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Consensus clinical scoring for suspected perioperative immediate hypersensitivity reactions

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Conception of the study: all authors

Design of the study: PMH, PC, ABG, PS, RC, PP

Data collection, analysis & interpretation: all authors

Drafting of manuscript: PMH, PC, ABG, PS, RC, PP

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Abstract

Background

Grading schemes for severity of suspected allergic reactions have been applied to the perioperative setting but there is no scoring system that estimates the likelihood that the reaction is an immediate hypersensitivity reaction. Such a score would be useful in evaluating current and proposed tests for the diagnosis of suspected perioperative immediate hypersensitivity reactions and culprit agents.

Methods

We conducted a Delphi consensus process involving a panel of international multidisciplinary experts in suspected perioperative allergy. Items were ranked according to appropriateness (on a scale of 1 – 9) and consensus, which informed the development of a clinical scoring system. The scoring system was assessed by comparing scores generated for a series of clinical scenarios against ratings of panel members. Supplementary scores for mast cell tryptase were generated.

Results

Twenty-five panel members participated. Two rounds of the Delphi process achieved stopping criteria for all statements. From an initial 60 statements, 43 were rated appropriate (median score 7 or more) and met agreement criteria (disagreement index < 0.5) and were used in the clinical scoring system. The rating of clinical scenarios supported the validity of the scoring system. Although there was some variability in the interpretation of changes in mast cell tryptase by the panel we were able to include supplementary scores for mast cell tryptase.

Conclusion

We have used a robust consensus development process to devise a clinical scoring system for suspected perioperative immediate hypersensitivity reactions, which will enable objectivity and uniformity in the assessment of the sensitivity of diagnostic tests.

Keywords

Drug hypersensitivity; anaphylaxis; allergy; perioperative period; anaesthesia, scoring; surgery

Adverse perioperative events that meet published criteria for suspected immediate hypersensitivity reactions (IHRs) have been reported in up to 1:353 general anaesthetics[1, 2]. The clinical diagnosis of an IHR (allergic or non-allergic) is difficult in the perioperative patient because many of the clinical features occur frequently at various grades of severity through non-immune mechanisms. Additionally patients under general anaesthesia are unable to report symptoms[3]. If an IHR is diagnosed, identifying the culprit agent can be difficult because of the routine almost simultaneous exposure of multiple potential culprits[4]. The diagnosis of an IHR in the perioperative period is important because it has implications for the provision of safe anaesthesia for the patient in the future. Furthermore, having identified that a patient has had an IHR, identification of the mechanism and culprit agent along with safe alternative drugs within the same class of the culprit is required to enable the goal of safe future anaesthesia.

Guidelines for the investigation of suspected perioperative IHRs emphasise the need to combine clinical information, measurement of biomarkers of acute allergic responses and skin testing[5-10]. *In vitro* tests to improve diagnosis have been the subject of research [11-13] and these are reviewed in detail elsewhere in this issue of the *British Journal of Anaesthesia*. A key requirement for the interpretation of any test is an understanding of its accuracy[14]. The accuracy of a test is described most simply in terms of its sensitivity (the proportion of truly positive patients or samples that have a positive test) and specificity (the proportion of truly negative patients or samples that have a negative test). Calculation of the sensitivity and specificity with different cut-off values can be used to determine the optimum cut-off value for diagnosis. In combination with an estimate of the *a priori* likelihood of a condition, the sensitivity and specificity can be used to calculate the predictive positive and negative values of a test.

To estimate the sensitivity of any test to confirm an IHR or identify a culprit agent it is necessary to evaluate the test in patients who are known to have had an IHR, i.e. they are true positives. For this to be an unbiased evaluation, identification of true positive cases should be independent of the results of the test or related tests, in other words circular arguments should be avoided[15-18]. Fundamentally, this requires an objective approach to identifying true perioperative IHRs with a high degree of

likelihood based on clinical information alone. Some workers have used classification systems of allergic reactions for this purpose[19-23], mostly based on the Ring and Messmer[24] classification. There are newer systems proposed by Niggemann and Beyer[25] (primarily for food allergy) and, specifically for perioperative reactions, by Rose et al[26] and Cook et al[27] to classify the severity of the reaction. However, none of these classification systems describe how likely the reaction was to be an IHR. Indeed, the assumption underlying such classification systems is that the patient is having an allergic reaction because there is no likely alternative explanation for the features. This is a reasonable assumption in the absence of all of the potential confounding factors present in the perioperative period. For example, no account is taken for alternative causes of bronchospasm or hypotension[28] with the classification systems derived from Ring and Messmer. Therefore, we aimed to generate a clinical scoring system to assess the likelihood of an adverse event in the perioperative period being an IHR.

Methods

Although this paper does not represent the development of a guideline *per se*, the methodology shares several aspects of guideline development. We therefore used the AGREE checklist[29], where relevant, to advise our approach.

Panel selection

An international multidisciplinary panel of allergists, anaesthetists and immunologists with a track record of publication in the field of perioperative anaphylaxis were invited to participate. From within the panel, a "writing group" was formed from those members of the panel expressing a specific interest in taking an additional role with this project.

Literature search

We used the PICO (population, intervention, comparators, outcomes) framework to formulate our literature search strategy as follows:

Population/problem

Patients undergoing an operative procedure for diagnosis or treatment involving care from an anaesthetist

Intervention

Diagnosis of suspected IHR in the perioperative period

Comparators

Confounding factors for diagnosis of suspected IHR

Outcomes

Clinical diagnosis, classification or grading of suspected perioperative IHR.

We searched PubMed and Embase databases and included publications from 1997 to the present but also key publications (first reports of paradigms that remain central to the PICO criteria) prior to 1997.

Modified Delphi Process

We adopted the approach of Fitch et al [30] in which statements are rated for appropriateness on a scale of 1 (completely inappropriate) to 9 (completely appropriate). Disagreement was determined using the disagreement index (DI), where the lower the value below 1, the greater is the consensus: a value > 1 is considered to represent lack of consensus [31]. The median appropriateness score was used to rate each statement as inappropriate (median score 1 – 3.4), uncertain (median score 3.5-6.9) or appropriate (median score 7-9). We planned at least two rounds to generate a series of statements rated as appropriate with a clear consensus (DI < 0.5). The process was to continue until a clear consensus was reached for each statement (DI < 0.5) or the DI failed to improve by more than 15% in successive rounds [32]. The Delphi process was managed by the convener of the writing group (PMH): all other members of the panel were invited to participate in each round and were given at least 2 weeks to respond.

Round 1.

A series of statements describing clinical manifestations of suspected IHRs was generated by the writing group based on relevant publications identified from the literature search and their clinical experience. The statements were sent to panel members using an online questionnaire tool (Google forms) in which panel members were asked to rate each statement on a scale of 1 (completely inappropriate) to 9 (completely appropriate). Panel members had the option of responding N/A (not applicable) to statements which they felt to be outside their expertise. Panel members were also invited to provide freehand comments on the wording of existing statements or to propose new statements.

Round 2 and subsequent rounds:

Prior to Round 2, panel members received their scores from Round 1 alongside de-identified scores of the other panel members (as raw data and as summary bar charts), and the calculated median appropriateness and DI values. Information on interpretation of median appropriateness and DI values was provided. In addition, median appropriateness values were calculated separately for panel members who were anaesthetists and those who were either allergists or immunologists and these values were also circulated to panel members.

In generating the statements for Round 2, the writing group reviewed the responses to the statements in Round 1, including the freehand comments, and agreed whether each statement should be included in Round 2 unchanged, included in amended form or not included in Round 2. The revised statements were formatted as an online questionnaire as for Round 1, which the panel members were invited to complete. If the stopping criteria were not met after Round 2, the process for subsequent rounds would follow that of Round 2.

<u>Generation of the Clinical Scoring System</u>

The results of the final round of the Delphi process were used to rank clinical features as to their contribution to predicting the likelihood of an IHR based first on the median appropriateness rating and then on the DI. These rankings were used to assign points within the scoring system, such that clinical features increasing the likelihood of an immediate hypersensitivity reaction were assigned positive values and those decreasing the likelihood (confounding features) were assigned negative values. The relative points allocation within positive and negative categories was made on the basis of the Delphi rankings supplemented by the clinical experience of the writing group who agreed the initial scoring scheme. The content validity of the scoring scheme was initially assessed subjectively by the writing group before testing for criterion and discriminant validity using the whole panel. For this exercise, a series of hypothetical case scenarios of suspected perioperative IHRs was developed and panel members were asked to independently rate the likelihood of the case as either “almost certain”, “very likely”, “likely” or “unlikely” to be an IHR. The case scenarios were compiled by the writing group convener (PMH) and were designed to evaluate how experts assessed the relative discriminant ability of items within and between scoring

system categories and their combination. Minor adjustments of the points allocation within the scoring system were made in order to maximise its discriminant validity before the median likelihood ratings of the panel were used to calibrate the scoring system.

In addition to asking panel members to rate the case scenarios on clinical features alone, they were also asked to rate the scenarios when accompanied by mast cell tryptase results. The mast cell tryptase values used were intended to assess how experts assessed: a) "borderline" tryptase rise; b) the impact of no or minimal tryptase change on their evaluation of a clinical scenario with relatively high likelihood of being an IHR; c) the impact of a large tryptase rise on their evaluation of a clinical scenario with relatively low likelihood of being an IHR. These responses were used to produce and calibrate a scheme for supplementing the clinical scoring system when tryptase results are available (and assuming that the purpose of generating the score is not to evaluate the sensitivity of tryptase changes themselves).

Results

We approached by email 33 international experts in suspected perioperative allergic reactions of which 18 were anaesthetists, 14 allergists or immunologists and one dually accredited in anaesthesia and allergy. Of these, 15 anaesthetists, 9 allergists/immunologists and the dually accredited colleague agreed to participate. The details of the panel members are provided in the list of authors of this paper. The six members of the writing group are all anaesthetists.

Delphi process

From the review of the literature (literature search terms and results are provided in Supplementary Online Appendix 1) and their clinical experience, the writing group generated a list of 60 statements to be used in Round 1. Twenty-three of 24 members (96%) of the panel responded (the final panel member, PMH, managed the Delphi process). Thirty-nine of the statements were rated as appropriate, 20 as of uncertain appropriateness and one inappropriate. The DI was < 0.5 for 41 statements, between 0.5 and 1 for 18 statements and > 1 for one statement ("Patients with a history of allergy are at increased risk of developing an immediate hypersensitivity reaction in the perioperative period"). This latter statement was one of only eight statements where

the median appropriateness scores for anaesthetists differed by more than 2 from that of the non-anaesthetists (Supplementary Online Appendix 2). Panel members contributed a total of 17 freehand comments in Round 1 although no completely new statements were proposed.

In Round 2, 32 of the statements were unchanged from Round 1, 17 statements were amended and 11 statements from Round 1 were excluded. Twenty-four members (100%) of the panel responded. Supplementary Online Appendix 3 shows the Round 2 statements ranked in order of the highest median appropriateness score and then by the lowest DI. All of the statements met one or other stopping criteria for the iterative Delphi process. All but six of the statements have a median appropriateness score of 7 or more and a DI < 0.5. The remaining statements were considered for use in construction of the clinical scoring system.

From Supplementary Online Appendix 3 it can be seen that clinical features associated with the cardiovascular system, the respiratory system and skin or mucous membranes were perceived to have value in predicting the likelihood of a perioperative IHR. Within each of these systems several confounding factors were identified that reduced the likelihood of a perioperative IHR (Supplementary Online Appendix 3). Supplementary Online Appendix 3 also highlights the high ratings for appropriateness and consensus for co-occurrence of features from more than one system. The other aspect that the writing group reflected in the initial clinical scoring system was the timing of the onset of clinical features in relation to administration of a potential culprit agent.

In transforming the consensus statements into the clinical scoring system we realised that clinical terms needed to be defined so that the scoring system had construct validity and could be applied reproducibly. The writing group developed a series of definitions of clinical features and tested these for appropriateness with a single round Delphi process involving all panel members. Table 1 shows the definitions agreed and the high level of appropriateness and consensus of the panel for these definitions in this context.

The writing group structured the scoring system based on key areas of consensus from the Delphi process. These were: positive and confounding features within each of cardiovascular, respiratory and dermal/mucosal categories; the added weight of combinations of features from more than one of these categories; the importance of timing of onset of features in relation to exposure to potential triggers, except for dermal or mucosal features. The writing group agreed a provisional scoring system before conducting a validity-testing exercise involving the whole panel. The clinical scenarios used in this exercise are presented in Supplementary Online Appendix 4 along with the ratings of the panel members. These ratings are presented for the whole group and also for anaesthetists separately.

The writing group used the feedback from the clinical scenario ratings of the panel members to make minor adjustments to the clinical scoring system while maintaining the principles derived from the initial consensus exercise. The final clinical scoring system is shown in Table 2. The median clinical scenario ratings were used to calibrate the clinical scoring system by converting scoring ranges to indicate almost certain, very likely, likely or unlikely IHRs. During writing of the manuscript it was agreed to subdivide the "likely" category into "likely" and "possible" as we think this will aid clinical utility. The likelihood categories are shown in Table 3.

In order to incorporate changes in mast cell tryptase concentration into the clinical scoring system we evaluated the impact of various tryptase changes on the clinical likelihood rating of the panel members. Ratings are shown in Supplementary Online Appendix 4. If the peak tryptase after a suspected IHR showed no change from the baseline value most panel members considered this to have a negative impact on their assessment of the likelihood of an IHR. A change in tryptase of (1.2 x baseline) + 2 ng ml^{-1} with the peak tryptase remaining within the reference range was considered a better indicator of a likely IHR than a smaller relative change even if the peak tryptase was outside the reference range (greater than the upper 95% confidence limit of the reference range). If a relative change of (1.2 x baseline) + 2 ng ml^{-1} was combined with a peak value greater than the upper limit of the reference range, the tryptase was considered to have a greater impact on likelihood of an IHR. An even greater relative change combined with the peak being outside the normal range had the greatest impact. These rankings were used to produce an algorithm for increasing points

allocation to tryptase changes to supplement the clinical scoring system, when appropriate. These values are shown in table 4.

Discussion

We have used an established methodological approach to generate consensus from an international multidisciplinary panel of experts in suspected perioperative allergic reactions for clinical criteria that have predictive value for estimating the likelihood that an adverse perioperative event was the result of an IHR. We used the ranking of appropriateness and consensus of the criteria to construct a clinical scoring system and went on to ensure its content, construct, criterion and discriminant validity.

One of the key differences between previously published classification systems and our clinical scoring system is that we have enabled the impact of potential confounding factors and the time interval between potential culprit exposure and onset of signs to be assimilated. Although this increases the complexity of the final scoring system, it reflects the complexity that can be involved in forming an expert clinical judgement of the potential cause of an adverse perioperative event. Indeed, the need to exclude other causes of suspected adverse drug reactions is an accepted and integral part of causality assessment used in pharmacovigilance [33]. Our validity assessments suggest that the scoring system will be able to identify with high likelihood IHRs that present with relatively subtle features involving 2 or more systems and IHRs with more severe features confined to a single system. The scoring system also implicitly reflects the expert consensus that timing of skin manifestations is a poor discriminator as these may be obscured by surgical drapes or delayed in appearance until a shocked patient has been resuscitated.

The value of the availability of a clinical scoring system for rare perioperative adverse reactions has been demonstrated by the enduring use of the Larach clinical grading scale for malignant hyperthermia which was developed using a Delphi consensus approach [34] . This has been used to great effect to evaluate the sensitivity of the two principally applied protocols for the laboratory diagnosis of malignant hyperthermia susceptibility [35,36] and in studies of the epidemiology of malignant hyperthermia[37,38]. As with our scoring system for IHRs, the Larach clinical grading scale was not intended

for use in real-time clinical diagnosis, which for both IHR and malignant hyperthermia should be based on early pattern recognition of clinical features and rapid evaluation of differential diagnoses with a relatively low threshold for initiating treatment.

Implementation of the IHR clinical scoring system requires experience of interpretation of perioperative records, including anaesthetic charts, in order to accurately extract the data needed. Our recommendation is that this is done by an individual with the necessary expertise who was not involved directly with the case in order to minimise subconscious bias. The relevant and sufficient information to apply the scoring system to cases of suspected perioperative allergic reactions should be routinely available when patients are assessed in a specialist anaesthetic allergy clinic setting. However, the scoring should be done blinded to the results of subsequent investigations to avoid hindsight bias.

The definitions of various clinical terms, such as hypotension, bronchospasm and tachycardia, that we have adopted for use in the clinical scoring system (Table 1) are intended to maximise the utility of the scoring system. Using hypotension as an example, our definitions differ from the physiological definition, definitions used in the context of allergy in general[39] and even definitions used elsewhere in the context of perioperative allergy [40,41]. It is inevitable that our definitions will exclude clinical features that occur in some true IHRs from contributing to the score for that reaction. It is our collective view that such subtle changes in the perioperative context have too low a predictive value for our purpose. Similarly, although a low end-tidal CO_2 has been shown to be a superior predictor of the severity of an IHR to, for example, hypotension[42], our expert consensus was that this sign did not add to the discriminant ability of hypotension and bronchospasm to distinguish between hypersensitivity and non-hypersensitivity reactions, while potentially introducing additional confounders such as iatrogenic hyperventilation, hypothermia, pulmonary embolus or right-to-left shunt.

A potential advantage of using a scoring system generated by expert consensus is that it is likely to reduce the potential inter-rater variability inherent in forming an assessment of causality from an unstructured review of clinical information. The 6th National Audit Project (NAP6) of the Royal College of Anaesthetists addressed this

issue by using a large multidisciplinary panel to assess each potential case of anaphylaxis [27,43,44]. Although we have not formally assessed inter-rater variability for application of the clinical scoring system, our validity exercise demonstrated the variability of an opinion-based assessment of some relatively straightforward clinical scenarios. We had anticipated that this variability would be greatest when comparing anaesthetists and non-anaesthetists. However, on the whole this was not the case with within-specialty variability being similar to between-specialty variability: this is likely to reflect the common factor of expertise in perioperative allergy.

Our evaluation of expert opinion of the interpretation of changes in mast cell tryptase indicates that uncertainty persists in how such changes impact on the clinical evaluation of suspected perioperative IHRs. The majority of laboratories use the same supplier for mast cell tryptase testing kits and reagents. The test has a low coefficient of variation with a high level of reproducibility between laboratories [45]. This makes it even more surprising perhaps that there is not better agreement on the interpretation of acute changes in the perioperative period. One of the issues may be the lack of robust estimates for the sensitivity and specificity of mast cell tryptase changes in suspected perioperative allergic reactions. For many years, it was assumed that if the peak tryptase in the 1 to 2 hours after a suspected perioperative allergic reaction was within the normal reference range then the tryptase result was “negative”. In the meantime, Brown and colleagues investigated tryptase changes in volunteers in whom allergic reactions where provoked in a controlled experimental setting with venom [46]. Such studies demonstrated that relative change from baseline was perhaps more important in detecting mast cell activation than the absolute value of the peak tryptase concentration. Meanwhile, Garvey and colleagues found that the upper 95% CI for relative change in tryptase during elective orthopaedic surgery was 39% [47]. A consensus process was used to develop a criterion for mast cell activation based on the principle of relative change [45]. It is clear from the responses of our expert panel to the hypothetical tryptase changes presented alongside clinical scenarios, that not all expert opinion is confident that the use of this formula in the perioperative setting is discriminatory. Egner and colleagues conducted perhaps the largest evaluation of mast cell tryptase in suspected perioperative allergic reactions [48]. Their data, although having to rely on the Ring and Messmer classification, suggest that smaller changes in tryptase in the perioperative setting may indeed be relevant if the sensitivity of

tryptase changes is to be optimised. Baretto and colleagues [49] produced similar findings but they used the World Allergy Organisation criteria [50] for identifying their "true positive" cases, which again do not account for confounding factors. We propose that evaluation of tryptase changes in a large cohort of patients categorised as "almost certain" by our clinical scoring system would provide the best estimate to date of the sensitivity of tryptase changes in identifying perioperative IHRs. We should emphasise that the time of sampling for the peak tryptase (ideally 1 -2 h after the onset of the reaction) is extremely important, especially when considering discrete increases.

Limitations

While we have demonstrated several aspects of the validity of the scoring system, independent external validation was not possible within the constraints of this project. The main purpose of external validation of such a tool is to ensure that it is generalizable but we expect that inclusion of global representation on our expert panel makes generalizability of the scoring system likely. One possible means of independent validation of the scoring system would be to utilize the NAP6 cases and compare their scores with the ratings of the NAP6 panel [27,44]. A further potential limitation is that we do not expect the clinical scoring system to be reliable when relevant clinical information is missing, emphasizing the necessity to include copies of all perioperative records when referring a patient with a suspected IHR for investigation [7,8,43].

When applying the clinical scoring system to evaluate the sensitivity of mast cell tryptase changes or skin test results, the user should appreciate that the score makes no presumption about the mechanism of the suspected IHR. This means that one can evaluate a test for its sensitivity to detect an IHR but not IHRs with a defined mechanism (allergic or non-allergic). Therefore, any test that can identify only IHRs with an allergic mechanism, for example, may not achieve 100% sensitivity to detect IHRs even though it has 100% sensitivity to detect allergic reactions. At present, we can only guess what proportion of IHRs are allergic because mast cell tryptase changes and skin test results have been used to define a reaction as allergic, even in the absence of a clear clinical history of an IHR. We now know that both mast cell tryptase and skin tests can be "positive" through non-allergic and even non-immune mechanisms [51-54]. From a pragmatic clinical perspective we need to know the sensitivity of tests to detect

an IHR of any mechanism, because non-allergic as well as allergic IHRs can occur with re-exposure to the culprit agent.

Conclusion

Our clinical scoring system, with or without the incorporation of tryptase results as appropriate, has the potential to better assess the sensitivity of currently used tests that are intended to confirm that an IHR has occurred and the agent responsible. It can also provide a consistent framework for the evaluation in research settings of proposed new tests. A robust estimate of sensitivity of skin tests, for example, will also aid interpretation of investigations of cross-reactivity of chemically and pharmacologically related agents.

Contribution of authors

Conception of the study: all authors

Design of the study: PMH, PC, ABG, PS, RC, PP

Data collection, analysis & interpretation: all authors

Drafting of manuscript: PMH, PC, ABG, PS, RC, PP

All authors reviewed drafts of the manuscript and approved the final version

Declaration of Interests

PD: i) has received lecture and travel fees from MSD France (Courbevoie, France)
ii) has received lecture and travel fees from Bracco Imaging France (Courcouronnes, France)
iii) Agence Nationale de Sécurité du Médicament et des Produits de Santé (Saint-Denis, France), Expert for a task force group dedicated to "neuromuscular blocking agents and anaphylactic reactions" (until 2016)
iv) belongs until October 2019 to a MSD Expert Board on "neuromuscular blocking agents and fast-tracking anesthesia "
LHG: Consultant & adjudication committee member for Merck, New Jersey USA & Consultant & adjudication committee member for Novo Nordisk Denmark.
PMH: is an Editorial Board Member of BJA.
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Tables

Table 1. Definitions for clinical terms used in the clinical scoring scheme

Clinical term	Definition	Median	DI
Hypotension	A fall in systolic blood pressure to < 70 mmHg (at induction or during maintenance of anaesthesia) or by > 20% from a previously stable value (during maintenance of anaesthesia)	8	0.140
Severe hypotension	A fall in systolic blood pressure to < 60 mmHg (at induction or during maintenance of anaesthesia) or by > 40% from a previously stable value (during maintenance of anaesthesia)	8	0.132
Cardiac arrest	The requirement for cardiopulmonary resuscitation not explained by the surgical pathology, complications of the surgical procedure, co-existing medical problems or drugs, malignant hyperthermia or technical anaesthetic problems	8	0.292
Tachycardia	An otherwise unexplained increase in heart rate of 50% or more from a previously stable value	8	0.074
Bronchospasm	The onset of wheeze on auscultation and/or any manifestation of otherwise unexplained increased airway resistance	8	0.074
Severe bronchospasm	Bronchospasm associated with SpO2 <85%	7.5	0.164
Urticaria	A skin rash characterised by raised pink or white raised areas of skin (wheals)	9	0.132
Angioedema	Dermal or mucosal swelling	8.5	0.132

Median = Median appropriateness score
DI = Disagreement index

Table 2. The clinical scoring system. Items contributing to the clinical score for suspected perioperative immediate hypersensitivity reactions (IHRs)- for definitions see Table 1. Points are awarded within five categories, with features suggestive of an IHR (colour-coded pink) having positive points values and features against an IHR (colour-coded green) having negative points values. How points may be allocated to items is indicated for each category. The overall clinical score is the sum of the net scores of all categories.

1. Cardiovascular **(Choose hypotension, severe hypotension or cardiac arrest if appropriate, then any other items that apply)**	**Points**
Hypotension	4
Severe hypotension	6
Cardiac arrest	9
Tachycardia	2
A poor or unsustained response of hypotension to standard doses of sympathomimetics used to treat pharmacological hypotension during anaesthesia (e.g., ephedrine, phenylephrine, metaraminol)	2
A point-of-care echocardiogram showing a hyperdynamic and poorly-filled heart	2
Recurrence or worsening of hypotension after a further dose of a drug given prior to the initial event	1
Cardiovascular Confounders (in the presence of hypotension or cardiac arrest choose any that apply)	
Excessive dose of anaesthetic drug or drugs	-2
Surgically induced hypovolaemia or relative hypovolaemia from prolonged fasting/dehydration	-1
Acute illness predisposing to hypotension	-1
Medications affecting cardiovascular responses during anaesthesia	-2
Neuraxial regional anaesthesia (epidural/spinal)	-1
Onset of hypotension after development of increased peak airway pressure during mechanical ventilation of the lungs	-2
2. Respiratory **(Choose bronchospasm or severe bronchospasm if appropriate then any other items that apply)**	
Bronchospasm	2
Severe Bronchospasm	4
Recurrence or worsening of bronchospasm after a further dose of a drug given prior to the initial event	1
Bronchospasm occurring before airway instrumentation (having excluded airway obstruction)	2
Respiratory Confounders (in the presence of bronchospasm choose any that apply)	
Respiratory disease associated with reactive airways	-1
Prolonged or multiple attempts at tracheal intubation	-1
Inadequate dose of drugs to obtund airway responses prior to airway instrumentation	-1
3. Dermal/mucosal **(Choose any items that apply)**	
A generalised rash is itchy in the awake patient who has not received epidural/spinal opioids	1
Angioedema	3
Generalised erythema	3
Generalised urticaria	4
Dermal/mucosal Confounder	

Angioedema in a patient taking an ACE inhibitor	-3
4. Combinations **(Choose a maximum of one item)***	
CVS>2 & RS > 2	5
CVS>2 & D/M >2	5
RS>2 & D/M >2	5
CVS>2 & RS>2 & D/M >2	8
5. Timings **(Choose a maximum of one item)**	
Onset of cardiovascular or respiratory features within 5 min of possible IV trigger	7
Onset of cardiovascular or respiratory features within 15 min of possible IV trigger	3
Onset of cardiovascular or respiratory features within 60 min of possible non-IV trigger	2
Onset of cardiovascular or respiratory features more than 60 min after possible non-IV trigger	-1

* For a score from one of the 3 organ systems, cardiovascular (CVS), respiratory (RS), dermal/mucosal (D/M) to contribute to a combination score, the net score for that system must be > 2. The net score is the sum of scores for positive features minus the sum of scores for confounders within scores for that system.

Table 3. Clinical Grading Scale for interpretation of Clinical Score for suspected perioperative immediate hypersensitivity reactions (IHRs).

Interpretation	**Total (net) score**
Almost certain to be an IHR	>21
Very likely to be an IHR	15 to 21
Likely to be an IHR	11 to 14
Possible IHR	8 to 10
Unlikely to be an IHR	< 8

Table 4. Algorithm for allocating points for mast cell tryptase changes to supplement the clinical scoring system. Points should be subtracted from or added to the net score from the clinical scoring system (Table 2) with the resulting score interpreted as defined in Table 3.

Mast Cell Tryptase Change	**Points**
No criteria	-4
Formula -ve but > ULN	-2
Formula +ve & < ULN	0
Formula +ve & > ULN	4
> 2 x BL & > ULN	12

Criteria for mast cell tryptase changes:

a. Formula +ve: Peak tryptase is > [(1.2 x baseline tryptase) + 2 ng ml^{-1}]
b. Formula -ve: Peak tryptase is < [(1.2 x baseline tryptase) + 2 ng ml^{-1}]
c. ULN: upper 95% confidence limit of the reference range (11.4 ng ml^{-1})
d. > 2 x BL: Peak tryptase is > 2 x baseline tryptase

Supplementary online appendix 1. Literature search terms and results

1. Pubmed: . ("Drug Hypersensitivity/classification"[Mesh] OR "Drug Hypersensitivity/diagnosis"[Mesh] OR "Latex Hypersensitivity/classification"[Mesh] OR "Latex Hypersensitivity/diagnosis"[Mesh] OR ("Anaphylaxis/classification"[Mesh] OR "Anaphylaxis/diagnosis"[Mesh]) AND ("Anesthesia"[Mesh] OR "Perioperative Period"[Mesh] OR perioperative). (237 items)

2. Embase

Search Strategy:

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1 *drug hypersensitivity/di [Diagnosis] (1819)

2 *latex allergy/di [Diagnosis] (11)

3 1 or 2 (1829)

4 *anaphylaxis/di [Diagnosis] (1409)

5 3 or 4 (3165)

6 anesthesia/ (58954)

7 perioperative period/ (38934)

8 perioperative.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (114784)

9 6 or 7 or 8 (168301)

10 5 and 9 (113)

Searching the two databases retrieved 350 items, 92 of which were duplicates. After review of 258 articles, 64 were considered relevant and are listed below[1-64].

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Supplementary Online Appendix 2

Round 1 statements where median appropriateness differed by more than 2 between anaesthetists and non-anaesthetists

Statement	DI for whole panel	Median appropriateness rating*		
		All panel members	Anaesthetists only	Non-anaesthetists
Following IV induction of anaesthesia, the lowest absolute blood pressure is a better indicator of a likely immediate drug hypersensitivity reaction than change in blood pressure relative to the pre-induction value	0.909	5	6	3
A poor or unsustained response of hypotension to standard doses of sympathomimetics used to treat pharmacological hypotension during anaesthesia (e.g., ephedrine, phenylephrine, metaraminol) increases the likelihood of true drug hypersensitivity	0.243	7	7.5	5
Increasing patient age over 60 years reduces the certainty that any degree of hypotension can be attributed to true drug hypersensitivity	0.975	5	5.5	2
Angioedema as an isolated feature in the perioperative period does not indicate a high likelihood of true immediate drug hypersensitivity	0.634	6	7.5	3
Generalized urticaria as an isolated feature in the perioperative period does not indicate a high likelihood of true immediate drug hypersensitivity	0.519	4	5.5	3
Patients with a history of allergy are at increased risk of developing an immediate hypersensitivity reaction in the perioperative period	1.55	6	7	2
A point-of-care echocardiogram showing a hyperdynamic and poorly-filled heart increases the likelihood of immediate hypersensitivity	0.652	8	8	3.5[#]
The administration of a potential trigger with a high incidence of anaphylaxis (muscle relaxant, antibiotic, patent blue, gelofusine, etc) prior to the physiological derangement increases the risk of anaphylaxis	0.413	7	8.5	4

DI = Disagreement index where the lower the value, the greater the consensus

* On a scale of 1 (completely inappropriate) to 9 (completely appropriate)

[#] Three non-anaesthetists omitted a response to this statement

Supplementary Online Appendix 3

Rank order of rating appropriateness and consensus of Round 2 statements

Rank	Statement	Median	DI
1	Co-occurrence of generalized urticaria increases the likelihood that any degree of hypotension is a result of true drug hypersensitivity	8.5	0.132
2=	In defining perioperative hypotension associated with suspected allergic reactions both the lowest absolute blood pressure and the change in blood pressure relative to baseline need to be considered	8	0
2=	Co-occurrence of bronchospasm developing after the onset of hypotension increases the likelihood that any degree of hypotension is a result of true drug hypersensitivity	8	0
2=	Co-occurrence of generalized urticaria increases the likelihood that angioedema is a result of true drug hypersensitivity	8	0
5	Onset of bronchospasm before airway instrumentation (having excluded upper airway obstruction) increases the likelihood that any degree of bronchospasm is a result of true drug hypersensitivity	8	0.118
6=	Co-occurrence of angio-oedema (dermal or mucosal swelling) increases the likelihood that any degree of hypotension is a result of true drug hypersensitivity	8	0.132
6=	Co-occurrence of angioedema increases the likelihood that any degree of bronchospasm is a result of true drug hypersensitivity	8	0.132
6=	Co-occurrence of generalized urticaria increases the likelihood that any degree of bronchospasm is a result of true drug hypersensitivity	8	0.132
9=	A poor or unsustained response of hypotension to standard doses of sympathomimetics used to treat pharmacological hypotension during anaesthesia (e.g., ephedrine, phenylephrine, metaraminol) increases the likelihood of true drug hypersensitivity	8	0.164
9=	Co-occurrence of an otherwise unexplained increase in heart rate of 50% or more from a previously stable value increases the likelihood that any degree of hypotension is a result of true drug hypersensitivity	8	0.164
9=	Co-occurrence of generalized or patchy erythema increases the likelihood that any degree of hypotension is a result of true drug hypersensitivity	8	0.164
9=	Excessive dose of anaesthetic drug or drugs reduces the certainty that any degree of hypotension can be attributed to true drug hypersensitivity	8	0.164
13=	Surgically induced hypovolaemia or relative hypovolaemia from prolonged fasting/dehydration reduces the certainty that any degree of hypotension can be attributed to true drug hypersensitivity	7.5	0.164
13=	Respiratory disease associated with reactive airways reduces the certainty that any degree of bronchospasm can be attributed to true drug hypersensitivity	7.5	0.164
15=	Cardiac arrest not explained by the surgical pathology, complications of the surgical procedure, co-existing medical problems or drugs, malignant hyperthermia or technical anaesthetic problems is very likely to be caused by an immediate drug hypersensitivity reaction	7	0
15=	Determining the timing of onset of angio-oedema is difficult during anaesthesia	7	0
17	Hypotension that is sufficiently outside the expected drop in blood pressure for the patients known pathology and anaesthetic or surgical technique is likely to indicate an immediate drug hypersensitivity reaction,Äô	7	0.033
18	Co-occurrence of a generalized erythematous rash increases the likelihood that any degree of bronchospasm is a result of true drug hypersensitivity	7	0.114

19=	With hypotension, in the absence of alternative causes, the greater the fall in blood pressure from baseline, the more likely is the hypotension to indicate an immediate drug hypersensitivity reaction.	7	0.164
19=	With hypotension, in the absence of obvious alternative causes, the lower the absolute blood pressure, the more likely is the hypotension to indicate an immediate drug hypersensitivity reaction.	7	0.164
19=	If the onset of hypotension is delayed beyond 15 minutes after an IV drug, the likelihood of an immediate drug hypersensitivity reaction becomes progressively less	7	0.164
19=	Recurrence or worsening of hypotension after a further dose of a drug given prior to the initial event increases the likelihood that any degree of hypotension is a result of true drug hypersensitivity	7	0.164
19=	Acute illness predisposing to hypotension reduces the certainty that any degree of hypotension can be attributed to true drug hypersensitivity	7	0.164
19=	If the onset of bronchospasm is delayed beyond 60 minutes after a drug administered by any non-I.V. route, the likelihood of an immediate drug hypersensitivity reaction becomes progressively less	7	0.164
19=	Recurrence or worsening of bronchospasm after a further dose of a drug given prior to the initial event increases the likelihood that any degree of bronchospasm is a result of true drug hypersensitivity	7	0.164
19=	Prolonged or multiple attempts at tracheal intubation reduces the certainty that any degree of bronchospasm can be attributed to true drug hypersensitivity	7	0.164
19=	Inadequate dose of drugs to obtund airway responses prior to airway instrumentation reduces the certainty that any degree of bronchospasm can be attributed to true drug hypersensitivity	7	0.164
19=	Co-occurrence of a generalized erythematous rash increases the likelihood that angioedema is a result of true drug hypersensitivity	7	0.164
19=	Determining the timing of onset of any skin rash is difficult during anaesthesia	7	0.164
19=	A point-of-care echocardiogram showing a hyper dynamic and poorly-filled heart increases the likelihood of immediate hypersensitivity	7	0.164
31=	Medications affecting cardiovascular responses during anaesthesia reduces the certainty that any degree of hypotension can be attributed to true drug hypersensitivity	7	0.217
31=	Neuraxial regional anaesthesia (epidural/spinal) reduces the certainty that any degree of hypotension can be attributed to true drug hypersensitivity	7	0.217
31=	Hypotension or angioedema is less likely to indicate drug hypersensitivity in a patient taking ACE inhibitors	7	0.217
34=	Any degree of hypotension can be an indicator of an immediate drug hypersensitivity reaction.	7	0.243
34=	The administration of a potential trigger with a high incidence of anaphylaxis (muscle relaxant, antibiotic, patent blue, gelofusine, etc) prior to the physiological derangement increases the risk of anaphylaxis	7	0.243
36	If the onset of bronchospasm is delayed beyond 15 minutes after an IV drug, the likelihood of an immediate drug hypersensitivity reaction becomes progressively less	7	0.314
37=	Absence of hypotension after a further dose of a drug given prior to the initial event reduces the certainty that any degree of hypotension can be attributed to true drug hypersensitivity	7	0.328
37=	If the onset of hypotension is delayed beyond 60 minutes after a drug administered by any non-I.V. route, the likelihood of an immediate drug hypersensitivity reaction becomes progressively less	7	0.374
37=	Co-occurrence of bronchospasm with increased peak airway pressures that precedes the onset of hypotension in a mechanically ventilated patient	7	0.374
37=	Any degree of bronchospasm can be an indicator of an immediate drug hypersensitivity reaction	7	0.374

37=	In the awake perioperative patient, a complaint of difficulty in swallowing or feeling of fullness in the throat could indicate airway swelling	7	0.374
37=	In the awake perioperative patient, a complaint of feeling unwell immediately after the administration of an intravenous drug is a common precursor of an immediate drug hypersensitivity reaction	7	0.374
37=	In the awake perioperative patient, a rash is more likely to be associated with an immediate drug hypersensitivity reaction if it is itchy	7	0.374
44	A history of exposure to pholcodine increases the likelihood of anaphylaxis to muscle relaxants	6.5	0.519
45	Cardiovascular disease reduces the certainty that any degree of hypotension can be attributed to true drug hypersensitivity	6	0.328
46	Increasing patient age over 80 years reduces the certainty that any degree of hypotension can be attributed to true drug hypersensitivity	6	0.365
47=	Absence of bronchospasm after a further dose of a drug given prior to the initial event reduces the certainty that any degree of bronchospasm can be attributed to true drug hypersensitivity	6	0.519
47=	In the awake perioperative patient with no history of respiratory disease, dyspnoea is an indicator of bronchospasm	6	0.519
49	Patients with a history of atopy are at increased risk of developing an immediate hypersensitivity reaction in the perioperative period	5	0.580

Supplementary Online Appendix 4

A series of hypothetical case scenarios of suspected perioperative immediate hypersensitivity reactions (IHRs) was developed and panel members were asked to independently rate the likelihood of the case as either "almost certain", "very likely", "likely" or "unlikely" to be an IHR.

In addition to asking panel members to rate the case scenarios on clinical features alone, they were also asked to rate the scenarios when accompanied by mast cell tryptase results.

Panel member instructions

Please rate each of the following scenarios as unlikely, likely, very likely or almost certain to be an immediate hypersensitivity reaction. In each case you should refer to the definitions below and assume that you have been provided with all relevant information (in support of a diagnosis of immediate hypersensitivity or not). For example, if any feature of immediate hypersensitivity is not mentioned, you should assume that it was not present.

Clinical term	Definition
Hypotension	A fall in systolic blood pressure to < 70 mmHg (at induction or during maintenance of anaesthesia) or by > 20% from a previously stable value (during maintenance of anaesthesia)
Severe hypotension	A fall in systolic blood pressure to < 60 mmHg (at induction or during maintenance of anaesthesia) or by > 40% from a previously stable value (during maintenance of anaesthesia)
Cardiac arrest	The requirement for cardiopulmonary resuscitation not explained by the surgical pathology, complications of the surgical procedure, co-existing medical problems or drugs, malignant hyperthermia or technical anaesthetic problems
Tachycardia	An otherwise unexplained increase in heart rate of 50% or more from a previously stable value
Bronchospasm	The onset of wheeze on auscultation and/or any manifestation of otherwise unexplained increased airway resistance
Severe bronchospasm	Bronchospasm associated with SpO2 <85%
Urticaria	A skin rash characterised by raised pink or white raised areas of skin (wheals)
Angioedema	Dermal or mucosal swelling

Clinical Scenarios

1. Severe hypotension and tachycardia develop within 5 min of possible triggers. There is a poor response to ephedrine and metaraminol
2. Severe bronchospasm develops after induction of anaesthesia and before airway instrumentation.
3. Severe bronchospasm develops after induction of anaesthesia and before airway instrumentation. Generalised erythema is observed 10 min later.
4. Hypotension develops within 5 min of a potential trigger. Generalised urticaria is observed 15 min later.
5. A patient who has been fasted for 16 hr develops hypotension after induction of anaesthesia that includes a NMBA and a large dose (based on patient age & weight) of propofol. Generalised erythema is also observed.

6. The patient takes an ACE inhibitor for hypertension (normally well-controlled) and has COPD. A spinal anaesthetic is sited before induction of general anaesthesia that includes an opioid, a NMBA and an appropriate dose of propofol. Hypotension and tachycardia develop within 2 minutes and, after a difficult intubation bronchospasm develops. After 15 min angioedema and generalised urticaria are observed.
7. Bronchospasm develops within 5 min of induction and insertion of a laryngeal mask but resolves spontaneously over a 10 min period. After 20 min angioedema is observed around the eyes and lips.
8. The patient is asthmatic and reports an exacerbation 3 weeks prior to surgery. Induction is with fentanyl 1 mcg/kg and appropriate doses of propofol and NMBA. A difficult intubation is achieved but is followed by severe bronchospasm with very high airway pressure required for ventilation. The blood pressure starts to fall and hypotension develops.
9. A patient with hypertension contolled by an ACE inhibitor develops hypotension during maintenance of anaestheisa but 20 min after administration of potential allergic trigger. There is a poor response to phenylephrine. At the end of surgery, 20 min later, the drapes are removed to reveal generalised urticaria and facial angioedema.
10. In the recovery room after spinal anaesthesia, with no drugs given in the previous 40 minutes, the patient develops hypotension and a generalised itchy erythematous rash.
11. In the recovery room after spinal anaesthesia for knee replacement, with no drugs given in the previous 40 minutes, the patient develops hypotension and a generalised itchy erythematous rash. Hypotension progresses to cardiac arrest, with resuscitation successful after 20 min of CPR and IV fluid.

Supplementary Online Appendix 4 (contd)

Ratings of clinical scenarios for likelihood of then being an immediate hypersensitivity reaction

	% panel members rating scenario almost certain/very likely/likely/unlikely							
	Clinical information only		**Clinical information with peak and baseline tryptase concentrations* (whole panel)#**					
Clinical Scenario	Whole panel	Anaesthetists only	Peak 6 Baseline 4	Peak 9 Baseline 5	Peak 13 Baseline 10	Peak 21 Baseline 5	Peak 3 Baseline 3	Peak 15 Baseline 9
1	25/45/25/5	33/41/25/0	5/15/25/55	30/35/30/5	5/30/55/10	-	-	-
2	5/45/50/5	8/50/41/0	0/10/60/30	15/40/30/15	0/20/60/30	-	-	-
3	35/55/10/0	50/41/8/0	10/45/25/20	35/30/35/10	25/25/35/20	-	-	-
4	45/50/5/0	41/50/8/0	10/40/45/5	40/40/20/0	20/45/35/0	-	-	-
5	0/30/55/20	0/17/58/25	0/5/37/58	10/30/50/15	0/20/45/35	70/25/5/0	-	-
6	35/45/15/5	17/50/25/8	-	30/25/35/10	-	-	0/20/50/30	-
7	5/15/45/35	8/8/50/33	-	-	-	-	-	-
8	0/11/42/47	0/8/41/50	0/5/45/50	10/26/47/26	5/21/31/42	63/32/5/0	-	-
9	10/45/25/20	0/41/33/25	-	-	-	-	-	-
10	15/20/25/45	8/17/25/50	-	20/15/35/30	-	-	-	35/25/35/10
11	15/50/15/20	8/41/25/25	-	30/15/40/15	-	-	-	40/20/25/5

Not all combinations of tryptase changes were run for each scenario

*Tryptase units are ng ml^{-1}