study of 402 patients with anaphylaxis, cardiovascular risk and medication usage had highly significant associations with age but provided no additional predictive value for reaction severity using multivariate logistic regression (126).

**Sex/gender and age:** Food is the most frequent cause of anaphylaxis in children (11,127,128) and is more frequent in young male children; this reverses after puberty (129). The exact contribution of biological and sociological factors for these observations is poorly understood. The NORA Registry reported a slightly higher risk of more severe anaphylaxis in postpubertal males (13-56 years) compared to age-matched females (130). However, no differences have been seen for fatal food-anaphylaxis in UKFAR (11).

**Genetic predisposition**: The UKFAR dataset includes a notable excess of milk-allergic male children with at least one parent of African, Middle-East or Far-East descent (131). Whether this might be due to genetic predisposition or cultural factors is unclear, and requires further investigation.

*4. Ability of the host to compensate for the allergic reaction*

Little is known about factors which might protect against severe reactions. Clearly, many individuals experiencing anaphylaxis recover spontaneously, without the need for rescue adrenaline or other medical intervention (4). There may be variations in the inherent ability of individuals to compensate for an allergic insult, for example through endogenous catecholamine production. Individuals who are less able to metabolise inflammatory mediators generated during food-allergic reactions, such as platelet activating factor (132) and kinins (65,133), may be more likely to experience severe symptoms, however more data are needed to confirm these findings.

**Defining severity in practice – are we all speaking the same language?**

The management of food allergy involves multiple stakeholders, from allergic individuals and those assisting with their care, to the food industry and government bodies charged with regulation. Severity may be defined and perceived very differently by these groups.

*Discrepancies in severity perception between healthcare professionals (HCPs) and allergic individuals*

Perceptions of severity are dependent on an individual’s previous experience – and *lack* of experience – of reactions, both their own and others’. This is consistent with research demonstrating improved HRQoL in individuals undergoing controlled food challenges, regardless of outcome (16,134,135). Perceptions may be affected by ‘visual severity’: young children often develop significant skin signs (such as marked facial angioedema) which parents may perceive as a life-threatening reaction. In contrast, parents may not consider the possibility of wheezing (in a child prone to recurrent wheeze) as indicating anaphylaxis, resulting in a failure to initiate appropriate management. In the acute setting, HCPs both undertreat anaphylaxis (136-138) and, arguably, over-treat visually-severe but non-anaphylactic reactions, particularly in young children in whom the diagnosis of anaphylaxis may be difficult (136,137). This pattern is also seen at discharge, with provision of AAI when it may not be indicated, and more concerningly, under-prescription when it is (32,33,137-140).

Mild symptoms following minimal allergen exposure or reactions without ingestion may be considered as implying a more severe allergy; there is little evidence for this (31,141,142). Confusion can result from reactions to ‘traces’ of allergen, whereas in reality, many such events are caused by substantial contamination and not a ‘trace’ (143). Most (>95%) foods with “may contain” precautionary allergen labelling (PAL) do not contain detectable allergen (144-147). Some allergic individuals may consider the absence of reaction when consuming food products with PAL as implying a milder phenotype (148), providing false reassurance. Events following a reaction will alter perceptions: whether emergency medical services are contacted and/or the person is taken to hospital; comments made by HCPs during these episodes; whether an AAI is recommended. Prescription of AAI may be perceived by the public as indicating a “more severe” food allergy. Severe reactions are frequently not dissimilar from more mild reactions at onset, so individuals experiencing life-threatening reactions may not initially realise the potential severity (26). Cultural differences in language use, health beliefs, interpretation of symptoms and general health literacy levels are also likely to be modifying factors.

*The challenge for HCPs*

An assessment of severity is an essential component of an allergy-focussed history (149). It may determine whether immunomodulatory treatments are indicated, if AAI are recommended and the degree of dietary, occupational and/or family lifestyle change required. HCPs are currently unable to reliably identify those patients most at risk (Table 1). HCPs and allergic individuals differ in their understanding of risk: HCPs may view an incidence of fatal food-triggered anaphylaxis of <1 per 100,000 as low, taking an objective, rationale approach. In contrast, parents interpret risk in a more emotion-led context, considering their child to be ‘the one in a million’ who is ‘sure to die’ from an anaphylactic reaction (154). It can be difficult to strike a balance, allowing safe dietary practice while minimizing the impact on dietary choice, social activities and HRQoL (155). HCPs must emphasise that normal family activities – without drastic lifestyle modifications – can continue if appropriate and proportionate precautions are taken. Simple guidelines from expert groups rarely penetrate to the point of care (140) and should be augmented with iterations of education, web-based resources (including from patient support groups) and school/workplace support programmes.

**Incorporating severity into risk allergen management in food production**

Assessing the risk from allergen exposure is critical to effective allergen management by the food industry. The concept of risk encompasses two elements: the probability (likelihood) of an adverse event and a consideration of the characteristics of such an event, including severity (156). The development of dose-distribution curves (describing the probability of reaction in a defined population of allergic individuals as a function of eliciting dose) has enabled the former to be reasonably well characterised (39,157), although as discussed above, the relationship between dose and severity is poorly described.

A clear distinction must be made between food *allergen* management and food *allergy* management. Food allergen management should be based on risk assessment using quantitative benchmarks (“reference doses”) to inform the need for PAL (158). However, there is a trade-off: a reference dose which protects the largest proportion of the allergic population may be too low to be practical for implementation, paradoxically increasing the use of PAL; individuals who react at very low doses may not therefore be completely protected by current published reference doses.

Finally, food manufacturers may consider a reaction to be severe where this results in an unscheduled visit to a healthcare facility or possible legal consequences. This may not be a valid determinant of severity, as there are multiple factors which might prompt someone to seek medical attention. Many individuals experiencing anaphylaxis manage their reactions (often inappropriately) in the community, without recourse to medical services (4).

**Considering the likelihood of severity of a reaction – a food regulator’s perspective**

Food regulatory authorities, as public health risk managers, need to consider both the likelihood of occurrence and the characteristic of any reaction, including its severity – something particularly pertinent when considering the risk associated with unintended allergen presence, including through cross-contamination. It is generally accepted that “zero risk” is not possible (157,159), although this view is not shared by all regulators. Currently, there are inconsistent approaches across regulators when defining what is an “acceptable risk” and what constitutes a “severe reaction”, which leads to inconsistencies in enforcement. In common with industry, regulators will often consider a severe reaction to be one which prompts an unintended visit to a medical facility, despite the clear limitations to this definition. The degree of regulatory oversight may also be context dependent – an allergic reaction to a “free-from” product may be viewed as particularly concerning, irrespective of symptom severity. There is a need for an internationally-agreed quantitative measure for severity, which could be applied to inform reference doses and derived action levels for PAL, claims (such as “free-from”) and allergen labelling exemptions. This would provide greater consistency for food manufacturers and regulatory bodies, whilst protecting the consumer in a more proportionate, transparent and risk-based way.

**Current limitations in applying the concept of severity…**

*1) …to an individual’s allergy risk management*

There are no validated tests which offer sufficient discrimination to be useful in clinical practice. HCPs are therefore unable to reliably identify allergic individuals most at risk of severe anaphylaxis (Table 1). A previous anaphylactic episode and asthma are risk factors, but both are limited in terms of predictive value in clinical practice. Further research is required to understand the interplay of factors which result in severe life-threatening or fatal anaphylaxis, in order to improve risk-stratification of allergic individuals.

*2) …to allergen risk management*

Severity assessment is the main driver *and* the largest knowledge gap in the advancement of protection for the allergic consumer. There is a lack of consensus on the definition of severity with respect to food allergen management. Dose may be an important modifiable factor for any anaphylaxis, but the relationship between dose and severity of anaphylactic reaction is unclear. Food challenges generally commence at lower doses (160) and stopping criteria are designed to prevent anaphylaxis, so severe reactions are uncommon (40). These observations underline two of the main data gaps: (1) can we identify those allergic individuals who will experience (severe) anaphylaxis if exposure is sufficiently high; and (2) for those at risk of severe reactions, can we define the likelihood that a specified dose would elicit them? Useful data will be obtained from single-dose challenge studies, designed to test the validity of population allergen thresholds derived from dose-distribution modelling, and to assess the resulting symptoms (161). Studies are ongoing to assess the reproducibility of thresholds (and resulting symptoms) within individuals. Cofactors, such as exercise, stress and infection, are well-documented to influence allergic reactions, but more data is needed to define the precise effect on eliciting dose and resulting symptoms. This situation will be improved by research currently in progress (e.g. TRACE Study, NCT01429896; iFAAM project, NCT02295397), which may help to define a tolerable level of risk as a benchmark for food allergen management at a population level. Patient advocates understand very well and accept that total elimination of risk is impossible and impractical, although a consensus on what constitutes tolerable risk needs to be reached (159,162).

These gaps in knowledge contribute to the allergic individuals’ lack of control over their environment and the resulting impact on their quality of life. They are currently under study as a focus of the iFAAM study and an ongoing EAACI taskforce. Addressing them will reduce the uncertainty which is at the root of this anxiety, and thus help in the ultimate goal of improving an individual’s allergy management.

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**Author contributions**

Paul Turner, Barbara Ballmer-Weber and Graham Roberts developed the concept, facilitated the writing and edited the manuscript. Barbara K. Ballmer-Weber, Kirsten Beyer, René Crevel, Audrey DunnGalvin, Hazel Gowland, Linus Grabenhenrich, Jonathan Hourihane, Ben Remington, Paul Turner, Carina Venter and Margitta Worm all led the writing of specific sections. All the authors contributed to the development of the manuscript and approved the final version.

**Conflicts of interest…**

Barbara K. Ballmer-Weber has received grants from EU Framework programme and from ThermoFisher, and is a member of an industry sponsored ILSI expert group on predicting reaction severity.

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REFERENCES

1. Johansson SGO, Bieber T, Dahl R, Friedmann PS, Lanier B, Lockey R et al. A revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of World Allergy Organization. *J Allergy Clin Immunol* 2004;**113**:832-836.
2. Muraro A, Roberts G, Worm M, Bilò MB, Brockow K, Fernández Rivas M et al, on behalf of EAACI Food Allergy and Anaphylaxis Guidelines Group. Anaphylaxis: Guidelines from the European Academy of Allergy and Clinical Immunology. *Allergy* 2014;**69**:1026-1045.
3. Turner PJ, Boyle RJ. Food allergy in children: what is new? *Curr Opin Clin Nutr Metab Care* 2014;**17**:285-293.
4. Noimark L, Wales J, Du Toit G, Pastacaldi C, Haddad D, Gardner J et al. The use of adrenaline autoinjectors by children and teenagers. *Clin Exp Allergy* 2012;**42**:284-292.
5. Panesar SS, Javad S, de Silva D, Nwaru BI, Hickstein L, Muraro A et al. on behalf of the EAACI Food Allergy and Anaphylaxis Group. The epidemiology of anaphylaxis in Europe: a systematic review. *Allergy* 2013;**68**:1353-1361.
6. van der Velde JL, Dubois AE, Flokstra-de Blok BM. Food allergy and quality of life: what have we learned? *Curr Allergy Asthma Rep* 2013;**13**:651-661.
7. Umasunthar T, Leonardi-Bee J, Turner PJ, Hodes M, Gore C, Warner JO, et al. Incidence of food anaphylaxis in people with food allergy: a systematic review and meta-analysis. *Clin Exp Allergy* 2015;**45**:1621-1636.
8. Grabenhenrich L, Hompes S, Gough H, Ruëff F, Scherer K, Pföhler C et al. Implementation of anaphylaxis management guidelines: a register-based study. *PLoS One* 2012;**7**(5):e35778.
9. Kanny G, Moneret-Vautrin DA, Flabbee J, Beaudouin E, Morisset M, Thevenin F. Population study of food allergy in France. *J Allergy Clin Immunol* 2001;**108**:133-140.
10. Jerschow E, Lin RY, Scaperotti MM, McGinn AP. Fatal anaphylaxis in the United States, 1999-2010: temporal patterns and demographic associations. *J Allergy Clin Immunol* 2014;**134**:1318-1328.e7.
11. Turner PJ, Gowland MH, Sharma V, Ierodiakonou D, Harper N, Garcez T et al. Increase in hospital admissions due to anaphylaxis but no increase in fatalities: an analysis of UK national anaphylaxis data, 1992–2012. *J Allergy Clin Immunol* 2015;**135**:956-963.e1.
12. Liew WK, Williamson E, Tang ML. Anaphylaxis fatalities and admissions in Australia. *J Allergy Clin Immunol* 2009;**123**:434-442.
13. Umasunthar T, Leonardi-Bee J, Hodes M, Turner PJ, Gore C, Habibi P et al. Incidence of fatal food anaphylaxis in people with food allergy: a systematic review and meta-analysis. *Clin Exp Allergy* 2013;**43**:1333-1341.
14. Flokstra-de Blok BM, DunnGalvin A, Vlieg-Boerstra BJ, Oude Elberink JN, Duiverman EJ, Hourihane JO, et al. Development and validation of a self-administered Food Allergy Quality of Life Questionnaire for children. *Clin Exp Allergy* 2008;**39**:127-137.
15. DunnGalvin A, Flokstra-de Blok BM, Burks AW, Dubois AE, Hourihane JO. Food allergy QoL questionnaire for children aged 0-12 years: content, construct, and cross-cultural validity. *Clin Exp Allergy* 2008;**38**:977-986.
16. DunnGalvin A, Cullinane C, Daly DA, Flokstra-de Blok BM, Dubois AE, Hourihane JO. Longitudinal validity and responsiveness of the Food Allergy Quality of Life Questionnaire - Parent Form in children 0-12 years following positive and negative food challenges. *Clin Exp Allergy* 2010;**40**:476-485.
17. Branum AM. Among children with Food Allergy, do sociodemographic factors and healthcare use differ by severity? *Matern Child Health J* 2012;**16**:44-50.
18. Menon G, Raghubir P, Agrawal N. Health Risk Perceptions and Consumer Psychology. In: Haugtvedt C, Herr P, Kardes F, editors, The Handbook of Consumer Psychology. New York: Taylor & Francis Group, Psychology Press, 2008; 981-1010.
19. DunnGalvin A, Chang WC, Laubach S, Steele PH, Dubois AE, Burks AW et al. Profiling families enrolled in food allergy immunotherapy studies. *Pediatrics* 2009;**124**:503-509.
20. Kastner M, Harada L, Wasserman S. Gaps in anaphylaxis management at the level of physicians, patients and the community: a systematic review of the literature. *Allergy* 2010;**65**:435-444.
21. Lebovidge JS, Strauch HM, Kalish LA, Schneider LC. Assessment of psychological distress among children and adolescents with food allergy. *J Allergy Clin Immunol* 2009;**124**:1282-1288.
22. Niggemann B, Beyer K. Factors augmenting allergic reactions. *Allergy* 2014;**69**:1582-1587.
23. Wölbing F, Biedermann T. Anaphylaxis: opportunities of stratified medicine for diagnosis and risk assessment. *Allergy* 2013;**68**:1499-1508.
24. Clark AT, Ewan PW. Good prognosis, clinical features, and circumstances of peanut and tree nut reactions in children treated by a specialist allergy center. *J Allergy Clin Immunol* 2008;**122**:286-289.
25. Nguyen-Luu NU, Ben-Shoshan M, Alizadehfar R, Joseph L, Harada L, Allen M et al. Inadvertent exposures in children with peanut allergy. *Pediatr Allergy Immunol* 2012;**23**:133-139.
26. Pumphrey RS, Gowland MH. Further fatal allergic reactions to food in the United Kingdom, 1999–2006. *J Allergy Clin Immunol* 2007;**119**:1018-1019.
27. Flinterman AE, Pasmans SG, Hoekstra MO, Meijer Y, van Hoffen E, Knol EF et al. Determination of no-observed-adverse-effect levels and eliciting doses in a representative group of peanut-sensitized children. *J Allergy Clin Immunol* 2006;**117**:448-454.
28. Vetander M, Ly DH, Håkansson N, Lilja G, Nilsson C, Östblom E et al. Recurrent reactions to food among children at paediatric emergency departments: epidemiology of allergic disease. *Clin Exp Allergy* 2014;**44**:113-120
29. Eller, E. Hansen TK, Bindslev-Jensen C. Clinical thresholds to egg, hazelnut, milk and peanut: results from a single-center study using standardized challenges. *Ann Allergy Asthma Immunol* 2012;**108**:332-336.
30. Ma L, Danoff TM, Borish L. Case fatality and population mortality associated with anaphylaxis in the United States. *J Allergy Clin Immunol* 2014;**133**:1075-1083.
31. Turner P, Ng I, Kemp A, Campbell D. Seafood allergy in children: a descriptive study. *Ann Allergy Asthma Immunol* 2011;**106**:494-501.
32. Asai Y, Yanishevsky Y, Clarke A, La Vieille S, Delaney JS, Alizadehfar R et al. Rate, triggers, severity and management of anaphylaxis in adults treated in a Canadian emergency department. *Int Arch Allergy Immunol* 2014;**164**:246-252.
33. Huang F, Chawla K, Järvinen KM, Nowak-Węgrzyn A. Anaphylaxis in a New York City pediatric emergency department: triggers, treatments, and outcomes. *J Allergy Clin Immunol* 2012;**129**:162-168.e1-3.
34. Levy MB, Goldberg MR, Nachshon L, Tabachnik E, Katz Y. Lessons from cases of mortality due to food allergy in Israel: cow's milk protein should be considered a potentially fatal allergen. *Isr Med Assoc J* 2012;**14**:29-33.
35. Trendelenburg V, Enzian N, Bellach J, Schnadt S, Niggemann B, Beyer K. Detection of relevant amounts of cow's milk protein in non-pre-packed bakery products sold as cow's milk free. *Allergy* 2015;**70**:591-597.
36. Turner PJ. Persistent allergy to cow's milk: of greater a clinical concern than other food allergies. *Pediatr Allergy Immunol* 2013;**24**:624-626.
37. Nowak-Wegrzyn A, Bloom KA, Sicherer SH, Shreffler WG, Noone S, Wanich N, et al. Tolerance to extensively heated milk in children with cow’s milk allergy. *J Allergy Clin Immunol* 2008;**122**:342-347,e1-2.
38. Grabenhenrich LB, Dölle S, Moneret-Vautrin A, Köhli A, Lange L, Spindler T et al. Anaphylaxis in children and adolescents: The European Anaphylaxis Registry. *J Allergy Clin Immunol* 2016;**137**:1128-1137.e1.
39. Ballmer-Weber BK, Fernandez-Rivas M, Beyer K, Defernez M, Sperrin M, Mackie AR et al. How much is too much? Threshold dose distributions for 5 food allergens. *J Allergy Clin Immunol* 2015;**135**:964-971.
40. Rolinck-Werninghaus C, Niggemann B, Grabenhenrich L, Wahn U, Beyer K. Outcome of oral food challenges in children in relation to symptom-eliciting allergen dose and allergen-specific IgE. *Allergy* 2012;**67**:951-957.
41. Taylor SL, Moneret-Vautrin DA, Crevel RW, Sheffield D, Morisset M, Dumont P et al. Threshold dose for peanut: risk characterization based upon diagnostic oral challenge of a series of 286 peanut-allergic individuals. *Food Chem Toxicol* 2010;**48**:814-819.
42. van Erp FC, Knulst AC, Kentie PA, Pasmans SGM, van der Ent CK, Meijer Y. Can we predict severe reactions during peanut challenges in children? *Pediatr Allergy Immunol* 2013;**24**:596-602.
43. Blumchen K, Beder A, Beschorner J, Ahrens F, Gruebl A, Hamelmann E et al. Modified oral food challenge used with sensitization biomarkers provides more real-life clinical thresholds for peanut allergy. *J Allergy Clin Immunol* 2014;**134**:390-398.
44. Wainstein BK, Studdert J, Ziegler M, Ziegler JB. Prediction of anaphylaxis during peanut food challenge: usefulness of the peanut skin prick test (SPT) and specific IgE level. *Pediatr Allergy Immunol* 2010;**21**:603-611.
45. Bock SA, Muñoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. *J Allergy Clin Immunol* 2001;**107**:191-193.
46. Nowak-Wegrzyn A, Fiocchi A. Rare, medium, or well done? The effect of heating and food matrix on food protein allergenicity. *Curr Opin Allergy Clin Immunol* 2009;**9**:234-237.
47. Mills ENC, Sancho AI, Rigby NM, Jenkins JA, Mackie AR. Impact of food processing on the structural and allergenic properties of food allergens. *Mol Nutr Food Res* 2009;**53**:963-969.
48. Mills ENC, Jenkins JA, Alcocer MJC, Shewry PR. Structural and Biological Relationships of Plant Food Allergens. *CRC Critical Reviews in Nutrition and Food Science* 2004;**44**:379-407.
49. Kato Y, Oozawa E, Matsuda T. Decrease in antigenic and allergenic potentials of ovomucoid by heating in the presence of wheat flour: dependence on wheat variety and intermolecular disulfide bridges. *J Agric Food Chem* 2001;**49**:3661-3665.
50. Bloom KA, Huang FR, Bencharitiwong R, Bardina L, Ross A, Sampson HA, Nowak-Węgrzyn A. Effect of heat treatment on milk and egg proteins allergenicity. *Pediatr Allergy Immunol* 2014;**25**:740-746.
51. Mackie A, Knulst A, Le TM, Bures P, Salt L, Mills EN et al. High fat food increases gastric residence and thus thresholds for objective symptoms in allergic patients. *Mol Nutr Food Res* 2012;**56**:1708-1714.
52. van Odijk J, Ahlstedt S, Bengtsson U, Borres MP, Hulthén L. Double-blind placebo-controlled challenges for peanut allergy the efficiency of blinding procedures and the allergenic activity of peanut availability in the recipes. *Allergy* 2005;**60**:602-605.
53. Grimshaw KE, King RM, Nordlee JA, Hefle SL, Warner JO, Hourihane JO. Presentation of allergen in different food preparations affects the nature of the allergic reaction - a case series. *Clin Exp Allergy* 2003;**33**:1581-1585.
54. Libbers L, Flokstra-de Blok BM, Vlieg-Boerstra BJ, van der Heide S, van der Meulen GN, Kukler J et al. No matrix effect in double-blind, placebo-controlled egg challenges in egg allergic children. *Clin Exp Allergy* 2013;**43**:1067-1070.
55. Van Winkle RC, Chang C. The biochemical basis and clinical evidence of food allergy due to lipid transfer proteins: a comprehensive review. *Clin Rev Allergy Immunol* 2014;**46**:211-224.
56. Djurtoft R, Pedersen HS, Aabin B, Barkholt V. Studies of food allergens: soybean and egg proteins. *Adv Exp Med Biol* 1991;**289**:281-293.
57. Lemon-Mule H, Sampson HA, Sicherer SH, Shreffler WG, Noone S, Nowak-Wegrzyn A. Immunologic changes in children with egg allergy ingesting extensively heated egg. *J Allergy Clin Immunol* 2008;**122**:977-983,e1.
58. Tan JW, Campbell DE, Turner PJ, Kakakios A, Wong M, Mehr S et al. Baked egg food challenges - clinical utility of skin test to baked egg and ovomucoid in children with egg allergy. *Clin Exp Allergy* 2013;**43**:1189-1195.
59. Flinn A, Hourihane JO. Allergic reaction to peanuts: can we predict reaction severity in the wild? *Curr Allergy Asthma Rep* 2013;**13**:645-650.
60. Neuman-Sunshine DL, Eckman JA, Keet CA, Matsui EC, Peng RD, Lenehan PJ, et al. The natural history of persistent peanut allergy. *Ann Allergy Asthma Immunol* 2012;**108**:326-331.e3.
61. Hourihane JO, Grimshaw KE, Lewis SA, Briggs RA, Trewin JB, King RM et al. Does severity of low-dose, double-blind, placebo-controlled food challenges reflect severity of allergic reactions to peanut in the community? *Clin Exp Allergy* 2005;**35**:1227-1233.
62. Rancé F, Abbal M, Lauwers-Cancès V. Improved screening for peanut allergy by the combined use of skin prick tests and specific IgE assays. *J Allergy Clin Immunol* 2002;**109**:1027-1033.
63. Clark AT, Ewan PW. Interpretation of tests for nut allergy in one thousand patients, in relation to allergy or tolerance. *Clin Exp Allergy* 2003;**33**:1041-1045.
64. Perry TT, Matsui EC, Conover-Walker MK, Wood RA. Risk of oral food challenges. *J Allergy Clin Immunol* 2004;**114**:1164-1168.
65. Summers CW, Pumphrey RS, Woods CN, McDowell G, Pemberton PW, Arkwright PD. Factors predicting anaphylaxis to peanuts and tree nuts in patients referred to a specialist center. J Allergy Clin Immunol 2008;**121**:632-638.e2.
66. Ta V, Weldon B, Yu G, Humblet O, Neale-May S, Nadeau K. Use of specific IgE and skin prick test to determine clinical reaction severity. *Br J Med Med Res* 2011;**1**:410-429.
67. Steckelbroeck S, Ballmer-Weber BK, Vieths S. Potential, pitfalls, and prospects of food allergy diagnostics with recombinant allergens or synthetic sequential epitopes. *J Allergy Clin Immunol* 2008;**121**:1323-1330.
68. Sancho AI, Wangorsch A, Jensen BM, Watson A, Alexeev Y, Johnson PE et al. Responsiveness of the major birch allergen Bet v 1 scaffold to the gastric environment: Impact on structure and allergenic activity. *Mol Nutr Food Res* 2011;**55**:1690-1699.
69. Turner PJ, Campbell DE. A food allergy syndrome by any other name? *Clin Exp Allergy* 2014;**44**:1458-1460.
70. Amlot PL, Kemeny PM, Zachary C, Parkes P, Lessof MH. Oral Allergy Syndrome (OAS): symptoms of IgE mediated hypersensitivity to foods. *Clin Allergy* 1987;**17**:33-42.
71. Masthoff LJ, Mattsson L, Zuidmeer-Jongejan L, Lidholm J, Andersson K, Akkerdaas JH et al. Sensitization to Cor a 9 and Cor a 14 is highly specific for a hazelnut allergy with objective symptoms in Dutch children and adults. *J Allergy Clin Immunol* 2013;**132**:393-399.
72. Hansen KS, Ballmer-Weber BK, Sastre J, Lidholm J, Andersson K, Oberhofer H. Component-resolved in vitro diagnosis of hazelnut allergy in Europe. *J Allergy Clin Immunol* 2009;**123**:1134-1141.
73. Datema MR, Zuidmeer-Jongejan L, Asero R, Barreales L, Belohlavkova S, de Blay F et al. Hazelnut allergy across Europe dissected molecularly: A EuroPrevall outpatient clinic survey. *J Allergy Clin Immunol* 2015;**136**:382-391.
74. Fernández-Rivas M, Bolhaar S, González-Mancebo E, Asero R, van Leeuwen A, Bohle B et al. Apple allergy across Europe: how allergen sensitization profiles determine the clinical expression of allergies to plant foods. *J Allergy Clin Immunol* 2006;**118**:481-488.
75. Nicolaou N, Murray C, Belgrave D, Poorafshar M, Simpson A, Custovic A. Quantification of specific IgE to whole peanut extract and peanut components in prediction of peanut allergy. *J Allergy Clin Immunol* 2011;**127**:684-685.
76. Ballmer-Weber BK, Lidholm J, Fernández-Rivas M, Seneviratne S, Hanschmann KM, Vogel L et al. IgE recognition patterns in peanut allergy are age dependent: perspectives of the EuroPrevall study. *Allergy* 2015;**70**:391-407.
77. González-Mancebo E, González-de-Olano D, Trujillo MJ, Santos S, Gandolfo-Cano M, Meléndez A et al. Prevalence of sensitization to lipid transfer proteins and profilins in a population of 430 patients in the south of Madrid. *J Investig Allergol Clin Immunol* 2011;**21**:278-282.
78. Asarnoj A, Moverare R, Ostblom E, Poorafshar M, Lilja G, Hedlin G et al. IgE to peanut allergen components: relation to peanut symptoms and pollen sensitization in 8-year olds. *Allergy* 2010;**65**:1189-1195.
79. Movérare R, Ahlstedt S, Bengtsson U, Borres MP, van Hage M, Poorafshar M et al. Evaluation of IgE antibodies to recombinant peanut allergens in patients with reported reactions to peanut. *Int Arch Allergy Immunol* 2011;**156**:282-290.
80. Peeters KA, Koppelman SJ, van Hoffen E, van der Tas CW, den Hartog Jager CF, Penninks AH et al. Does skin prick test reactivity to purified allergens correlate with clinical severity of peanut allergy? *Clin Exp Allergy* 2007;**37**:108-115.
81. Astier C, Morisset M, Roitel O, Codreanu F, Jacquenet S, Franck P et al. Predictive value of skin prick tests using recombinant allergens for diagnosis of peanut allergy. *J Allergy Clin Immunol* 2006;**118**:250-256.
82. Eller E, Bindslev-Jensen C. Clinical value of component-resolved diagnostics in peanut-allergic patients. *Allergy* 2013;**68**:190-194.
83. Sicherer SH, Wood RA. Advances in diagnosing peanut allergy. *J Allergy Clin Immunol Pract* 2013;**1**:1-13.
84. Lewis SA, Grimshaw KE, Warner JO, Hourihane JO. The promiscuity of immunoglobulin E binding to peanut allergens, as determined by Western blotting, correlates with the severity of clinical symptoms. *Clin Exp Allergy* 2005;**35**:767-773.
85. Flinterman AE, Knol EF, Lencer DA, Bardina L, den Hartog Jager CF, Lin J et al. Peanut epitopes for IgE and IgG4 in peanut-sensitized children in relation to severity of peanut allergy. *J Allergy Clin Immunol* 2008;**121**:737-743.e10.
86. Shreffler WG, Beyer K, Chu T-H, Burks AW, Sampson HA. Microarray immunoassay: association of clinical history, in vitro IgE function, and heterogeneity of allergenic peanut epitopes. *J Allergy Clin Immunol* 2004;**113**:776-782.
87. Wood RA, Kim JS, Lindblad R, Nadeau K, Henning AK, Dawson P, et al. A randomized, double-blind, placebo-controlled study of omalizumab combined with oral immunotherapy for the treatment of cow's milk allergy. *J Allergy Clin Immunol* 2015;**137**:1103-1110.e11.
88. Santos AF, Du Toit G, Douiri A, Radulovic S, Stephens A, Turcanu V et al. Distinct parameters of the basophil activation test reflect the severity and threshold of allergic reactions to peanut. *J Allergy Clin Immunol* 2015;**135**:179-186.
89. El-Khouly F, Lewis SA, Pons L, Burks AW, Hourihane JO. IgG and IgE avidity characteristics of peanut allergic individuals. *Pediatr Allergy Immunol* 2007;**18**:607-613.
90. Song Y, Wang J, Leung N, Wang LX, Lisann L, Sicherer SH et al. Correlations between basophil activation, allergen-specific IgE with outcome and severity of oral food challenges. *Ann Allergy Asthma Immunol* 2015;**114**:319-326.
91. Turner PJ, Ruiz-Garcia M, Parkin RV, McMahon O, Clark AT, Boyle RJ et al. Basophil activation during - but not prior to - IgE-mediated allergic reactions to peanut correlates with symptom severity. *Allergy* 2015;**70**(Suppl. 101),48.
92. Baban A, Craciun C. Changing health-risk behaviours: a review of theory and evidence-based interventions in health psychology. *J Evidence-Based Psychother* 2007;**7**:45-67.
93. Monks H, Gowland M, MacKenzie H, Erlewyn-Lajeunesse M, King R, Roberts G et al. How do teenagers manage their food allergies? *Clin Exp Allergy* 2010;**40**:1533-1540.
94. Marrs T, Lack G. Why do few food-allergic adolescents treat anaphylaxis with adrenaline? - reviewing a pressing issue. *Pediatr Allergy Immunol* 2013;**24**:222-229.
95. Stjerna ML, Vetander M, Wickman M, Olin Lauritzen S. The management of situated risk: A parental perspective on child food allergy. *Health (London)* 2014;**18**:130-145.
96. DunnGalvin A, Hourihane J, Frewer L, Knibb R, Oude Elberink J, Klinge I. Incorporating a gender dimension in food allergy research: a review. *Allergy* 2006;**61**:1336-1343.
97. Nassiri M, Babina M, Dölle S, Edenharter G, Ruëff F, Worm M. Ramipril and metoprolol intake aggravate human and murine anaphylaxis: Evidence for direct mast cell priming. *J Allergy Clin Immunol* 2015;**135**:491-499.
98. Hompes S, Dölle S, Grünhagen J, Grabenhenrich L, Worm M. Elicitors and co-factors in food-induced anaphylaxis in adults. *Clin Transl Allergy* 2013;**3**:38.
99. Worm M, Vieth W, Ehlers I, Sterry W, Zuberbier T. Increased leukotriene production by food additives in patients with atopic dermatitis and proven food intolerance. *Clin Exp Allergy* 2001;**31**:265-273.
100. Ehlers I, Hipler UC, Zuberbier T, Worm M. Ethanol as a cause of hypersensitivity reactions to alcoholic beverages. *Clin Exp Allergy* 2002;**32**:1231-1235.
101. Serghini-Idrissi N, Ravier I, Aucouturier H, Ait Tahar H, Sonneville A. [Food allergy in the chronic alcoholic and alcohol in food allergy: apropos of 38 cases]. *Allerg Immunol (Paris)* 2001;**33**:378-382.
102. González-Quintela A, Vidal C, Lojo S, Pérez LF, Otero-Antón E, Gude F et al. Serum cytokines and increased total serum IgE in alcoholics. *Ann Allergy Asthma Immunol* 1999;**83**:61-67.
103. Hompes S, Köhli A, Nemat K, Scherer K, Lange L, Rueff F et al. Provoking allergens and treatment of anaphylaxis in children and adolescents - data from the anaphylaxis registry of German-speaking countries. *Pediatr Allergy Immunol* 2011;**22**:568-574.
104. Worm M, Edenharter G, Ruëff F, Scherer K, Pföhler C, Mahler V et al. Symptom profile and risk factors of anaphylaxis in Central Europe. *Allergy* 2012;**67**:691-698.
105. Fagiolo U, Paganelli R, Ossi E, Quinti I, Cancian M, D’Offizi GP et al. Intestinal permeability and antigen absorption in rheumatoid arthritis. Effects of acetylsalicylic acid and sodium chromoglycate. *Int Arch Allergy Appl Imm*unol 1989;**89**:98-102.
106. Wölbing F, Fischer J, Köberle M, Kaesler S, Biedermann T. About the role and underlying mechanisms of cofactors in anaphylaxis. *Allergy* 2013;**68**:1085-1092.
107. Anagnostou K, Clark A, King Y, Islam S, Deighton J, Ewan P. Efficacy and safety of high-dose peanut oral immunotherapy with factors predicting outcome. *Clin Exp Allergy* 2011;**41**:1273-1281.
108. Varshney P, Steele PH, Vickery BP, Bird JA, Thyagarajan A, Scurlock AM et al. Adverse reactions during peanut oral immunotherapy home dosing. *J Allergy Clin Immunol* 2009;**124**:1351-1352.
109. Kim CW, Figueroa A, Park CH, Kwak YS, Kim KB, Seo DY et al. Combined effects of food and exercise on anaphylaxis. *Nutr Res Pract* 2013;**7**:347-351.
110. Wylon K, Hompes S, Worm M. [Exercise-induced anaphylaxis]. *Hautarzt* 2013;**64**:97-101.
111. Ansley L, Bonini M, Delgado L, Del Giacco S, Du Toit G, Khaitov M et al. Pathophysiological mechanisms of exercise-induced anaphylaxis: an EAACI position statement. *Allergy* 2015;**70**:1212-1221.
112. Barg W, Medrala W, Wolanczyk-Medrala A. Exercise-induced anaphylaxis: an update on diagnosis and treatment. *Curr Allergy Asthma Rep* 2011;**11**:45-51.
113. Mazur N, Patterson R, Perlman D. A case of idiopathic anaphylaxis associated with respiratory infections. *Ann Allergy Asthma Immunol* 1997;**79**:546-548.
114. Chen W, Mempel M, Schober W, Behrendt H, Ring J. Gender difference, sex hormones, and immediate type hypersensitivity reactions. *Allergy* 2008;**63**:1418-1427.
115. Jeziorska M, Salamonsen LA, Woolley DE. Mast cell and eosinophil distribution and activation in human endometrium throughout the menstrual cycle. *Biol Reprod* 1995;**53**:312-320.
116. Hox V, Desai A, Bandara G, Gilfillan AM, Metcalfe DD, Olivera A. Estrogen increases the severity of anaphylaxis in female mice through enhanced endothelial nitric oxide synthase expression and nitric oxide production. *J Allergy Clin Immunol* 2015;**135:**729-736.e5
117. Järvinen KM, Sicherer S, Sampson HA, Nowak-Wegrzyn A. Use of multiple doses of epinephrine in food-induced anaphylaxis in children. *J Allergy Clin Immunol* 2008;**122**:133-138.
118. Colver AF, Nevantaus H, Macdougall CF, Cant AJ. Severe food allergic reactions in children across the UK and Ireland, 1998–2000. *Acta Paediatr* 2005;**94**:689-695.
119. Hourihane JO, Kilburn SA, Dean P, Warner JO. Clinical characteristics of peanut allergy. *Clin Exp Allergy* 1997;**27**:634-639.
120. Bock SA, Muñoz-Furlong A, Sampson HA. Further fatalities caused by anaphylactic reactions to food, 2001-2006. *J Allergy Clin Immunol* 2007;**119**:1016-1018.
121. Pumphrey RS. Lessons for management of anaphylaxis from a study of fatal reactions. *Clin Exp Allergy* 2000;**30**:1144-1150.
122. Worm M, Moneret-Vautrin A, Scherer K, Lang R, Fernández-Rivas M, Cardona V et al. First European data from the network of severe allergic reactions (NORA). *Allergy* 2014;**69**:1397-1404.
123. Rudders SA, Banerji A, Vassallo MF, Clark S, Camargo CA Jr. Trends in pediatric emergency department visits for food-induced anaphylaxis. *J Allergy Clin Immunol* 2010;**126**:385-388.
124. Vetander M, Helander D, Flodström C, Ostblom E, Alfvén T, Ly DH et al. Anaphylaxis and reactions to foods in children - a population-based case study of emergency department visits. *Clin Exp Allergy* 2012;**42**:568-577.
125. Lee S, Hess EP, Nestler DM, Bellamkonda Athmaram VR, Bellolio MF, Decker WW et al. Antihypertensive medication use is associated with increased organ system involvement and hospitalization in emergency department patients with anaphylaxis. *J Allergy Clin Immunol* 2013;**131**:1103-1108.
126. Brown SG, Stone SF, Fatovich DM, Burrows SA, Holdgate A, Celenza A et al. Anaphylaxis: clinical patterns, mediator release, and severity. *J Allergy Clin Immunol* 2013;**132**:1141-1149.e5.
127. Decker WW, Campbell RL, Manivannan V, Luke A, St Sauver JL, Weaver A et al. The etiology and incidence of anaphylaxis in Rochester, Minnesota: a report from the Rochester Epidemiology Project. *J Allergy Clin Immunol* 2008;**122**:1161-1165.
128. Poulos LM, Waters AM, Correll PK, Loblay RH, Markus GB. Trends in hospitalizations for anaphylaxis, angioedema, and urticaria in Australia, 1993-1994 to 2004-2005. *J Allergy Clin Immunol* 2007;**120**:878-884.
129. Soost S, Leynaert B, Almqvist C, Edenharter G, Zuberbier T, Worm M. Risk factors of adverse reactions to food in German adults. *Clin Exp Allergy* 2009;**39**:1036-1044.
130. Francuzik W, Nassiri M, Babina M, Worm M. Impact of sex on anaphylaxis severity-data from the Anaphylaxis Registry. *J Allergy Clin Immunol* 2015;**136**:1425-1426.
131. Pumphrey RSH. An epidemiological approach to reducing the risk of fatal anaphylaxis. In Anaphylaxis and hypersensitivity reactions. In: Castells MC, editor. Anaphylaxis and Hypersensitivity Reactions. Asthma and COPD. New York, Dordrecht, Heidelberg, London: Springer Science Ltd, Humana Press, 2011; 13-31.
132. Vadas P, Gold M, Perelman B, Liss GM, Lack G, Blyth T et al. Platelet-activating factor, PAF acetylhydrolase, and severe anaphylaxis. *N Engl J Med* 2008;**358**:28-35.
133. Sala-Cunill A, Björkqvist J, Senter R, Guilarte M, Cardona V, Labrador M. Plasma contact system activation drives anaphylaxis in severe mast cell-mediated allergic reactions. *J Allergy Clin Immuno*l 2015;**135**:1031-1043.e6.
134. Kemp AS, Allen CW, Campbell DE. Parental perceptions in egg allergy: does egg challenge make a difference? *Pediatr Allergy Immunol* 2009;**20**:648-653.
135. van der Velde JL, Flokstra-de Blok BM, de Groot H, Oude-Elberink JN, Kerkhof M, Duiverman EJ et al. Food allergy-related quality of life after double-blind, placebo-controlled food challenges in adults, adolescents, and children. *J Allergy Clin Immunol* 2012;**130**:1136-1143.e2
136. Ahmad Z, Cainer L, Tam H, Salter R, Boyle RJ. An audit of anaphylaxis management in a paediatric accident and emergency department. Presented at the British Society for Allergy and Clinical Immunology 2011 Annual Meeting. *Clin Exp Allergy* 2011;**41**:1853.
137. Hemler JA, Sharma HP. Management of Children with Anaphylaxis in an Urban Emergency Department. *J Allergy Clin Im*munol 2015;**135**(2 Suppl):AB203.
138. Grossman SL, Baumann BM, Garcia Peña BM, Linares MY, Greenberg B, Hernandez-Trujillo VP. Anaphylaxis Knowledge and Practice Preferences of Pediatric Emergency Medicine Physicians: A National Survey. *J Pediatr* 2013;**163**:841-846.
139. Jacobs TS, Greenhawt MJ, Hauswirth D, Mitchell L, Green TD. A survey study of index food-related allergic reactions and anaphylaxis management. *Pediatr Allergy Immunol* 2012;**23**:582-589.
140. Johnson MJ, Foote KD, Moyses H, Roberts G. Practices in the prescription of adrenaline autoinjectors. *Pediatr Allergy Immunol* 2012;**23**:125-128.
141. Simonte SJ, Ma S, Mofidi S, Sicherer SH. Relevance of casual contact with peanut butter in children with peanut allergy. *J Allergy Clin Immunol* 2003;**112**:180-182.
142. Wainstein BK, Kashef S, Ziegler M, Jelley D, Ziegler JB. Frequency and significance of immediate contact reactions to peanut in peanut-sensitive children. *Clin Exp Allergy* 2007;**37**:839-845.
143. Brough HA, Turner PJ, Wright T, Fox AT, Taylor SL, Warner JO et al. Dietary management of peanut and tree nut allergy: what exactly should patients avoid? *Clin Exp Allergy* 2015;**45**:859-871.
144. Remington BC, Baumert JL, Marx DB, Taylor SL. Quantitative risk assessment of foods containing peanut advisory labeling. *Food Chem Toxic*ol 2013;**62**:179-187.
145. Robertson ON, Hourihane JO, Remington BC, Taylor SL. Survey of peanut levels in selected Irish food products bearing peanut allergen advisory labels. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess* 2013;**30**:1467-1472.
146. Zurzolo GA, Koplin JJ, Mathai ML, Taylor SL, Tey D, Allen KJ. Foods with precautionary allergen labeling in Australia rarely contain detectable allergen. *J Allergy Clin Immunol Pract* 2013;**1**:401-403.
147. Food Standards Agency (FSA). Survey of allergen labelling and allergen content of processed foods. 2014. Available at: http://www.food.gov.uk/science/research/allergy-research/fs241038
148. Turner PJ, Skypala I, Fox AT. Advice provided by health professionals regarding precautionary allergen labelling. *Pediatr Allergy Immunol* 2013;**25**:290–292.
149. Skypala IJ, Venter C, Meyer R, deJong NW, Fox AT, Groetch M et al; Allergy-focussed Diet History Task Force of the European Academy of Allergy and Clinical Immunology. The development of a standardised diet history tool to support the diagnosis of food allergy. *Clin Transl Allergy* 2015;**5**:7.
150. Nowak-Wegrzyn A, Assa'ad AH, Bahna SL, Bock SA, Sicherer SH, Teuber SS et al; Adverse Reactions to Food Committee of American Academy of Allergy, Asthma & Immunology. Work Group report: oral food challenge testing. *J Allergy Clin Immunol* 2009;**123**(6 Suppl):S365-383.
151. Turner PJ, Mehr S, Joshi P, Tan J, Wong M, Kakakios A, Campbell DE. Safety of food challenges to extensively heated egg in egg-allergic children: a prospective cohort study. Pediatr Allergy Immunol 2013;**24**:450-455.
152. Sahiner UM, Yavuz ST, Buyuktiryaki B, Cavkaytar O, Yilmaz EA, Tuncer A et al. Serum basal tryptase may be a good marker for predicting the risk of anaphylaxis in children with food allergy. *Allergy* 2014;**69**:265-268.
153. Bonadonna P, Zanotti R, Pagani M, Caruso B, Perbellini O, Colarossi S et al. How much specific is the association between hymenoptera venom allergy and mastocytosis? *Allergy* 2009;**64**:1379-1382.
154. Hu W, Grbich C, Kemp A. When doctors disagree: a qualitative study of doctors’ and parents’ views on the risks of childhood food allergy. *Health Expect* 2008;**11**:208-219.
155. Klinnert MD, McQuaid EL, Fedele DA, Faino A, Strand M, Robinson J et al. Children’s Food Allergies: Development of the Food Allergy Management and Adaptation Scale (FAMAS). *J Pediatr Psychol* 2015;**40**:572-580.
156. Crevel RW, Baumert JL, Baka A, Houben GF, Knulst AC, Kruizinga AG et al. Development and evolution of risk assessment for food allergens. *Food Chem Toxicol* 2014;**67**:262-276.
157. DunnGalvin A, Chan C, Crevel R, Grimshaw K, Poms R, Schnadt S et al. Precautionary allergen labelling: perspectives from key stakeholder groups. *Allergy* 2015;**70**:1039-1051.
158. Allen KJ, Remington BC, Baumert JL, Crevel RW, Houben GF, Brooke-Taylor S, Kruizinga AG, Taylor SL. Allergen reference doses for precautionary labeling (VITAL 2.0): clinical implications. *J Allergy Clin Immunol* 2014;**133**:156-164.
159. Madsen CB, Hattersley S, Allen KJ, Beyer K, Chan CH, Godefroy SB et al. Can we define a tolerable level of risk in food allergy? Report from a EuroPrevall/UK Food Standards Agency workshop. *Clin Exp Allergy* 2012;**42**,30-37.
160. Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, Sicherer S, Teuber SS, Burks AW et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. *J Allergy Clin Immunol* 2012;**130**:1260-1274.
161. Zurzolo GA, Allen KJ, Taylor SL, Shreffler WG, Baumert JL, Tang ML et al. Peanut Allergen Threshold Study (PATS): validation of eliciting doses using a novel single-dose challenge protocol. *Allergy Asthma Clin Immunol* 2013;**9**:35.
162. Madsen CB, Crevel R, Chan CH, Dubois AE, DunnGalvin A, Flokstra-de Blok BM et al. Food allergy: stakeholder perspectives on acceptable risk. *Regul Toxicol Pharmacol* 2010;**57**:256-265.

**FIGURE LEGENDS**

**Figure 1**: Annual incidence rate for different events in food-allergic people aged 0–19 years. Data are estimated risk of self-reported/medically coded/fatal food anaphylaxis and hospital admission for food anaphylaxis. Continuous bars represent means with 95% CI, dotted bars represent the range of point estimates from individual studies, in a systematic review undertaken by Umasunthar et al. (13). Wherein reference risks vary markedly between European and US populations, they are

stated separately. Otherwise, reference risks are for the US population. Reproduced with permission from (3).

**Figure 2: Factors which may modulate the severity of a food-allergic reaction.** Cofactors have been divided into 2 groups: those linked to host behaviours such as exercise, and those occurring independently, such as infections. IgE, Immunoglobulin E; BHR, bronchial hyperreactivity; GI, gastrointestinal; AAI, adrenaline autoinjector device; EMS, emergency medical services.

**Figure 3: Allergen related factors affecting reaction severity.** The severity of *outcome* of the reaction will also depend on other factors, such as the treatment administered, and the ability of the individual to compensate physiologically, for example through endogenous catecholamine release.