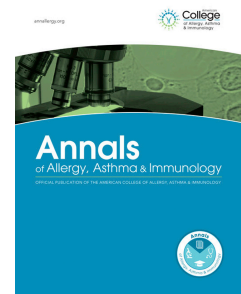


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Reaction phenotypes in IgE-mediated food allergy and anaphylaxis

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TITLE PAGE**Reaction phenotypes in IgE-mediated food allergy and anaphylaxis**

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Keywords: Anaphylaxis, food allergy, severity

Abbreviations:

AIT: allergen immunotherapy

CRD: Component resolved diagnostics

EAI: Epinephrine autoinjector devices

ICU: Intensive Care Unit

LTP: Lipid transfer protein

OAS: Oral Allergy Syndrome

OIT: Oral immunotherapy

PFAS: Pollen Food Allergy Syndrome

Word Count: 2037 words

Figures: 3

Tables: 1

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Objective: Food allergy encompasses a range of food hypersensitivities. Different clinical phenotypes for food allergy are likely to exist, in much the same way as endotype discovery is now a major research theme in asthma. We discuss the emerging evidence for different reaction phenotypes i.e. symptoms experienced following allergen exposure in food-allergic individuals, and their relevance for clinical practice.

Data Sources: Published and unpublished literature relating to reaction phenotypes in food allergy. **Study Selections** Authors assessment of the available data.

Results: Food anaphylaxis may have a different pathophysiology to anaphylaxis caused by nonfood triggers. Currently, there are no robust, clinically useful predictors of severity in food allergy. It is likely that patient-specific reaction phenotypes exist in food allergy, which may impact upon risk of severe anaphylaxis. Allergen immunotherapy may modulate these phenotypes.

Conclusion: Data are emerging to confirm our clinical experience that many food-allergic patients experience stereotypical symptoms following allergen exposure, both in the community and at supervised oral food challenge, in a manner that varies from one patient to another. Integrating datasets from different cohorts and applying unbiased machine-learning analyses may demonstrate specific food allergy endotypes, in a similar way to asthma. Whether this results in improvements in patient management (e.g. through facilitating risk stratification or impacting on the decision to prescribe EAI and, perhaps, the number of devices) remains to be determined – but given our current inability to predict patients most at risk of severe food-allergic reactions, this will clearly be an important area of research in the future.

Introduction

Food allergy encompasses a range of food hypersensitivities. Different clinical phenotypes for food allergy are likely to exist, in much the same way as endotype discovery is now a major research theme in asthma. In this review, we discuss the emerging evidence for different reaction phenotypes i.e. symptoms experienced following allergen exposure in food-allergic individuals, and their relevance for clinical practice.

Primary IgE-mediated food allergy versus Pollen Food Allergy Syndrome

Primary food allergy results from primary sensitization to a food allergen. In contrast, secondary food allergy – also known as Pollen Food Allergy Syndrome (PFAS) – refers to where the primary sensitization is to aeroallergens, with symptoms occurring due to exposure to cross-reactive allergens in food. Patients with PFAS experience oropharyngeal symptoms of itching/tingling with or without mild lip swelling, following ingestion of specific fresh fruit or vegetable.¹ The term Oral Allergy Syndrome (OAS) is often confused and used interchangeably with PFAS, but is a more general term describing *any* oropharyngeal symptoms occurring as part of an allergic reaction,² and will often progress to systemic symptoms including anaphylaxis i.e. OAS occurs in both PFAS and primary food allergy. Indeed, over 50% of patients reported by Amlot et al in the first case series of OAS went on to experience systemic symptoms and anaphylaxis.²

Drawing a distinction between primary and secondary food allergy is vital in both risk stratification and management advice,¹ but may be tricky as patients will often have a mix of both primary food allergy and PFAS to different allergens, while others may even demonstrate a pattern of sensitization consistent with primary allergy and PFAS to the same allergen e.g. IgE positivity to both Ara h 2 and Ara h 8 for peanut, or Cor a 1 and Cor a 8 for

hazelnut. PFAS is usually considered to be a relatively “benign” condition, where systemic symptoms are rare due to lability of the causative allergens such as Bet v 1 homologues and profilins.³ However approximately 10% of PFAS presentations are associated with systemic symptoms and 1–2% with anaphylaxis.⁴ It is not clear why some patients experience more significant symptoms, and whether this is due to polysensitization to more stable allergens such as lipid transfer proteins (LTPs)⁵ or diagnostic misclassification.^{6,7} Component resolved diagnostics (CRD) has improved our ability to discriminate between PFAS and primary food allergy, although is only of limited use in identifying patients with PFAS at risk of severe systemic reactions.^{8,9} Whether prescription of epinephrine autoinjector devices (EAI) is indicated in patients with PFAS remains unclear.^{4,6,7}

Food-induced anaphylaxis - different pathophysiology from non-food anaphylaxis?

Anaphylaxis is defined as “a serious systemic hypersensitivity reaction that is usually rapid in onset and may cause death. Severe anaphylaxis is characterized by potentially life-threatening compromise in breathing and/or the circulation, and may occur without typical skin features or circulatory shock being present.”¹⁰

Distinct differences appear to exist in the epidemiology and clinical presentations of anaphylaxis caused by food, compared to other triggers such as medication or insect venom (Table 1).¹¹ These differences raise key questions as to the underlying mechanisms involved. Food-related anaphylaxis (as defined according to the latest WAO criteria¹⁰) tends to result in predominantly respiratory symptoms (with or without other organ involvement); cardiovascular compromise tends to be less common, and if present, occurs in the context of severe respiratory symptoms; the most common mode of death in fatal food anaphylaxis is

respiratory arrest;^{12,13} where cardiovascular arrest occurs in food anaphylaxis, it is usually secondary to respiratory compromise.¹¹

These differences could, perhaps, be explained by the different routes of exposure i.e. food allergens need to be absorbed through the gastrointestinal tract resulting in slower onset of symptoms and slower systemic absorption, compared to parenteral allergens. Furthermore, food processing can affect the kinetics of any ensuing reaction (for example, many patients with allergy to egg in a baked food matrix (such as a cake) present with more delayed (and typically abdominal) symptoms^{14,15} than when challenged to the native allergen, which might reflect the more complex food presentation resulting in delayed absorption. Interestingly, modifying the presentation of the allergen through baking does not appear to change the sensitivity or reaction threshold (i.e. amount of allergen needed to trigger an objective reaction), just the nature of the resulting symptoms.¹⁶

Despite this, there is evidence that food allergens can be rapidly absorbed through the buccal mucosa: Dirks et al reported a study in which 6 non-allergic individuals chewed peanut for 2 minutes in the mouth, following which they expelled the peanut without swallowing; under these circumstances, chewing alone resulted in allergen levels in the circulating blood which were sufficient to trigger an effector cell response.¹⁷ Furthermore, oral medications (e.g. antibiotics) frequently result in cardiovascular symptoms, despite the need to undergo gastrointestinal absorption.¹² Therefore, the route of exposure does not explain these differences.

Alternatively, the association between food anaphylaxis and respiratory compromise could be because food allergy is strongly associated with asthma and bronchial reactivity: around 50% of food-allergic individuals have asthma,¹⁸⁻²⁰ and many of those without a formal diagnosis of

asthma have underlying bronchial hyperreactivity.²⁰ Whether food-allergic patients without underlying bronchial hyperreactivity and aeroallergen sensitization are less likely to experience respiratory symptoms has not, to our knowledge, been evaluated.

Clinical phenotypes in food allergy

There are now a limited number of published studies where food-allergic patients have undergone repeated food challenge, usually to assess changes in eliciting dose (amount of allergen needed to trigger an objective reaction) over time.^{21,22} We have extensively characterised peanut-allergic individuals (n=57 adults; n=64 children), all of whom underwent double-blind, placebo-controlled food challenge (DBPCFC), a proportion of whom subsequently underwent a second food challenge months later. We observed a very similar pattern of symptoms/organ involvement at the two challenges in most individuals (Fig. 1). These data are consistent with our clinical observations: many participants report ‘stereotypical’ reactions, for example some always suffer abdominal pain and nausea, others do not experience gut symptoms but present with lower respiratory tract involvement; the former might not constitute anaphylaxis, while the latter would) – although exposure dose is a clear confounder, as explained below.

This may reflect intra- and inter-individual variability in reaction thresholds, with different patients needing to consume different amounts of allergen in order to develop specific symptoms on any given reaction occasion.²³ Furthermore, a range of factors potentially interact with both sensitivity of an individual to a given allergen on any given day, as well as severity.²⁴ Many individuals will experience initially subjective symptoms, with objective symptoms appearing only with the administration of further doses, as shown in Figure 2A. In some individuals, further dosing will cause anaphylaxis, while in others, the threshold for any

objective symptom and anaphylaxis are similar and these patients present with anaphylaxis as their first objective symptom (Figure 2B).

We recently undertook unbiased, data-driven analyses to identify differences in the ability of patient sera (from peanut-allergic individuals) to elicit responses in the mast cell activation test (MAT).²⁵ Interestingly, using this approach, 5 different ‘clusters’ of patient phenotypes were identified characterized by different MAT responses. The differences between the different patient groups were linked to both a patient’s threshold of reactivity (i.e. sensitivity, or dose needed to trigger objective symptoms) and the resulting severity of those symptoms. This raises the possibility of undertaking unbiased, machine-based analyses to better understand the existence of different clinical phenotypes in food allergy, and whether laboratory tests might be helpful in determining these and potentially identifying patients at greater risk of severe reactions.

Severe food allergic phenotypes

There is a consensus that severity of reactions cannot be reliably predicted in food allergy;²⁴ however, predicting the occurrence of anaphylaxis (the majority of which are not truly life-threatening) and life-threatening anaphylaxis (for example, reactions which are refractory to initial treatment with epinephrine) are different concepts.

Prior anaphylaxis appears to be the best predictor of future anaphylaxis (of *any* severity) in studies,²⁴ although this is confounded by the fact that the occurrence of anaphylaxis is of course dependent on sufficient exposure. In a unique study, Wainstein et al demonstrated that up to 75% of peanut-allergic children will experience anaphylaxis with sufficient peanut ingestion, but most experienced dose-limiting symptoms first.²⁶ Thus, the absence of a

history of anaphylaxis in patients is more likely due to insufficient allergen exposure at previous reactions, rather than an inability to have anaphylaxis.

Patients with a history of prior severe anaphylaxis (i.e. refractory to initial first line treatment with 2+ doses of epinephrine) may be a separate phenotype, but this is a group that to date have not been well-studied. In the UK Fatal Anaphylaxis Registry, the majority of cases did not have a prior history of anaphylaxis.²⁷ Pouessel et al followed up 39 children admitted to Intensive Care (ICU) due to food-related anaphylaxis;²⁸ 30 (77%) experienced at least one further food-related reaction during the follow-up period, 27 of them to the same allergen as the reaction requiring ICU. At least 10 (26%) children experienced anaphylaxis, and half required a further ICU admission for management. Although these data are limited, they imply some patients may have a more allergic phenotype which places them at greater risk of refractory anaphylaxis.

Why do some patients react with a more severe phenotype?

We propose a mechanism for more severe food allergic reactions in Figure 3. In some individuals, systemic absorption of the food allergen (either across the oral mucosa¹⁷ or via the gastrointestinal tract) can occur to a greater degree, more quickly. This results in rapid distribution through the blood stream including to the airways. Some individuals, for example those with underlying sensitization to aeroallergen, may have increased mast cell density in the airways^{29,30} and could therefore experience more severe respiratory compromise. Release of mast cell mediators in the respiratory tract could lead to bronchospasm, mucus plugging and also to secondary cardiac compromise when these inflammatory mediators reach the heart via the pulmonary circulation. In other individuals, perhaps with lower airway mast cell density, mediator release is lower and therefore these individuals might be at lower risk of

severe systemic reactions with lower respiratory or cardiac involvement. Alternatively, individuals at greater risk of severe reactions (the minority of patients) may have impaired switch-off mechanisms, such as an inability to compensate for the allergic trigger. Some evidence for this has been reported with respect to the metabolism of platelet activating factor.³¹ Thus, severity could result from a combination of both initial insult but also an inability to compensate once the reaction has been initiated.

Impact of allergen immunotherapy on clinical phenotype

The increase in data from trials of food allergen immunotherapy (AIT) have provided some insight into the impact of AIT on the phenotype of food-allergic individuals. AIT, and specifically oral immunotherapy (OIT), is effective in raising the threshold of reactivity (eliciting dose) to the specific food allergen while on treatment.³² Interestingly, both the PALISADE³³ and ARTEMIS³⁴ Phase 3 randomized controlled trials, using Aimmune's AR101 formula for peanut-OIT, have demonstrated a reduction in severity of reactions and the use of rescue epinephrine at exit food challenge. For example, in PALISADE, 10% of challenges in the active group were given rescue epinephrine, compared to 53% in the placebo group, despite a similar rate (36% and 37% respectively) in both groups at baseline challenge.³³ These data are not entirely surprising, in that by raising the reaction threshold, fewer reactions occur at exit challenge, and consistent with Figure 2, increasing a patient's threshold is likely to also increase the threshold for experiencing anaphylaxis.

Chu et al recently published a meta-analysis of AIT which included 1041 participants across 12 randomized controlled trials.³⁵ Although AIT induces desensitization, patients also experience an increased rate of allergic reactions *including anaphylaxis* when on treatment. For peanut-OIT, the risk of anaphylaxis increases three-fold, with a relative risk of 3·12 [95%

CI 1·76–5·55]. In PALISADE, patients receiving the top dose of active peanut OIT – but not yet established on maintenance – were five times as likely to have systemic allergic reactions (8.7% vs. 1.7%) as those on placebo.³³ As we have previously highlighted, there is a paradox: despite this increased risk, there is clearly demand for OIT from patients and their families.³⁶ Many patients/families are clearly willing to tolerate a higher rate of reactions while on OIT; one factor may be that when these reactions occur, they happen in a more predictable and controlled way, often with a reduction in severity of symptoms. There may also be other quality of life, psychological or emotional benefits to OIT, although these remain to be demonstrated. Clearly, we need to understand the impact of AIT on reaction severity and clinical phenotype in order to better inform patients and families of the risks of AIT, and allow them to make a fully informed choice.

Finally, a significant proportion of patients (typically around 20%) do not tolerate current OIT regimes. These patients tend to have specific characteristics, for example, higher levels of IgE sensitization and a history of anaphylaxis to the causative allergen, although these features do not currently allow us to predict outcomes in OIT.³⁷ The available data suggest a specific patient phenotype who may be prone to more severe and persistent food allergy, which also impact on poorer outcomes during OIT. Ironically, it is these patients who arguably have most to gain from desensitization. Further work is needed to evaluate different protocols – perhaps involving different routes of AIT used in combination, or in conjunction with adjunct therapies such as anti-IgE immunotherapy.

Conclusion

190 Data are emerging to confirm our clinical experience that many food-allergic patients
191 experience stereotypical symptoms following allergen exposure, both in the community and
192 at supervised oral food challenge, in a manner that varies from one patient to another.
193 However, the existing published data do not yet provide sufficient evidence-base to guide
194 management decisions which would impact on patient care. Integrating datasets from
195 different cohorts and applying unbiased machine-learning analyses may demonstrate specific
196 food allergy endotypes, in a similar way to asthma.³⁸ Whether this results in improvements in
197 patient management (e.g. through facilitating risk stratification or impacting on the decision
198 to prescribe EAI and, perhaps, the number of devices) remains to be determined – but given
199 our current inability to predict patients most at risk of severe food-allergic reactions,²⁴ this
200 will clearly be an important area of research in the future.

Acknowledgements

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Figure Legends

Figure 1: Heat map of symptom severity by organ involvement (Skin/gut/lower respiratory) in 19 children and 28 adults under-going peanut-DBPCFC on 2 separate occasions (labelled 1 and 2).

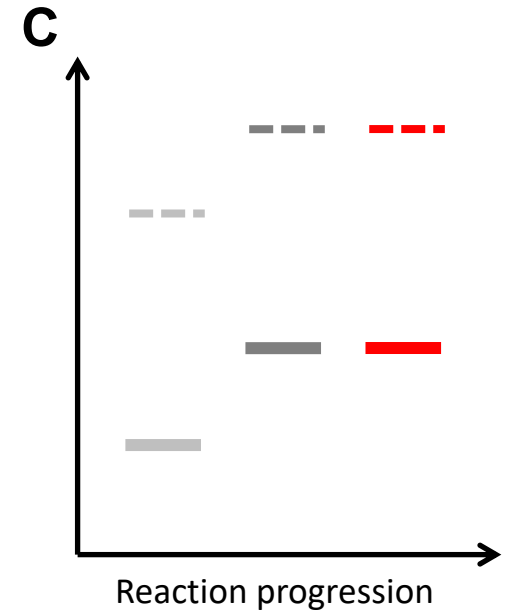
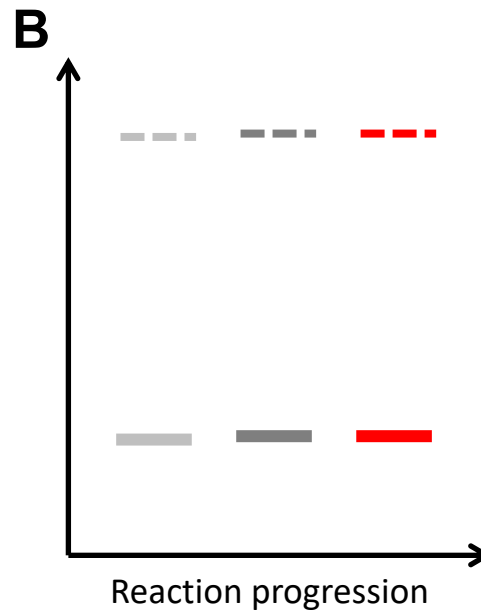
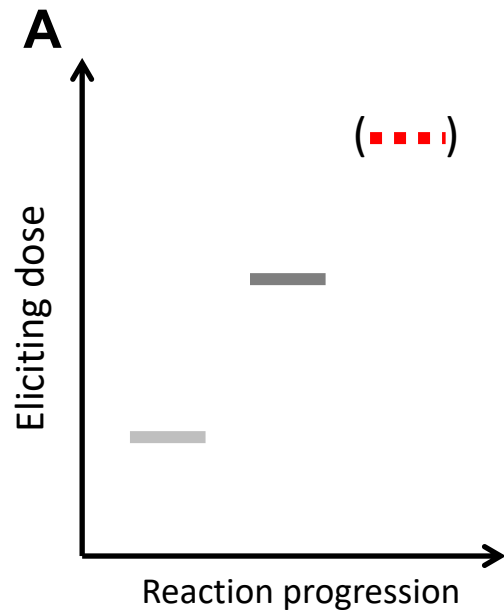
Figure 2. Different patterns of clinical reactivity are seen at food challenge. Many individuals will experience initially subjective symptoms, with objective symptoms appearing with further doses (A). Anaphylaxis will only develop if the food challenge continues. Others will experience anaphylaxis as their first objective symptom: either at a dose of allergen exposure with no preceding subjective symptoms (B), or with prior subjective symptoms (C). Note that anaphylaxis can occur at all levels of exposure (both at low levels of allergen exposure, represented by the solid bars, and higher doses indicated by dotted lines). Reproduced (with permission) from reference 18.

Figure 3: Proposed mechanism for severe IgE-mediated food allergy. Food is initially absorbed in the mouth and across the gastrointestinal tract. The absorbed allergen passes into the blood stream when it quickly reaches the respiratory system, those participants who have a higher mast cell density in the lungs have more severe respiratory compromise. Mediators released in the lungs rapidly reach the heart through pulmonary venous circulation and responsible for the cardiac response during IgE-mediated food allergy.

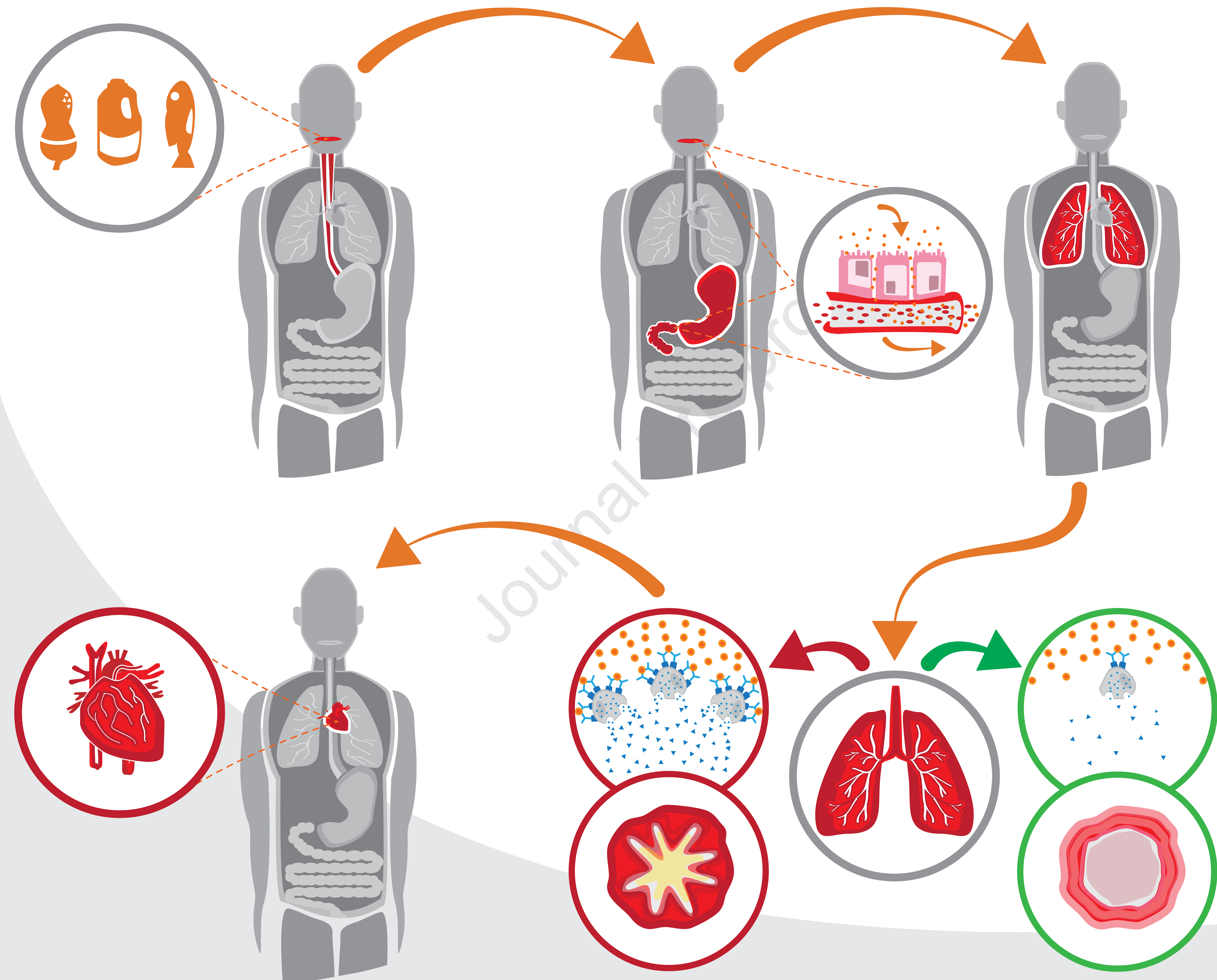
Table 1: Differences in the epidemiology and pathophysiology of anaphylaxis due to food versus non-food causes (adapted from reference 11)

	Food	Medication / iatrogenic causes	Venom sting
Age distribution for anaphylaxis	Most common in preschool children, less common in older adults	Predominantly older ages	All ages, but less common in children
Age distribution for fatal reactions	Adolescents and young adults. Rare in younger children and older adults.	Older adults and the elderly.	Middle age or older adults.
Symptoms	Predominantly respiratory	Cardiovascular (respiratory less common)	Cardiovascular (respiratory less common)
Asthma/atopy	Common	Uncommon	Uncommon
Reaction onset	Typically within 2 hours of ingestion	More rapid	More rapid
Route of Antigen presentation	Usually orogastric route	Usually parenteral	Parenteral
Mast cell tryptase (MCT)	Usually no or only a relatively modest increase observed	Usually increases	Usually increases
Sex	M=F	M=F	M>>F





- Dose triggering subjective symptoms
- Dose triggering mild objective symptoms
- Dose causing anaphylaxis



Key Messages

1. Food anaphylaxis may have a different pathophysiology to anaphylaxis caused by non-food triggers.
2. Currently, there are no robust, clinically useful predictors of severity in food allergy.
3. It is likely that patient-specific reaction phenotypes exist in food allergy, which may impact upon risk of severe anaphylaxis.
4. Allergen immunotherapy may modulate these phenotypes.
5. Machine-based learning may help with endotype discovery in anaphylaxis.