

Review of procedures for investigation of anaesthesia-associated anaphylaxis in Newcastle, Australia

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SUMMARY

The procedures, results and outcomes of investigation of 50 patients with clinical episodes of anaesthesia-associated anaphylaxis were retrospectively reviewed. Assessment was performed by measurement of serum tryptase and specific IgE and a combination of skin prick and intradermal skin testing. Testing was performed both for agents received during the anaesthetic and for agents the patient may encounter in future procedures. Twenty of 50 patients underwent a subsequent procedure after assessment. Sensitisation to neuromuscular blocking agents was identified in 18 patients (36%). Sensitisation to propofol (14 patients; 28%) and latex (four patients; 8%) was also frequently identified. No precise cause was identified in 11 cases (22%). Reactivity to more than one agent was identified in 14 patients (28%). Serum tryptase was measured within six hours of the episode in only 28 of the 50 cases. All the patients with elevated serum tryptase had clinically severe reactions. One patient initially found to be sensitised to propofol had another reaction during a second procedure, prompting further assessment where chlorhexidine reactivity was identified. Subsequent surgery in that patient and in 19 other patients where agents implicated in the testing were avoided, proceeded without incident. The results reaffirm that neuromuscular blocking agents are the most common cause of anaphylaxis during anaesthesia. The importance of serum tryptase measurement at the time of the acute episode needs to be emphasised. Investigation should include screening for chlorhexidine and latex in all patients, as exposure to both these agents is common and may be overlooked.

Key Words: anaphylaxis, investigation, anaphylactoid

Advances in medicine and surgery and the high level of safety of anaesthesia have increased the use of general anaesthesia for both therapy and diagnosis. The number of anaesthetic procedures has risen at about 4% per annum¹ and there are now about 2.5 million procedures per year in Australia.

Although rare, anaphylactic and anaphylactoid reactions are one of the more common causes of anaesthetic-related morbidity and mortality in an otherwise healthy population^{2,3}. The true incidence of hypersensitivity reactions is difficult to determine due to uncertainties over the completeness of the data, with previous estimates ranging between 1 in 5,000 and 1 in 20,000 procedures²⁻⁵. In this environment there is increasing interest in reducing the risks associated with anaesthesia by improved resuscitation and crisis management and by post-resuscitation investigation to guide prevention of anaphylaxis⁶.

Commonly recommended approaches to the post-resuscitation investigation of suspected cases of anaphylaxis include measurement of serum tryptase at the time of the reaction and at one hour and six hours after the reaction. Immunological assessment for potential sensitisation to the agents delivered during the anaesthetic is also recommended in an attempt to define a cause for the reaction⁷⁻⁹. These investigations are most commonly performed by skin prick and intradermal test, although recommended procedures vary.

The current project was undertaken to audit our outcomes of investigation of anaesthesia-associated anaphylaxis, at a regional referral centre in Australia. The aim was to identify areas of practice that could be improved and to review the relative frequency of sensitisation to specific agents used during general anaesthesia.

MATERIALS AND METHODS

This was a retrospective analysis of patients referred between June 2000 and February 2007 to the Immunology unit at the John Hunter Hospital for assessment after an anaphylactic or anaphylactoid reaction occurring during a general anaesthetic, as diagnosed by the anaesthetist managing the case.

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Patients were investigated by an immunologist, together with review of the case by a senior anaesthetist. Patients referred for assessment of local anaesthetic reactivity were excluded from this report. As follow-up testing for drug sensitisation is recommended as part of standard clinical practice, institutional ethics committee review was not required for this study.

Investigation was based on: 1) review of the history of the clinical event and investigations at the time; 2) the patient's health status and medical history; 3) the 'baseline' tryptase at the time of follow-up; 4) skin testing to individual agents, including specific IgE testing for sensitivity to latex.

Case review

Individual patient case histories were obtained by review of the documentation sent by the referring anaesthetist, by review of the anaesthetic and surgical records and by patient interview. Where possible, the full hospital case records of patients were reviewed, although for some patients referred from other hospitals and districts these were unavailable. The clinical details and time course of events before, during and after treatment of the reaction and details regarding both the severity of the reaction and the response to therapy were noted. The severity of the reaction was graded using a standard approach^{9,10}. When the serum tryptase sample had been collected within six hours of the reaction the results were obtained from hospital records or from data provided by the treating anaesthetist and their preferred pathology provider. Serum tryptase assays (including those by alternative providers) were performed using the Pharmacia uniCAP system. (Pharmacia Diagnostics, Uppsala, Sweden).

Past medical history

Other medical data collected included patient age, gender, intercurrent medical issues, chronic medications being taken at the time of the procedure and history of previous allergy including previous anaesthetic outcomes.

Baseline tryptase

In order to exclude mastocytosis, serum tryptase was measured in all patients as a baseline at the time of the assessment in the immunology unit using the Pharmacia uniCAP system (Pharmacia Diagnostics). The normal range for the test was tryptase <13 µg/l.

Skin testing to individual agents

Skin testing was performed using both skin prick and intradermal tests for all neuromuscular

blocking agents, hypnotics, opiates and antibiotics encountered during the initial anaesthetic and to other agents that may be required in future anaesthetics, as requested by the patient's anaesthetist. Cross-reactivity with neuromuscular blocking agents (NMBA) is well documented¹⁵ and patients identified as reactive to one NMBA were typically tested against other muscle relaxants to which they may later be exposed.

Tests were performed using drugs freshly diluted on the day of the assessment at dilutions previously described^{8,11,12}. Briefly, all agents were tested at increasing concentration up to a dilution of 1 in 10 of the commercially available preparation, except atracurium and opiates (maximum dilution 1 in 1,000), rocuronium, suxamethonium, cisatracurium (maximum dilution 1 in 100) and chlorhexidine (prick test performed at 0.5% and intradermal test at 0.0002%^{13,14}). Skin prick testing was performed on the volar aspect of the patient's forearm to assess the safety of the planned test dilution of the drug prior to intradermal testing. Intradermal injection of 0.02 to 0.05 ml was then performed in serial dilution. A positive (histamine HCL; Stallergenes, France) and a negative (normal saline) control were included with the skin prick test and a further negative control was included in each intradermal test for comparison with the test drug solutions. The prick test was regarded as positive when the wheal was equal or larger in size to the histamine control, while the negative control produced no significant dermal reaction. The intradermal test was regarded as positive when the diameter of the wheal from the test drug solution was twice or more than the diameter of the control (saline) injection. Typically the wheal reaction was associated with an erythematous reaction of greater size. Reactions were read at 10, 15 and 20 minutes after prick or intradermal injection.

Dermal reactivity to latex was assessed in all patients by prick test only, using a commercial reagent (Stallergens, France). Specific IgE to latex was assessed in all patients using the Pharmacia uniCAP assay.

RESULTS

Fifty patients were referred for assessment after clinical reactions suggestive of anaphylaxis during anaesthesia during the period of audit. Patients were aged between 14 and 80 years, with a mean age of 46 years. Twenty (40%) of the patients were male and 30 (60%) female. Thirteen (26%) of the patients received their anaesthetic at the John Hunter

Hospital and 27 of the remaining 37 cases were referred from other hospitals in the local area. The 10 remaining cases lived locally but had their procedures in various other parts of Australia.

Thirty-nine of the patients had severe reactions, while four were moderate and six mild by established criteria⁹. Acute serum tryptase values were available in 28 patients (56%). All 16 patients with elevated serum tryptase (mean level 35.7 µg/l) had had severe reactions. One of the 16 had an anaphylactoid reaction to morphine infusion, while the other 15 were determined to have had anaphylaxis secondary to operative exposures. The tryptase level was normal in nine patients with severe anaphylaxis and in all patients tested with mild and moderate features. The timing of the collection of serum tryptase in relation to the reaction was not consistently documented in the anaesthetic report.

A cause for the event was identified in 40 patients (80%; Table 1). NMBA were implicated as a cause of anaphylaxis in 19 patients (38%). A further two patients were identified on skin testing as reactive to NMBA, though they did not receive

those agents during the anaesthetic associated with the episode of anaphylaxis. Atracurium sensitisation was noted in seven patients, rocuronium in six patients and suxamethonium in seven patients (Table 1). Cross-reactivity among NMBA was identified in one patient with anaphylaxis. A further four patients demonstrated cross-reactivity to other agents when screened for alternative medications to consider during future anaesthetics, though they did not receive the agent during the anaesthetic that resulted in anaphylaxis (Table 1). When this occurred, the patient was reported as sensitised to all agents where the testing revealed skin test reactivity and it was recommended that all such agents be avoided in future anaesthetics.

Sensitisation to propofol was identified in 14 patients, but only five patients showed reactivity to propofol alone. The diagnosis of propofol sensitivity was based on the recommended dilution of 1:10 for this agent. Latex was identified as the cause of the hypersensitivity in four patients and opiates in three patients (Table 1). Reactivity to beta-lactam antibiotics was found in five cases, with two patients

TABLE 1
Causes of sensitivities identified by skin prick, intradermal and serum specific IgE testing

Agents	Number of patients where the agent was identified as cause of reaction*	Number of patients exposed to implicated agent	Number of patients tested for sensitivity	Number of patients with positive testing
<i>NMBA®</i>				
Atracurium	7	12	25	10
Suxamethonium	7	12	18	8
Rocuronium	6	20	29	7
Vecuronium	1	5	11	3
Mivacurium	1	2	6	1
Pancuronium	-	1	11	2
Cisatracurium	-	-	2	1
Propofol*	14	37	39	14
Latex	4	39	39	4
<i>Opiates</i>				
Pethidine	2	4	7	4
Morphine	1	5	9	2
Fentanyl	-	25	30	1
<i>Antibiotics</i>				
Penicillin	3	11	19	3
Cephalosporin	3	21	20	3
Chlorhexidine	2	6	6	6
Ondansetron	1	6	5	1
No cause found	11			

*Reactivity to more than one agent found in 14 patients, ®cross-reactivity against other NMBA (neuromuscular blocking agents) demonstrated in five patients,*reactivity to other agents in nine patients.

demonstrating sensitisation to cephalothin, two to benzylpenicillin and one to both agents.

Ondansetron was identified as a cause of hypersensitivity in one patient with documented severe reaction. This patient showed significant reactivity on skin prick testing to ondansetron at a dilution of 1:10.

Subsequent surgery was performed in 20 patients. The choice of techniques and agents used in these later anaesthetics was guided by the results of the allergy unit review. Of these 20 patients, nine had documented hypersensitivity against NMBA, although reactivity to other classes of agent was identified in three of the nine patients. Eight patients were reactive on testing to propofol, but in only three cases was propofol the only sensitivity identified. No reactivity was identified in five patients, while six patients had sensitivity identified to more than one class of agent. Details of subsequent anaesthetics were not available for all subsequent cases, but at least seven patients had further anaesthetics which included NMBA. Three patients had further surgery under spinal anaesthesia and a further two had sedation for minor surgery. Nineteen of these subsequent cases were uneventful.

One patient had a further episode of anaphylaxis during subsequent surgery, despite avoiding propofol, which had been identified as a cause of his previous reaction. Unfortunately, testing for chlorhexidine sensitisation had not been included in his initial investigations as chlorhexidine had not been identified as part of the operative process in his first procedure. Repeat testing for both propofol and chlorhexidine suggested reactivity to both substances. A third anaesthetic avoiding both propofol and chlorhexidine was completed without incident. After this experience, chlorhexidine testing was routinely included in our investigation procedure and one further patient sensitised to chlorhexidine was identified. Chlorhexidine was the only sensitivity identified in this latter patient.

DISCUSSION

Modern anaesthesia is achieved through the administration of multiple agents, as no single drug produces all the pharmacological effects required. This use of multiple vasoactive drugs via direct intravenous injection increases the chance both of anaphylactoid and anaphylactic reactions^{2,8}.

Anaphylactoid reactions are due to the vasodilator effects of the drugs, are non-IgE mediated and are negative on skin testing at appropriate non-irritant

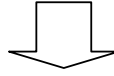
dilutions. Anaphylactoid reactions are generally more severe if the drug is infused at a rapid rate, are strongly influenced by drug dose and are associated with elevated serum tryptase levels when the drug acts through a mechanism of mast cell degranulation. It is thus useful to distinguish between anaphylactic and anaphylactoid reactions, although this is not always possible.

Opiates are known to cause both IgE mediated and non-IgE mediated degranulation of mast cells and may thus produce both anaphylactic and anaphylactoid reactions. Four patients were diagnosed as having reactivity to opiates. Three patients demonstrated a positive skin reaction at a dilution of 1:1000, consistent with an IgE mediated reactivity to the implicated opiate. In one patient, hypotension and urticaria occurred during anaesthesia when morphine was used and a further episode of urticaria and hypotension occurred during morphine infusion in the postoperative phase. The reaction terminated when the infusion was ceased. Negative intradermal testing was demonstrated in this case at the standard dilution of morphine of 1:1000 (0.01 mg/ml). Based on clinical history and skin testing, the diagnosis of an anaphylactoid reaction to morphine was made in this case.

The diagnosis of an IgE mediated anaphylactic reaction is based on the finding of a positive skin prick and/or intradermal reaction to an agent the patient received during anaesthesia, in the context of an appropriate clinical history and an elevated serum tryptase, performed at the appropriate time points after the reaction. The baseline serum tryptase should not be elevated, to exclude the presence of a mast cell disorder. Clinical pathways and check lists can be useful in ensuring that the key elements required to confirm the diagnosis and to define a cause for the reaction are clearly understood and documented (Figure 1 and checklist).

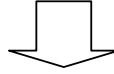
Serum tryptase is an indirect measure of mast cell degranulation and can be useful to distinguish mast cell dependent reactions from other causes of perioperative cardiovascular instability such as cardiogenic shock^{20,21}. A documented elevation of mast cell tryptase at the time of the reaction reliably predicted an anaphylactic or anaphylactoid reaction in this study. However, serum tryptase was not measured at the time of the reaction in more than half of the patients. This is clearly an area of practice that needs improvement. Failure to collect and fully document the timing of the collection of mast cell tryptase severely limited the utility of the test in this cohort.

Suspected hypersensitivity reaction



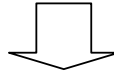
Acute management

- Acute resuscitation as appropriate.
- Collect serum Tryptase within one hour, again at six hours.



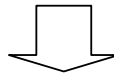
Anaesthetist follow-up

- Record clinical details to guide investigation.
 1. Drugs used during or preceding anaesthetic.
 - Include ALL drugs, including skin preparation, etc.
 - Note time of each drug exposure relative to reaction.
 2. Details of reaction including:
 - Urticaria;
 - Bronchoconstriction;
 - Hypotension (lowest BP and 'normal' BP);
 - Desaturation (lowest S_aO_2 and 'normal' S_aO_2).
 3. Resuscitation measures used and outcome during and after resuscitation.
- Explain to patient and counsel as appropriate.
- Refer for specific testing to define a cause for the reaction.



Allergist

- Review details of acute event (referral letter, anaesthetic and ICU notes etc). Discuss with anaesthetist if necessary to clarify details.
- Review patient history.
 1. History of allergy type symptoms in the past.
 2. History suggestive of reactivity to suspected allergens, e.g.
 - Latex: latex products; banana; kiwi fruit etc;
 - Reactions to products containing chlorhexidine;
 - Other symptoms suggestive of hypersensitivity reactions.
- Skin testing to all agents to which patient was exposed.
- Consider testing for agents that may be used in future.



Results

- Discuss implications of results with patient.
- If no agent identified, reassess history for unidentified allergens.
- Report results to referring anaesthetist and patient's GP.
- Enter details in local anaesthesia alert system.
- Consider registration with Medicalert system.
- Provide adrenaline for emergency use if indicated (e.g. specific food-associated anaphylaxis identified).

FIGURE 1: Suggested action plan for patients with suspected hypersensitivity under anaesthesia.

The sensitivity and specificity of skin testing is a significant issue. Non-immunologic mast cell release can occur, particularly if high concentrations of a drug are used in the test procedure, and produce false positive skin reactions¹⁷⁻¹⁹. Cross-reactive antibodies may produce a 'true positive' skin reaction mediated by IgE without being of sufficient avidity to produce clinical anaphylaxis *in vivo*^{2,15}. If testing for agents the patient did not receive during anaesthesia is performed, there is a risk of identifying sensitivities that are not clinically relevant and limiting the drugs available to the anaesthetist for future anaesthetics. Despite these potential problems, most anaesthetists requested testing for agents the patient did not receive. It was argued that in the absence of testing, all agents potentially cross-reactive to the implicated agents would be avoided in future procedures. Under these circumstances, the authors concluded that testing for alternative drugs not used during the procedure was appropriate. To reduce the risk of identifying drug reactivities that were not clinically relevant, skin testing was performed at previously validated dilutions for each individual compound^{8,11,12}.

Reactivity on skin testing to propofol was identified in 14 patients, but in nine of the cases, alternative reactivities were identified that could explain the observed anaphylactic event. This high rate of reactivity may be due to propofol being a common cause of anaphylaxis, but it may also be due to testing at a dilution that can cause irritant skin reactions. It is also possible that in some patients, the skin test reactivity identified is a true false positive, where patients develop IgE antibodies to propofol after exposure, but the IgE is not of sufficient avidity to cause anaphylaxis. Further study with a large cohort of both normal controls and patients with anaesthesia-associated anaphylaxis would be needed to definitively answer this question. In the absence of this data, we felt obliged to recommend avoidance of propofol in future anaesthetic procedures in all 14 patients.

No reactivity to a specific agent was identified in 11 patients (22%) despite the clinical suspicion of an anaphylactic reaction. This is in keeping with previous studies, where similar rates were found^{16,22,23}. Cardiac events in what is typically an elderly population can cause a similar clinical picture. Some anaesthetic agents are themselves vasoactive and promote hypotension and mast cell degranulation^{2,8}. In the absence of reliable collection of serum tryptase it is difficult to gauge how common such 'anaphylactoid reactions' might be, though one such

case with an anaphylactoid reaction to morphine was identified in this series.

This current study confirms both the relatively high frequency of NMBA reactivity^{1,4,22} and that cross reactivity between NMBA is relatively common, being identified in five patients (10%) in this study¹⁵. However, most patients with NMBA reactivity were not sensitised to all NMBA. Further surgery was required in 20 of the patients and was safely performed in all but one. NMBA were safely employed in seven of the 20 cases. The adverse reaction in the one patient could have been avoided had more extensive testing including all agents (including skin preparation solutions) used during the anaesthetic been performed. This patient highlights the need both to document the procedure fully and to review the history carefully to ensure all agents used in the procedure are assessed in the testing process. Chlorhexidine is an antiseptic widely used in creams, gels and wound dressings. Sensitisation to this antiseptic has been responsible both for anaphylaxis and for cases of oral allergy syndrome, contact dermatitis and local urticaria^{13,14}. The two cases reported in this series had severe reactions and highly significant skin prick reactivity with wheals of over 10 mm. This is consistent with the suggestion by Aalto-Korte et al that the size of the prick test reaction to chlorhexidine correlates with the severity of the hypersensitivity reaction¹⁴. The addition of testing for chlorhexidine to the testing strategy used by our unit should prevent such reactivity going unrecognised in the future.

Routine testing of latex has already been incorporated into our test strategy, as it is encountered in almost all procedures unless specifically avoided. Sensitisation to latex is also associated with reactivity to certain foods, including mango, kiwi fruit and chestnuts. A history of reactions to these foods is useful in predicting which patients may be sensitised to latex. Despite screening of patients by specific questioning in the pre-anaesthetic clinics at most hospitals in our region, including questioning around sensitisation to specific foods, four of our patients had unidentified reactivity to latex. One of the patients with latex hypersensitivity gave a history of previous episodes of idiopathic anaphylaxis prior to review at the clinic, but had been assessed before reliable agents for latex sensitisation were available. It is important to correctly identify the condition and to screen for any associated food reactivity to avoid the risk of subsequent reactions. One patient screened in this way was identified with sensitivity to banana.

Following testing, all patients were provided with a card outlining the nature of their reactivity to carry with them. They were also encouraged to wear a Medicalert bracelet outlining their sensitisation and an alert of their reactivity was entered on a regional anaesthetic database for future reference by local anaesthetists²⁴. Adrenaline for use in acute emergency was provided for two patients where sensitisation was identified to allergens likely to be encountered in daily life.

In conclusion, all patients with suspected hypersensitivity reactions require detailed and prompt assessment at appropriate centres. Diagnosis should be attempted through a combination of a thorough history, specific IgE and serum tryptase measurement and skin testing. Detailed investigation of patients having anaesthetic-associated anaphylaxis can facilitate safe provision of subsequent anaesthetics. Investigation of anaphylaxis is complex and requires involvement of both anaesthetist and allergist. Interpretation of clinical records associated with anaesthetics, and choice of drugs for testing, requires a thorough understanding of clinical anaesthetic practice. Interpretation of skin tests requires specialist immunological knowledge and ongoing experience. Cooperation between anaesthetist and allergist is crucial in the subsequent management of these patients, particularly when further surgical intervention is required.

REFERENCES

- Clergue F, Auroy Y, Pequignot F, Jouglu E, Lienhart A, Laxenaire MC. French Survey of Anesthesia in 1996. *Anesthesiology* 1999; 91:1509-1520.
- Watkins J. Skin testing and the anaesthetist. *Br J Anaesth* 2000; 85:814-817.
- Mertes PM, Laxenaire MC, Alla F. Anaphylactic and anaphylactoid reactions occurring during anesthesia in France in 1990-2000. *Anesthesiology* 2003; 99:536-545.
- Fisher MM, Baldo BA. Anaphylaxis during anaesthesia: Current aspects of diagnosis and prevention. *Eur J Anaesthesiol* 1994; 11:263-284.
- Vervloet D, Magnan A, Birnbaum J, Pradal M. Allergic emergencies seen in surgical suites. *Clin Rev Allergy Immunol* 1999; 17:459-467.
- Currie M, Kerridge RK, Bacon AK, Williamson JA. Crisis Management during anaesthesia: anaphylaxis and allergy. *Qual Saf Health Care* 2005; 14:e19.
- Suspected anaphylactic reactions associated with anaesthesia: revised edition 2003 from The association of Anaesthetists of Great Britain and Ireland and the British Society for Allergy and Clinical Immunology. From www.aagbi.org.
- Mertes PM, Laxenaire MC, Lienhart A, Aberer W, Ring J, Pichler WJ et al. Reducing the risk of anaphylaxis during anaesthesia: guidelines for clinical practice. *J Investig Allergol Clin Immunol* 2005; 15:91-101.
- Laxenaire MC, Mertes PM; Groupe d'Etudes des Réactions Anaphylactoides Peranesthésiques. Anaphylaxis during anaesthesia. Results of a two-year survey in France. *Br J Anaesth* 2001; 87:549-558.
- Brown SGA. Clinical Features and Severity Grading of Anaphylaxis. *J Allergy Clin Immunol* 2004; 114:371-376.
- Mertes PM, Laxenaire MC. Allergy and anaphylaxis in anaesthesia. *Minerva Anesthesiol* 2004; 70:285-291.
- Ebo DG, Hagendorens MM, Bridts CH, De Clerck LS, Stevens WJ. Allergic reactions occurring during anaesthesia: diagnostic approach. *Acta Clin Belg* 2004; 59:34-43.
- Garvey LH, Roed-Petersen J, Husum B. Anaphylactic reactions in anaesthetised patients—four cases of chlorhexidine allergy. *Acta Anaesthesiol Scand* 2001; 45:1290-1294.
- Aalto-Korte K, Makinen-Kiljunen S. Symptoms of immediate chlorhexidine hypersensitivity in patients with a positive prick test. *Contact Dermatitis* 2006; 55:173-177.
- Laxenaire MC, Gastin I, Moneret-Vautrin DA, Widmer S, Guéant JL. Cross-reactivity of rocuronium with other neuromuscular blocking agents. *Eur J Anaesthesiol Suppl* 1995; 11:55-64.
- Kroigaard M, Garvey LH, Menne T, Husum B. Allergic reactions in anaesthesia: are suspected causes confirmed on subsequent testing? *Br J Anaesth* 2005; 95:468-471.
- Fisher MM, Bowey CJ. Intradermal compared with prick testing in the diagnosis of anaesthetic allergy. *Br J Anaesth* 1997; 79:59-63.
- Levy JH, Gottge M, Szlam F, Zaffer R, McCall C. Weal and flare responses to intradermal rocuronium and cisatracurium in humans. *Br J Anaesth* 2000; 85:844-849.
- Mertes PM, Laxenaire MC, Malinovsky JM, Florvaag E, Moneret-Vautrin DA. Skin sensitivity to rocuronium and vecuronium: Prick tests are not intradermal tests. *Anesth Analg* 2005; 100:1539.
- Dybendal T, Guttormsen AB, Elsayed S, Askeland B, Harboe T, Florvaag E. Screening for mast cell tryptase and serum IgE antibodies in 18 patients with anaphylactic shock during general anaesthesia. *Acta Anaesthesiol Scand* 2003; 47:1211-1228.
- Fisher MM, Baldo BA. Mast cell tryptase in anaesthetic anaphylactoid reactions. *Br J Anaesth* 1998; 80:26-29.
- Harboe T, Guttormsen AB, Irgens A, Dybendal T, Florvaag E. Anaphylaxis during anesthesia in Norway: A 6-year single-center follow-up study. *Anesthesiology* 2005; 102:897-903.
- Hepner DL, Castells MC. Anaphylaxis during the perioperative period. *Anesth Analg* 2003; 97:1381-1395.
- Kerridge RK, Crittenden MB, Vutukuri VLSP. A multiple-hospital anaesthetic problem register: establishment of a regionally organized system for facilitated reporting of potentially recurring anaesthetic-related problems. *Anaesth Intensive Care* 2001; 29:106-112.

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