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 IgG_4 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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Conflicts of interest…

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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).

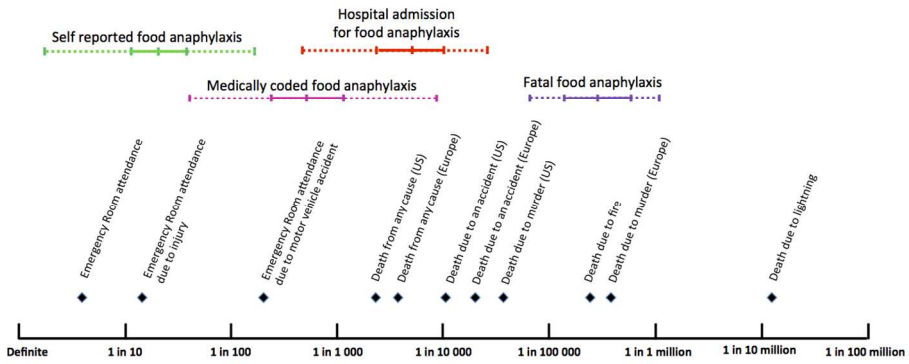
Figure 2: Factors which may modulate the severity of a food-allergic reaction. Cofactors have been divided into 2 groups: those linked to host behaviours such as exercise, and those occurring independently, such as infections. IgE, Immunoglobulin E; BHR, bronchial hyperreactivity; GI, gastrointestinal;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

Table 1: Factors proposed to predict severity of food-allergic reactions

Factor	Evidence	Conclusion
Age	Food-anaphylaxis is most common in young children but fatal anaphylaxis is rare in this age group. Fatal food-anaphylaxis is most common in the second and third decades of life (10-12).	Older children and adults up to the fourth decade of life appear to be most at risk of fatal food-anaphylaxis (11).
Asthma	Anaphylaxis frequently occurs in patients with asthma, but also in those without. Up to 50% of food-allergic children have asthma (24,123), yet almost none will experience a fatal food-allergic reaction. Thus, asthma is not, in itself, a strong predictor for fatal anaphylaxis. Suboptimal asthma control is a risk factor for severe and fatal anaphylaxis (11,26,120).	Food-allergic individuals with poorly controlled asthma are at greater risk of severe reactions.
Cardiovascular disease (CVD)	Individuals with cardiovascular disease or taking antihypertensive medication are at greater risk of severe food-allergic reactions (97,125).	The increased risk due to CVD may be due to associations with age, and not provide any additional predictive value for reaction severity (126).
Previous reaction severity	Many patients with prior anaphylaxis to food only experience mild symptoms at subsequent allergen exposures (24,25). Approximately half of food allergy-related deaths occur in subjects with previous mild reactions (24,26-28).	Severity of previous reactions cannot be used in isolation to predict future severity (150).
Dose of allergen	Dose is likely to be an important contributor to severity but data are limited. Severe reactions occur at all levels of allergen exposure (40). Peanut-allergic individuals with a history of anaphylaxis do not appear to be more 'sensitive' (i.e. have a lower threshold, and thus react to smaller amounts of peanut) than those without (29,41-43).	Severity and sensitivity should be considered as separate factors: a highly sensitive individual will not necessarily experience severe symptoms during an allergic reaction.
History of reaction to allergen through skin contact or inhalation	There is little evidence to suggest that systemic reactions are common in children following allergen contact via the skin or by inhalation (141,142). Reactions following inhalation of fish vapours (e.g. during cooking) are described, but this is not associated with a history of anaphylaxis (31).	No consistent evidence that individuals who develop symptoms with skin contact or via inhalation are more at risk of severe reactions.
Food allergen involved	Peanut and tree nuts appear more likely to cause anaphylaxis than other allergens but this is likely to be related to the higher prevalence of nut allergies (11,29,30). Peanut and tree nuts are the commonest triggers for fatal anaphylaxis in the UK and USA overall.	Any food allergen can potentially cause a fatal reaction. Cow's milk (and not nuts) is the most common cause of fatal anaphylaxis in British (11) and Israeli (34) children, after taking prevalence into account.
Skin prick testing (SPT) and/or specific IgE (spIgE) levels	There is contradictory evidence that the degree of sensitisation (to a food extract , either by SPT and/or spIgE) are predictive of severity (27,44,59-66).	Severe and life-threatening reactions to food have been shown to occur at all degrees of sensitisation (59).
Component Resolved Diagnostics (CRD)	Data are inconclusive that sensitisation to peanut Ara h 2 is related to severity (43,76,78-82). LTP sensitization does not always predict clinical reactivity or severity (55,75-77).	Sensitisation to Ara h 2 (or Ara h 1-3) does not predict severity (83). LTP sensitization is not currently useful in identifying patients at increased risk for severe reactions in unselected populations.
Oral Allergy	OAS describes the orophrayngeal pruritus that many food-allergic individuals	OAS does not imply a lower risk of anaphylaxis with future exposures.

Syndrome (OAS)	experience as an initial symptom to low doses of allergen (70).	
Pollen food allergy syndrome (PFAS)	Sensitisation to food proteins homologous with Bet v 1 and profilins are often associated with mild symptoms, but systemic reactions are common in hazelnut-allergic adults sensitized to no other component other than the Bet v 1 homologue Cor a 1 (71).	Individuals with PFAS may be wrongly classified as being at lower risk of severe reactions.
Allergy to extensively-heated allergen	Children with prior anaphylaxis to egg are just as likely to tolerate extensively heated egg (e.g. in a cake) as those with no such history (151). Children and young adults who are allergic to cow's milk, even in baked foods, may be more at risk of severe reactions (36,37).	Allergy to extensively-heated cow's milk in those with persistent milk allergy may imply a greater risk of severe reactions.
Mast Cell Tryptase (MCT)	There is a single report that baseline MCT may predict anaphylaxis in food-allergic children (152), but the study was not conducted in an unselected cohort and the cut-off levels proposed lack discrimination.	There is little evidence that the reported association of clonal mast cell disorders / raised baseline MCT with severe hymenoptera allergy also applies to food-triggered reactions (153).
Basophil activation test (BAT)	For peanut allergy, BAT may correlate with symptom severity (88,90). However, baseline basophil responsiveness can vary from day-to-day within the same participant, and so may not predict reaction severity on a different occasion (91).	More studies are needed to assess the use of BAT in predicting severity of food-allergic reactions.



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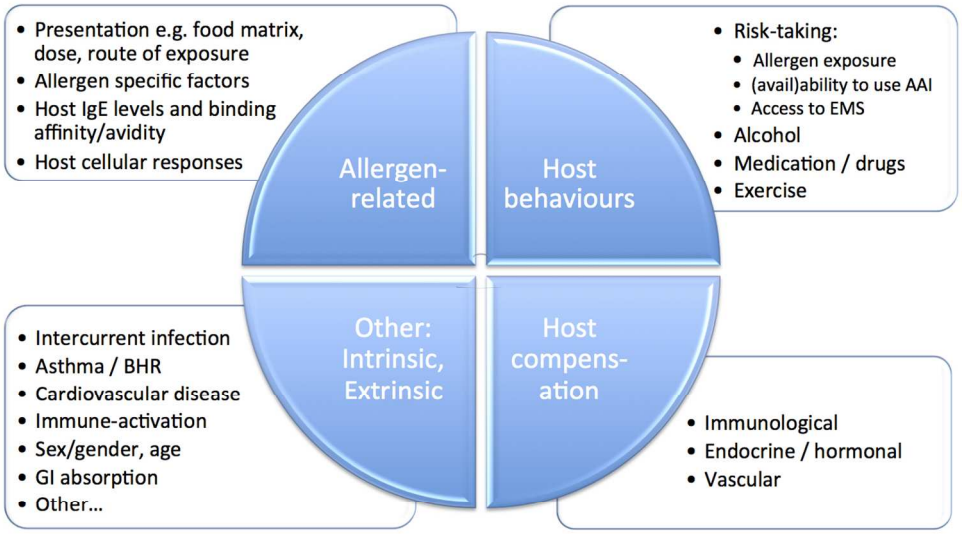

Figure 2: Factors which may modulate the severity of a food-allergic reaction. Cofactors have been divided into 2 groups: those linked to host behaviours such as exercise, and those occurring independently, such as infections. IgE, Immunoglobulin E; BHR, bronchial hyperreactivity; GI, gastrointestinal;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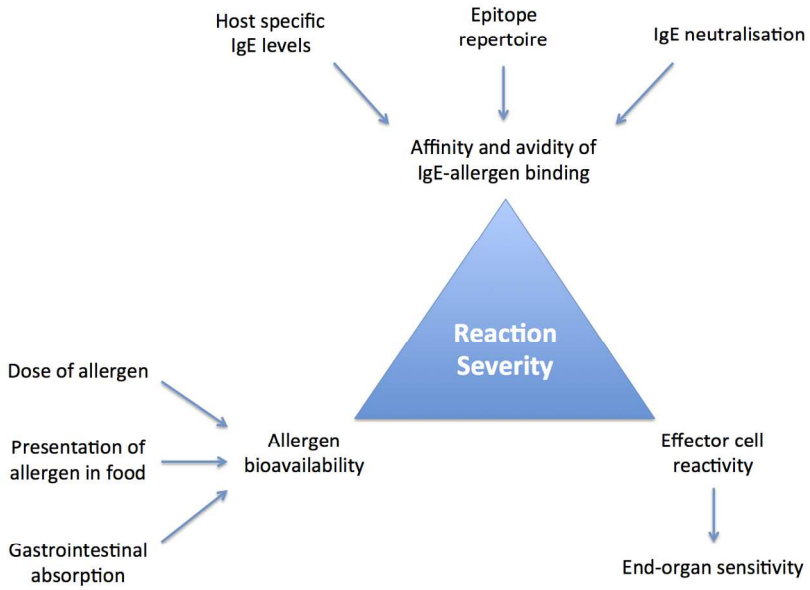

Figure 3: Allergen related factors affecting reaction severity. The severity of outcome of the reaction will also depend on other factors, such as the treatment administered, and the ability of the individual to compensate physiologically, for example through endogenous catecholamine release.
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