

EDITORIAL

Perioperative anaphylaxis grading system: ‘making the grade’

M. A. Rose^{1,*}, S. L. Green¹, H. M. Crilly² and H. Kolawole³

¹Department of Anaesthesia, Royal North Shore Hospital, St Leonards, NSW 2065, Australia,

²Department of Anaesthesia, The Tweed Hospital, Powell Street, Tweed Heads, NSW 2485, Australia, and

³Department of Anaesthesia, Peninsula Health, Hastings Road, Frankston, VIC 3199, Australia

*Corresponding author. E-mail: mikerose500@gmail.com

Perioperative anaphylaxis has a heterogeneous clinical presentation that ranges from mild to catastrophic. Mild presentations are easily managed, may not require specific treatment, and often allow completion of the intended surgical procedure. At the severe end of the spectrum, the cluster of multisystem derangements can cause cardiac arrest and the inability to oxygenate because of intractable bronchospasm or upper airway angioedema. It is here that fatalities may occur, especially if treatment has been delayed or epinephrine dosage misjudged.

A variety of anaphylaxis classification systems have been developed as a way of stratifying the severity of clinical anaphylactic reactions. At present, although there are similarities between published classification systems, there is no standardized grading system for defining severity. Furthermore, few systems quantify physiological parameters to help guide clinician treatment decisions. Anaphylaxis during anaesthesia frequently presents differently to that which is observed after oral ingestion of allergens or envenomation (e.g. skin signs may be absent or present only once treatment measures have been commenced). Although it may be desirable that a clinical grading system is applicable to all types of allergic reactions,¹ we propose that perioperative anaphylaxis is sufficiently different from other forms of acute hypersensitivity to be deserving of its own classification system and that an approach of ‘one size fits all’ does not serve the best interests of management of anaphylactic crises in the operating room.

The classification of the severity of perioperative anaphylaxis has two important roles: guiding treatment and facilitating reporting and research. Defining clinical severity has been used to guide the initial management of suspected anaphylactic reactions [e.g. guidelines by the Australian and New Zealand Anaesthetic Allergy Group (ANZAAG),² the Association of Anaesthetists of Great Britain and Ireland (AAGBI),³ the European Network for Drug Allergy/European Academy of Allergy and Clinical Immunology (ENDA/EAACI)]⁴ and to aid clinical decision-making

to proceed or abandon surgery. Epinephrine has a narrow therapeutic window, and the misclassification of the severity of anaphylaxis may lead to an epinephrine overdose with the potential for fatalities.

Standardized nomenclature and severity grading would also support qualitative research on perioperative anaphylaxis (e.g. comparisons of incidence, results of treatment, and survival rates could be performed). There are areas of overlap between anaphylaxis classification systems in current use, and no standard or consistent severity grade has been used in the literature to report on data about perioperative anaphylaxis. This lack of standardization has implications for patient safety when implementing treatment guidelines in the perioperative setting and for quality of evidence when comparing incidence, outcomes of treatment, or investigations in different patient cohorts.

In 2006, The National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID/FAAN) published an international consensus on definition and management of acute hypersensitivity⁵ in an attempt to standardize diagnostic criteria for anaphylaxis. This consensus definition includes the clinical entities of antigen challenge testing, immunotherapy, and unexpected anaphylaxis states. As such, the definition of anaphylaxis depends on whether the allergen is unknown, suspected, or known for an individual patient. Anaphylaxis in the perioperative environment is thus an instance of ‘anaphylaxis attributable to unknown allergens’ in the context of this consensus. A diagnosis of clinical anaphylaxis can be made when a patient exposed to an unknown allergen develops acute cutaneous features and respiratory compromise or reduced blood pressure or associated symptoms of end-organ dysfunction. This is problematic, as in perioperative anaphylaxis cutaneous features are frequently absent at the time of initial diagnosis, and in some instances, anaphylaxis may occur without any cutaneous signs.^{3,6}

As a clinical definition, the NIAID/FAAN consensus criteria have the advantage of facilitating diagnosis of anaphylaxis at

Table 1 Perioperative anaphylaxis grading system

Grade A Moderate perioperative anaphylaxis	Grade B Life-threatening perioperative anaphylaxis	Grade C Cardiac arrest with or without respiratory arrest associated with perioperative anaphylaxis
Measurable derangements in one or more major organ systems The derangements are unexpected for the stage of the patient's perioperative course Non-life-threatening	Life-threatening cardiovascular or respiratory derangement, or both	Cardiac or respiratory arrest, or both
Cardiovascular system	Cardiovascular system	Cardiovascular system
(i) Hypotension (ii) Tachycardia or bradycardia (iii) Arrhythmia	(i) Systolic blood pressure of <60 mm Hg (ii) Life-threatening tachy- or bradyarrhythmia	(i) Cardiac arrest
Respiratory system	Respiratory system	Respiratory system
(i) Cough (ii) Wheeze (iii) Difficult ventilation (iv) Oxygen desaturation (v) Difficulty swallowing (vi) Rhinorrhoea	(i) Oxygen saturation <90% (ii) Inspiratory pressures of >40 cm H ₂ O (iii) Severe difficulty inflating the lungs (iv) Airway angioedema	(i) Respiratory arrest or complete failure of ventilation
Other systems		
(i) Unexpected change in consciousness (ii) Agitation (iii) Gastrointestinal upset		
Cutaneous signs (e.g. flushing, urticaria, angioedema) may or may not be present At least one other system is involved for the diagnosis of anaphylaxis		

the time of reaction, regardless of causation (IgE or non-IgE mediated). With respect to management, the NIAID/FAAN paper recommends that it be guided by the severity of the signs present, but no quantitative severity gradation is described.

The seminal and most quoted grading system of clinical anaphylaxis severity in the literature was developed by Ring and Messmer in 1977.⁷ It features a scale from 1 to 4, with grade 1 being skin symptoms, a mild fever reaction, or both, through to grade 4 being cardiac or respiratory arrest. Since that time, most other systems have used similar numerical grading systems. A Scandinavian guideline⁸ added a fifth severity category, where grade 5 is death. The World Allergy Association⁹ published an Immunotherapy Systemic Reaction Grading System from 1 to 5 that is qualitatively different in that any hypotension scores 4, while grade 5 is death, as in the Scandinavian guideline, and hypotension is not quantified (Supplementary data, Table S1).

An alternative to the numerical severity scale was described by Brown¹⁰ in 2004 and classifies reactions as 'mild', 'moderate', or 'severe'. This system is simple, but it has limitations in the perioperative setting. For example, the 'severe' category does not differentiate between patients who have relatively mild reactions (systolic blood pressure slightly <90 mm Hg) or life-threatening reactions, or even those who have cardiac arrest (Supplementary data, Table S2).

Recent clinical definitions of anaphylaxis, such as the NIAID/FAAN consensus clinical definition,⁵ state that skin changes on their own do not constitute anaphylaxis. As such, grade 1 reactions in all of the previous classifications and mild reactions in

the Brown severity scale should be removed from any revised severity grading for perioperative anaphylaxis. The appearance of a rash in an otherwise stable perioperative patient should not prompt the use of epinephrine but rather anticipatory vigilance for other manifestations of anaphylaxis, with escalation of grading and commencement of treatment only if appropriate. Despite this, a new grading system described by Niggemann and Beyer¹ in April 2016 includes skin-only reactions in both grade I and grade IIA. In this system, grade III reactions are further subdivided into three categories with descriptions that align to grade 2–4 in other grading systems. This feature makes the grading system complex and unlikely to be applicable in the perioperative setting.

The common description of grade 2 reactions is non-specific; they are 'moderate' reactions with measurable changes in physiological variables (particularly cardiovascular and respiratory variables, and cutaneous signs). These reactions are described as 'not life-threatening'. With the exception of one description,¹⁰ the degree of alteration in physiological variables considered moderate is not defined; even in this paper, only moderate hypotension is defined, as 'a decrease of more than 30% in blood pressure associated with unexplained tachycardia'. It is now recognized that tachycardia, the most commonly observed alteration in heart rate, is not a universal sign associated with hypotension caused by anaphylaxis. In a more recent publication,⁵ the same first author has retained the description of 'measurable but not life-threatening symptoms' but removed the requirement for the reduction in blood pressure to be

>30%. The three anaesthesia-related papers have also recognized that a common respiratory manifestation of perioperative anaphylaxis is difficulty inflating the lungs rather than cough or audible wheeze.

In the anaphylaxis classification systems with 4 grades, cardiac or respiratory arrest, or both, is consistently defined as grade 4. The contentious area of the current classification systems is with those termed grade 3 reactions, which are uniformly referred to as 'life-threatening'. Immunoglobulin E-mediated perioperative anaphylaxis is commonly reported to be of grade 3 severity, quoted as approximately 60% in two studies.^{11 12} There is much inter-observer variability between clinicians regarding what 'life-threatening' entails, as this is a subjective assessment made in real time, against a backdrop of altering physiological variables that may also be deranged by anaesthesia, pre-existent pathology, or both. There is a need to make a clear distinction between classifying a reaction as 'non-life-threatening' (grade 2) vs 'life-threatening' (grade 3), because the initial management will be associated with a 5- to 10-fold difference in the i.v. epinephrine dose selected according to the guidelines of ANZAAG² (20 vs 100–200 µg).

The authors propose a more objective perioperative anaphylaxis grading system (PAGS; Table 1) in an effort to reduce the ambiguity of previous classifications and link signs and symptoms with appropriate epinephrine dosing. When dealing with an acute and potentially fatal disease and treatment that features epinephrine, a drug with a narrow therapeutic index, the matching of the severity of reaction and the treatment is an important goal.

Three severity grades replace four or five as described in other classification systems. The chosen nomenclature is alphabetical to lessen confusion with earlier numerical systems. The lack of precision regarding 'moderate' vs 'life-threatening' has been addressed by creating cardiovascular and respiratory variable cut-off points where it is deemed that derangement would become life-threatening in almost all patients.

We propose that a standardized and simplified grading system of perioperative anaphylaxis would reduce diagnostic confusion and promote rapid stratification of patients (see Table 1). Treatment can then be aligned to the individual and potential harm minimized through better correlation of event severity and epinephrine dose. As the research base for the phenomenon of perioperative anaphylaxis is limited to qualitative and low-grade quantitative evidence, formalized nomenclature could lead to more meaningful comparisons of data on diagnosis, treatment, and outcomes. The ultimate aim is to facilitate improvements in the care of patients who suffer this challenging and unexpected perioperative emergency.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

Declaration of interest

All authors are members of the Australian and New Zealand Anaesthetic Allergy Group, a not-for-profit organization involved in producing treatment guidelines for perioperative anaphylaxis and facilitating research in this area. M.A.R. has served as immediate past Chair of The Australian and New Zealand College of Anaesthetists Allergy Subcommittee.

References

1. Niggemann B, Beyer K. Time for a new grading system for allergic reactions? *Allergy* 2016; **71**: 135–6
2. ANZAAG Guidelines. Available from www.anzaag.com (accessed 22 June 2016)
3. Harper NJN, Dixon T, Dugué P, et al. Association of Anaesthetists of Great Britain and Ireland. Suspected anaphylactic reactions associated with anaesthesia. *Anaesthesia* 2009; **64**: 199–211
4. Mertes PM, Laxenaire MC, Lienhart A, et al. Reducing the risk of anaphylaxis during anaesthesia: guidelines for clinical practice. *J Invest Allergol Clin Immunol* 2005; **15**: 91–101
5. Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report–Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006; **117**: 391–7
6. Mertes PM, Lambert M, Guéant-Rodriguez RM, et al. Perioperative anaphylaxis. *Immunol Allergy Clin North Am* 2009; **29**: 429–51
7. Ring J, Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. *Lancet* 1977; **1**: 466–9
8. Kroigaard M, Garvey LH, Gillberg L, et al. Scandinavian Clinical Practice Guidelines on the diagnosis, management and follow-up of anaphylaxis during anaesthesia. *Acta Anaesthesiol Scand* 2007; **51**: 655–70
9. Cox L, Larenas-Linnemann D, Lockey RF, Passalacqua G. Speaking the same language: the World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System. *J Allergy Clin Immunol* 2010; **125**: 569–74
10. Brown SGA. Clinical features and severity grading of anaphylaxis. *J Allergy Clin Immunol* 2004; **114**: 371–6
11. Mertes PM, Alla F, Laxenaire MC. Anaphylactic and anaphylactoid reactions occurring during anaesthesia in France in 1999–2000. *Anesthesiology* 2003; **99**: 536–45
12. Mertes PM, Alla F, Tréchet P, Auroy Y, Jouglé E, Groupe d'Etudes des Réactions Anaphylactoïdes Peranesthésiques. Anaphylaxis during anaesthesia in France: An 8-year national survey. *J Allergy Clin Immunol* 2011; **128**: 366–73