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EDITORIAL

Anaphylaxis – moving beyond severity…

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Anaphylaxis – moving beyond severity…

Managing patients at risk of anaphylaxis involves multiple individuals and organisations: patients and their caregivers, healthcare professionals, researchers, regulatory authorities, and for food allergy, food businesses. The accurate assessment and communication of reaction severity between these different stakeholders is key to management. However, severity can mean different things to different stakeholders (Table 1).

Numerous severity grading systems have been developed to help address some of these issues, however there is a lack of consensus on how to define severity, particularly with respect to food allergy.[1-3] In this issue of the *Journal of Allergy and Clinical Immunology*, Dribin et al describe a severity grading system for acute allergic reactions, generated by a 21-member panel through a Delphi consensus process.[4] There are a number of important principles identified and supported by the panel: the acknowledgement that severity is a continuum, and that an allergic reaction can have different phases (such as is the case for biphasic reactions), each with differing severities. The explanatory detail with respect to specific symptoms is also welcome.

There are also some important "meta" issues that need unpacking. First, this is the latest of many severity scores that have been published in the literature.[2,5] Some were designed to be used for trigger-specific reactions, but have been subsequently applied to reactions irrespective of trigger. This causes difficulties: for example, Ring and Messmer proposed a system that was originally intended for drug-induced reactions; vomiting is therefore described as a relatively severe symptom. However, emesis is very common during food-

induced reactions; since this is almost certainly a local response of the gut to the presence of a food allergen, this is not a strong indicator of severity. The Ring and Messmer score therefore overstates severity when applied to food-induced reactions.

This example highlights the difficulties of a "one-size-fits-all" approach for severity grading. Gastrointestinal symptoms are common manifestations of food-induced reactions. This is why the clinical criteria used to define anaphylaxis in the United Kingdom and Australia do not include generally include gastrointestinal symptoms (in the context of a venom-induced reaction, such symptoms do imply a significant systemic reaction).[6] In contrast, in North America and parts of Europe, the clinical criteria used are aligned with those proposed by the National Institute of Allergy and Infectious Diseases (NIAID) in 2005, where "persistent gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting)" together with cutaneous symptoms can constitute anaphylaxis.[7] However, there is no consensus as to what constitutes *persistent* gastrointestinal symptoms – does an individual with persistent nausea and mild cutaneous symptoms qualify as having anaphylaxis? This ambiguity results in reactions being classified as anaphylaxis by some individuals, but not others – depending on how the NIAID criteria are interpreted. This not only impacts on the use of epinephrine, but also on the evaluation of treatment success (since one would expect more mild reactions to have a better response to epinephrine) – this is a major confounder in anaphylaxis research.

Dribin et al suggest a severity score should not dictate treatment, an argument which is not without merit. There is, however, a clear link between severity assignment and diagnosis of anaphylaxis. In the proposed scoring system, gastrointestinal symptoms do not loom large as a feature of severity – one might therefore interpret Dribin et al as implying that the

current inclusion of gastrointestinal symptoms in the NIAID criteria poses difficulties. The authors present an even greater paradox: that "a patient with isolated upper airway obstruction following Hymenoptera envenomation would be categorized as having a non-anaphylactic grade 5 allergic reaction" – and yet, based on the NIAID criteria, such a reaction with severe laryngeal obstruction would not constitute anaphylaxis (and arguably, therefore, not warrant treatment with epinephrine). This is similar to a not-uncommon scenario where patients undergoing oral immunotherapy develop isolated wheeze following a dose (without any other explanation). Such a reaction does not meet the NIAID criteria for anaphylaxis, and therefore perhaps would not be treated with epinephrine – something which can clearly compromise patient safety. To address at least some of these concerns, the World Allergy Organization (WAO) recently proposed new clinical criteria for the diagnosis of anaphylaxis (Table 2).[8] Although endorsed by 50 member societies of the WAO,[9] there is an apparent inertia in these criteria being adopted widely to inform both clinical allergy and research. Dribin et al imply that a critical review of the NIAID criteria is not only timely, but overdue. Afterall, it is completely logical for a severity grading system to align with a clinical definition of anaphylaxis (used to indicate the need for epinephrine treatment).

Whether a single severity score for acute allergic reactions is achievable is unclear. Severity gradings must be sensitive to the underlying purpose. If to guide acute treatment, there are already simple definitions (such as the Airway/Breathing/Consciousness mnemonic) to guide epinephrine use; a complicated severity score is not only unnecessary but might delay treatment and cause harm. If to assess the response to an intervention (such as allergen desensitisation or anti-IgE therapy), then ample evidence exists that a 5-grade severity score

confers insufficient discrimination, particularly for non-anaphylaxis reactions which constitute the majority of allergic reactions.[2,5] Whether severity scores can help define patient phenotypes and thus those at greater risk of severe reactions is controversial; such a score would need to include patient perception and opinion, something notably absent in the methodology chosen by Dribin et al. Historically, the development of disease severity scores have not, in general, involved patient input. However, severity does impact on patients (indeed, the COFAR severity score includes this as a determinant of severity)[10]. Severity scores for food allergy inform patient education.[2,3] Anaphylaxis is poorly recognized by patients/carers and healthcare professionals alike. Shared decision-making is increasingly well-established in allergy practice; it would therefore seem prudent to include Patient and Public involvement in the development of severity assessments, at least in the latter stages, to guide strategies to improve symptom recognition by patients (and adherence to appropriate management).

Improving anaphylaxis care does not need to be complicated. Having a standardised, internationally-agreed quantitative measure for severity might be useful in facilitating risk communication, both with patients and with industry/regulators. As research into the active treatment of food allergy increases, the need for consistency and translatability in recording results is essential. However, any severity score must be fit-for-purpose, informed by patient and clinician experience, and ideally be data-driven to minimise the impact of subjectivity and provide objective validation (Figure 1).[2,11] In the meantime, the severity score proposed by Dribin et al highlights the inconsistencies and limitations of the NIAID criteria for anaphylaxis. Developing our understanding of the relationship between anaphylaxis definition (and indication for epinephrine treatment) and severity grading of

symptoms is essential for further progress in this area. We need to achieve a global consensus on updated anaphylaxis criteria, to improve anaphylaxis recognition and thus patient care - it's what patients deserve.

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FIGURE LEGENDS

Figure 1: Approaches taken to develop severity scores involve a balance between expert opinion ("subjectivity") and the objective use of data.

Stakeholder	Perception of severity and possible implications
Allergic patients /caregivers	May under- or over-estimate severity: parents of children with food allergies may perceive significant skin signs (e.g. facial angioedema) as severe, while experienced clinicians recognise this is a common presentation of reactions in young children. In contrast, parents may attribute wheeze to a viral illness (particularly in a child prone to viral wheeze) and fail to recognise that this indicates anaphylaxis if occurring after exposure to a known allergen.
Emergency care givers e.g. paramedics, Emergency Department staff	Need to consider long lists of differential diagnoses. May have limited experience leading to inaccurate diagnosis or inappropriate treatment. Reactions have often resolved by arrival to hospital, so local staff may not appreciate potential risks of severe anaphylaxis.
Family medicine practitioners / Paediatricians	May have limited experience of severe reactions, leading to under- or over-treatment of reactions.
Allergy specialists	Trained to evaluate the spectrum of allergic disease, often retrospective assessment of severity. Often not involved in the provision of acute care.
Food industry and Food regulators	Necessity for objective risk assessment; in practice, severity may be defined as an unscheduled health encounter. Thus, mild reactions presenting to hospital are classified as more severe than anaphylaxis managed in the community which does not present to Emergency Departments.

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169 **Table 1**: Stakeholders perception of severity. Adapted from reference 1

Table 2: WAO amended criteria for the diagnosis of anaphylaxis

Anaphylaxis is highly likely when any <u>one</u> of the following 2 criteria are fulfilled:
1. Acute onset of an illness (minutes to several hours) with simultaneous involvement of the skin, mucosal tissue, or both (e.g. generalized hives, pruritus or flushing, swollen lips-tongue-uvula) *AND AT LEAST ONE OF THE FOLLOWING:* a. Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) b. Reduced BP or associated symptoms of end-organ dysfunction (e.g. hypotonia [collapse], syncope, incontinence) c. Severe gastrointestinal symptoms (e.g. severe crampy abdominal pain, repetitive vomiting), especially after exposure to non-food allergens
2. Acute onset of hypotension* or bronchospasm† or laryngeal involvement‡ after exposure to a known or highly probable allergen for that patient (minutes to several hours), even in the absence of typical skin involvement.

PEF, Peak expiratory flow; BP, blood pressure.

*Hypotension defined as a decrease in systolic BP greater than 30% from that person's baseline, OR

i. Infants and children under 10 years: systolic BP less than (70mmHg + [2 x age in years])

ii. Adults and children over 10 years: systolic BP less than <90 mmHg

†Excluding lower respiratory symptoms triggered by common inhalant allergens or food allergens perceived to cause "inhalational" reactions in the absence of ingestion.

‡Laryngeal symptoms include: stridor, vocal changes, odynophagia.

Figure No. 1

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