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Review Article

Scandinavian Clinical Practice Guidelines on the diagnosis, management and follow-up of anaphylaxis during anaesthesia*

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The present approach to the diagnosis, management and follow-up of anaphylaxis during anaesthesia varies in the Scandinavian countries. The main purpose of these Scandinavian Clinical Practice Guidelines is to increase the awareness about anaphylaxis during anaesthesia amongst anaesthesiologists. It is hoped that increased focus on the subject will lead to prompt diagnosis, rapid and correct treatment, and standardised management of patients with anaphylactic reactions during anaesthesia across Scandinavia.
The recommendations are based on the best available evidence in the literature, which, owing to the rare and unforeseeable nature of anaphylaxis, mainly includes case series and expert opinion (grade of evidence IV and V).
These guidelines include an overview of the epidemiology of anaphylactic reactions during anaesthesia. A treatment algorithm is suggested, with emphasis on the incremental titration of adrenaline (epinephrine) and fluid therapy as first-line treatment.
Recommendations for primary and secondary follow-up are given, bearing in mind that there are variations in geography and resources in the different countries. A list of National Centres from which anaesthesiologists can seek advice concerning follow-up procedures is provided. In addition, an algorithm is included with advice on how to manage patients with previous suspected anaphylaxis during anaesthesia. Lastly, Appendix 2 provides an overview of the incidence, mechanisms and possibilities for follow-up for some common drug groups.

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Key words: Allergy; anaesthesia; anaphylaxis; drug allergy; investigation; treatment.

Background

At present, the approach to the diagnosis, management and, especially, follow-up of anaphylaxis during anaesthesia varies in Scandinavia. Anaphylactic reactions during anaesthesia are rare events, quoted in the literature to occur in 1/5000 to 1/20,000 anaesthetics (1, 2). The diagnosis can be difficult to make, and treatment needs to be started promptly to ensure the best outcome for the patient (3). In most cases, a large number of drugs have been administered to the patient, and it is not possible to pinpoint the cause in the clinical situation (4). Follow-up investigation is therefore necessary in order to avoid a potentially life-threatening re-exposure of the patient to the offending substance (5, 6).

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The objectives of this working group were to create Scandinavian Clinical Practice Guidelines on the basis of the best available evidence in the literature, which, owing to the rare and unforeseeable nature of anaphylaxis, mainly includes expert opinion and case series (grade of evidence IV and V).

Guidelines prepared on the basis of consensus should place the focus on anaphylaxis amongst Scandinavian anaesthesiologists and ensure that patients will receive prompt and optimum treatment. In the future, it will hopefully also lead to all Scandinavian patients who have suffered these reactions being referred for follow-up. The quality of follow-up may increase through inter-Scandinavian collaboration and exchange of knowledge and experience, which may also enhance research in the field. The investigation programmes will be more uniform, allowing results to be used in larger epidemiological studies. It must be remembered, however, that Scandinavia is a large geographical area comprising many different regions with local differences and variations in the approach to follow-up, which must be accepted.

Mechanisms

The clinical presentation and management of anaphylaxis are the same regardless of the underlying mechanism.

Allergic anaphylaxis is most commonly caused by the interaction of an allergen with specific immunoglobulin E (IgE) antibodies, which are present on mast cells and basophils in sensitised individuals. This interaction stimulates the cells to release inflammatory mediators, e.g. histamine, leukotrienes and tryptase, which account for the clinical features (7). Allergic anaphylaxis for some substances, e.g. dextrans, may be caused by IgG antibodies that produce immune complexes with the antigen (dextran macromolecules), and thereby activate the complement system (8). In non-allergic anaphylaxis, the clinical features are a result of direct, pharmacological or 'toxic' stimulation of mast cells and basophils, causing them to release their inflammatory mediators. Non-allergic anaphylaxis does not involve an immunological mechanism and, therefore, previous contact with the substance is not necessary (9, 10).

Causes

In France (11–14), Australia (15–18) and Great Britain (19–22), follow-up investigations have been carried out after anaphylactic reactions in anaesthesia for the past 20–30 years. In France, surveys with results of follow-up have been published (13, 23, 24) for large numbers of patients, and these have repeatedly shown that neuromuscular blocking agents (NMBAs) are the most common causative agent, followed by latex and antibiotics. Follow-up investigations comprise a number of different tests, all with limitations, and no one test is thought to be the gold standard. Recently, the results of follow-up investigations, primarily skin testing, have been questioned (25–27), and therefore work is being carried out in order to standardise and validate test methods. As more countries start to investigate patients after anaphylactic reactions in anaesthesia, it has also become evident that different populations show different patterns of sensitisation, even within Scandinavia (1, 28–31). All drugs and substances used during surgery and anaesthesia have the potential to cause an anaphylactic reaction (32). It is therefore important to be aware of, and record on the anaesthetic chart, all substances to which the patient has been exposed, including those used by the surgeon and those not given intravenously, such as local anaesthetics, irrigating fluid, latex, disinfectants, markers (e.g. patent blue), etc.

Reactions to local anaesthetics are often reported, but less than 1% of these reactions are anaphylactic (33).

Appendix 2 provides a detailed description of the different groups of drugs and substances commonly used during anaesthesia.

Symptoms and diagnosis

Anaphylaxis during anaesthesia may present in many different ways, and the symptoms and signs, which do not vary from those of anaphylactic reactions in general, may be masked by hypovolaemia, light/deep anaesthesia or extensive regional blockade. Cutaneous symptoms, such as flushing, urticaria and oedema, are common, but, during anaesthesia, these are usually hidden by surgical drapings.

Cardiovascular symptoms often comprise hypotension and tachycardia, but may rapidly progress into severe arrhythmias and cardiovascular collapse if not recognised and treated. They are the most common and serious symptoms and, in some cases, cardiovascular collapse may be the only presenting symptom. Respiratory symptoms, such as bronchospasm, after the induction of anaesthesia are slightly less common, but may predominate in patients with pre-existing asthma (34). Multisystem involvement is most common, but not always the case (Table 1).

Table 1

Clinical features of anaphylaxis in anaesthesia in 555 patients. Reprinted from Balliere's Clin Anesthesiol, **12** (2), Whittington T, Fisher MM. Anaphylactic and anaphylactoid reactions, 301–21, 1998, with permission from Elsevier (34).

Clinical feature	Number of cases (%)	Sole feature (%)	Worst feature (%)
Cardiovascular collapse	490 (88)	61 (11)	434 (78.2)
Bronchospasm	207 (37)	32 (6)	100 (18)
Transient	84 (15)		
Asthmatics	91 (16)		
Cutaneous			
Rash	73 (13)		
Erythema	264 (48)		
Urticaria	45 (8)		
More than one	32 (6)		
Angioedema	135 (24)	7 (1)	18 (3.2)
Generalised oedema	37 (7)		
Pulmonary oedema	13 (24)	2 (0.3)	3 (0.5)
Gastrointestinal	38 (7)		

Table 2

Classification of clinical manifestations of anaphylaxis during anaesthesia. Based on Mertes et al. (6) and Ring and Messmer (86).

Class	Clinical manifestations
I	Generalised cutaneous signs: erythema, urticaria with or without angioedema
II	Moderate multiorgan involvement with cutaneous signs, hypotension and tachycardia, bronchial hyperreactivity (cough, ventilatory impairment)
III	Severe life-threatening multiorgan involvement that requires specific treatment: collapse, tachycardia or bradycardia, cardiac arrhythmias, bronchospasm; the cutaneous signs may be absent or occur only after the arterial blood pressure recovers
IV	Circulatory or respiratory arrest
V	Death due to a lack of response to cardiorespiratory resuscitation

The majority of anaphylactic reactions during anaesthesia occur within minutes of induction (up to 90% reported in one study) (1), and are linked mainly to agents administered intravenously (34). However, agents which are administered via other routes, e.g. on the skin and mucosa, in the urethra, in contact with the peritoneum or subcutaneously, may take some time to be absorbed and may therefore cause reactions after more than 15 min. This is the case with, for example, latex (35), chlorhexidine (29) and the dye patent blue (36), which have been seen to cause an increasing number of reactions over the past decade.

For diagnostic purposes and to aid decision making on the need for investigation after an anaphylactic reaction during anaesthesia, reactions are classified according to severity (Table 2).

Treatment (5, 6, 37–39) (Table 3)

Anaphylaxis during anaesthesia has a wide variety of presentations, and treatment will always depend on the clinical picture. During anaesthesia, the patient is usually monitored and has intravenous access, which gives the optimum conditions for prompt and successful treatment, provided that the diagnosis is made early by the attending anaesthetist. The cornerstones of treatment are adrenaline and fluid therapy. Adrenaline is a highly potent and efficient treatment in most cases of anaphylaxis. It should be administered as early as possible and titrated carefully to response, especially when administered intravenously. Its α-agonist property reverses vasodilatation and oedema, and its β-agonist property dilates the airways, increases myocardial contraction and suppresses the release of inflammatory mediators, such as leukotrienes and histamine (38).

If treated early, doses of 10–50 μg of intravenous adrenaline are sufficient to reverse anaphylaxis (6), but, in severe cases, doses of more than 5 mg within less than an hour by increments or infusion may be necessary (A. B. Guttormsen, personal observation). Continuous infusion of adrenaline is advantageous in patients who need repetitive doses of adrenaline (40).

The relatively rare fatalities in anaphylaxis are usually caused by delayed or no administration of adrenaline. In a few cases, excessive doses of adrenaline have been implicated (41), which emphasizes the need for careful titration.

Fluid therapy is important to counteract the large fluid shifts associated with vasodilatation and capillary leakage, and, in severe cases, several litres of crystalloid/colloid are needed.

In severe anaphylactic shock, refractory to adrenaline, vasopressin may be considered (42, 43). For patients on β-blocker treatment, large doses of adrenaline may be needed (6), and in cases of poor response to adrenaline, glucagon may be tried (38).

Corticosteroids and antihistamines have a place as secondary treatment for anaphylaxis, and help to prevent oedema, cutaneous symptoms and relapse of the anaphylactic reaction, which can occur up to 24 h after the initial reaction (44). Careful consideration must therefore be given to the level of monitoring/observation of the patient following successful treatment of an anaphylactic reaction.

Table 3

SSAI Guideline on treatment of anaphylactic reactions during anaesthesia.

Primary treatment	**Dosage**
Stop administration of suspected substance Call for help and inform the surgeon Trendelenburg position	
Maintain airway and give oxygen	F_iO_2 1.0
Adrenaline Use diluted adrenaline i.v. maximum concentration 0.1 mg/ml	*Adults:* Mild to moderate reaction: 0.01–0.05 mg i.v. Circulatory collapse: 0.1–1.0 mg i.v. i.v. infusion starting at: 0.05–0.1 μg/kg/min Without i.v. access: 0.5–0.8 mg i.m.
Titrate dose to response If large doses are needed, use i.v. infusion	*Children:* Mild to moderate reaction: 0.001–0.005 mg/kg i.v. Circulatory collapse: 0.01 mg/kg i.v. Without i.v. access: 0.005–0.01 mg/kg i.m.
Fluid therapy NaCl 9 mg/ml, Ringer's acetate or colloids	*Adults:* 20 ml/kg, more may be needed *Children:* 20 ml/kg, more may be needed
Secondary treatment	
Corticosteroids	*Adults:* Hydrocortisone 250 mg i.v. or Methylprednisolone 80 mg i.v. *Children:* Hydrocortisone 50–100 mg i.v. or Methylprednisolone 2 mg/kg i.v.
Antihistamines	*Adults:* H_1 antagonist, e.g. Clemastin 2 mg or Deksklorfeniramin 10 mg or Promethazin 50 mg given i.v. H_2 antagonist: consider Ranitidine 50 mg i.v. *Children:* e.g. Clemastin 0.0125–0.025 mg/kg or Deksklorfeniramin 5 mg or Promethazin 0.3–1.0 mg/kg given i.v./i.m.
Nebulised β_2-agonist may be used for symptomatic treatment of bronchospasm, but is not first-line treatment	
Lack of response to adrenaline	
Noradrenaline	i.v. infusion starting at: 0.05–0.1 μg/kg/min
Vasopressin	Increments of 2–10 IU i.v. until response
Glucagon (If lack of response to large doses of adrenaline in patients on β-blockers)	Increments of 1–2 mg i.v. until response

i.m., intramuscularly; i.v., intravenously.

Follow-up investigation

Patient selection

Ideally, all patients with moderate and severe anaphylactic reactions during anaesthesia (class II–IV) should have follow-up with immediate blood tests and secondary follow-up with allergy testing. Some patients with mild reactions (class I), such as localised erythema around intravenous injection sites, or with pre-existing bronchial hyperreactivity causing mild isolated bronchospasm during anaesthesia, do not require follow-up. However, patients who have localised or generalised urticaria after chlorhexidine exposure should be referred for allergy follow-up, as mild reactions in these cases have been seen to precede more serious reactions (29). Anaesthesiologists are encouraged to discuss indications for referral with the local anaesthesia allergy centre if in doubt.

Referral procedure (Table 4)

When referring a patient for follow-up, it is important to supply detailed information of the reaction (i.e. symptoms, severity, time course) and its treatment, as well as a complete list of all drugs and substances to which the patient was exposed prior to the reaction. A copy of the notes and anaesthetic chart should also be enclosed. The adverse reaction should be reported to the local or national pharmacovigilance authorities according to the national procedure.

Table 4

SSAI Guideline on immediate investigation of anaphylactic reactions during anaesthesia.

Initial blood sampling		Sample for serum tryptase analysis (in some countries also IgE analysis) • Ideally taken 1–4 h after the reaction • 5–10 ml of clotted whole blood • Record timing of sample in relation to start of the anaphylactic reaction • Send in protective plastic tube together with requisition at room temperature to local Anaesthesia Allergy Centre (see below)
Referral for allergological investigations		See below for referral procedure for each country
Denmark	*Use anaphylaxis kit*	List of contents can be downloaded from: www.daac.rh.dk
	Blood sample requisition	Download from: www.daac.rh.dk
	Blood sample should be sent to	Laboratoriet for Medicinsk Allergologi Rigshospitalet, Afsnit 7542 Blegdamsvej 9 2100 København Ø Denmark
	Referral papers	Download from: www.daac.rh.dk
	Referral papers should be sent to	Dansk Anæstesi Allergi Center Rigshospitalet, Afsnit 4231 Blegdamsvej 9 2100 København Ø Denmark
	Contact	Tel.: +45 3545 8209 E-mail: daac@rh.regionh.dk
Finland	*Blood sample information and requisition*	HUSLAB Download from: www.huslab.fi
	Blood sample should be sent to	Iho- ja allergiasairaalan laboratorio (Skin and Allergy Hospital) Meilahdentie 2 PL 160, Helsinki 00029 HUS Finland Tel.: +358-(0)9-471 86420 Contact local hospital laboratory to obtain more information about local routine
	Referral papers should be sent to	Local university or central hospital with Department of Allergy and/or Skin Disease
	Report anaphylaxis to	Lääkelaitos (National Agency for Medicines) Mannerheimintie 103 b PL 55, 00301 Helsinki Finland www.nam.fi/julkaisut/lomakkeet/hakemukset/index.html Iho- ja allergiasairaala, allergialaboratorio Meilahdentie 2, 4. krs PL160, Helsinki 00029 HUS Tel.: +358-(0)9-471 86430 Fax: +358-(0)9-471 86564
Iceland	*Blood sample should be sent to*	Rannsóknadeild LHS eða Rannsóknadeild FSA
	Referral papers should be sent to	Landlæknisembættið, Austurströnd 5 Seltjarnes, Iceland Tel.: 510 1900; Fax: 510 1919; E-mail: postur@landlaeknir.is
Norway	*Use the anaphylaxis kit*	List of contents/picture download from www.nafweb.no (choose NARA)
	Blood sample requisition	Download from www.nafweb.no (choose NARA)
	Blood sample should be sent to	Laboratorium for Klinisk Biokjemi Haukeland Universitetssjukehus 5021 Bergen
	Referral papers should be sent to	Northern Norway: Roald Bolle, Tromsø Middle Norway: Malcolm Sue Chu, Trondheim Western Norway: Erik Florvaag, Bergen Southern/Eastern Norway: Villum Wilhelmsen, Oslo Full addresses from www.nafweb.no (choose NARA)
	Contact	Tel.: +47 55 97 50 00 E-mail: anne.guttormsen@helse-bergen.no E-mail: erik.florvaag@helse-bergen.no

Table 4 Continued.

Sweden	*Blood sample requisition*	Download from www.sfai.se
	Blood sample should be sent to	Avdelningen för Klinisk Immunologi Karolinska Universitetssjukhuset Solna 171 76 Stockholm Contact your local hospital laboratory to obtain information about local routines
	Referral papers	Download from www.sfai.se
	Referral papers should be sent to	Anaesthesia Related Anaphylaxis in Sweden (ARAS) Anestesi- och intensivvårdskliniken Karolinska Universitetssjukhuset Solna 171 76 Stockholm

Primary investigation

Blood sampling (Table 4). In the hours following an anaphylactic reaction, blood samples for serum tryptase and, in some countries, also for IgE analysis should be taken. To make it simple for the referring anaesthesiologist, some centres (Norway and Denmark) have introduced an 'Anaphylaxis Kit' comprising what is needed to perform the initial follow-up. By introducing this concept, patient data and blood samples can be collected easily (45, 46), and this improves treatment and increases reporting and registration.

The optimum time for blood sampling for serum tryptase is 1–4 h after the start of the reaction (47). A blood sample can also be obtained post-mortem if necessary (48, 49). In order to make a valid interpretation of serum tryptase values, the timing of blood sampling in relation to the reaction should be recorded. Further, the serum tryptase value should be compared with a control value. A control sample should be taken either pre-operatively or a minimum of 24 h after the reaction. For the analysis of tryptase and IgE antibodies in the circulation, serum is preferable, but analyses may also be performed on plasma from ethylenediaminetetraacetic acid (EDTA) or heparinised tubes. Serum or plasma may be kept at room temperature for shipping, provided that it is sent by express mail. Otherwise, it should be stored at + 2 to + 8 °C if assayed within 1 week of collection, or at – 20 °C if assayed later (50).

Tryptase in serum. Tryptase is a neutral protease, found almost exclusively in mast cells, and, together with histamine, it is a marker of mast cell activation (7). The peak level of serum tryptase after an experimentally induced systemic anaphylactic reaction occurs 1–2 h after the initiating bee sting (51). However, Dybendal et al. (52) have reported that serum tryptase reaches its peak level as early as 10 min after the initiation of anaphylactic shock. Serum tryptase levels decline under apparent first-order kinetics with a half-life of approximately 2 h (51, 52).

An increased concentration of serum tryptase compared with the control sample is a highly sensitive indicator of an anaphylactic reaction during anaesthesia, and the presence of an elevated serum tryptase has been reported to support an IgE-mediated cause (47).

However, patients who present clinically with anaphylaxis, but in whom serum tryptase concentrations are not increased, still require investigation as false negatives do occur (47). If serum tryptase in the control sample is higher than the reference level, further investigation is needed to exclude mastocytosis (53).

IgE antibody in serum. Free circulating IgE antibodies in the blood may be measured by radioallergosorbent test (RAST) or fluoroimmunoassay (CAP System, Phadia AB, Uppsala, Sweden), the latter being used in Scandinavia. IgE antibody testing is only commercially available for very few drugs used during surgery and anaesthesia, e.g. suxamethonium, morphine, some antibiotics, chlorhexidine, thiopental and latex. As an alternative to suxamethonium, certain chemicals containing the quaternary ammonium ion have been used in some countries for screening for IgE sensitisation towards NMBAs.

IgE analysis may be performed on blood drawn at the time of reaction (54, 55), or later, but preferably within 6 months of the reaction, as the level of IgE antibodies in the blood may decline over time (B. Kristensen, Phadia, Copenhagen, Denmark, personal communication). For some allergens, e.g. chlorhexidine, it is known that IgE antibodies in the blood may be detectable for an even shorter time than 6 months (55).

Secondary investigation

Secondary investigation consists of skin testing, supplementary *in vitro* tests (e.g. basophil allergen challenge tests) if necessary and, in some countries, provocation testing. The secondary investigation will

vary between the Scandinavian countries depending on local tradition, experience and available resources.

Prior to secondary investigation, the results of serum tryptase and relevant *in vitro* tests should be available, together with a thorough clinical history, including a list of all the drugs and substances to which the patient was exposed prior to the reaction, as well as all notes and charts from the reaction. A history of known allergies, details of previous reactions during anaesthesia, a list of current medication and relevant previous medical history are also important.

Skin testing (skin prick test and intradermal test). In skin testing, IgE-mediated reactions are detected by exposing the mast cells of the skin to the suspected allergen. A negative control with saline and a positive control with histamine chloride (10 mg/ml for skin prick testing) should be carried out. In skin prick testing, a prick into the epidermis through a drop of (in most cases) undiluted allergen exposes the mast cells to a minute amount of allergen. In intradermal testing, the mast cells are exposed to a larger amount of allergen by injecting a standardised amount of a dilution of the drug into the epidermis. If the patient is sensitised, histamine will be released locally from the mast cells and a wheal and flare reaction will develop. Skin prick testing has a small tendency to produce false negative results, whereas intradermal testing carries a higher risk of false positive results (56), especially when testing drugs which cause non-specific direct histamine release from mast cells (e.g. some NMBAs and opioids) (25, 57). Testing requires a detailed knowledge of which dilutions of the incriminating drugs to use and how to interpret the results. The essential question is which drug concentration discriminates between allergic responses and those caused by pharmacological or toxic mechanisms. Investigations should therefore be carried out in specialist centres. In Scandinavia, it is recommended that the drug test concentrations and diagnostic criteria stated by the French Society for Anaesthesia and Intensive Care (SFAR) should be used (58). Furthermore, skin testing should be performed according to the guidelines and general considerations of the European Academy of Allergy and Clinical Immunology (59, 60).

It is recommended that skin testing should not be carried out earlier than 6 weeks after the reaction (6). All medications that could interfere with the results of testing (e.g. antihistamines, antidepressants, systemic and topical steroids, etc.) should be stopped in good time before testing. Resuscitation facilities and monitoring must be available as there is a small risk of anaphylaxis when performing intradermal testing. All drugs and substances (including latex and chlorhexidine) to which the patient has been exposed prior to the reaction should be tested. All dilutions should be freshly prepared, if possible.

If a test with a NMBA is positive, testing with all other NMBAs should be carried out because of the risk of cross-reactivity (61). Similarly, if the patient is found to be allergic to a local anaesthetic, a safe alternative (another local anaesthetic testing negative by subcutaneous provocation) should be found because of possible cross-reactivity (62).

Skin prick testing is recommended as the method of choice for routine skin testing, because it is simple and has a high sensitivity and specificity, given that the test performance is monitored according to international guidelines. In specialist centres, intradermal testing can prove to be useful for certain groups of drugs, but the risk of misinterpretation is considerable. There is a need for validated protocols for each drug.

Basophil allergen challenge tests. In patients with IgE antibodies, the basophils and mast cells are sensitised and can be triggered by allergen threshold stimulation. The basophils must be fresh (less than 24 h old) and the patient should not be on high-dose steroids at the time of sampling. The basophil response can be measured as leucocyte histamine release or CD63 expression.

Leucocyte histamine release test: The histamine release test measures liberated histamine and can be used for all drugs and substances. It may detect both IgE- and non-IgE-mediated reactions and, when performed with passive sensitisation (preincubation of donor basophils with patient serum prior to incubation with incriminated allergen and histamine measurement), only IgE-mediated reactions are detected (63). The histamine release test can be initiated at the local laboratory and sent for further analyses of liberated histamine (RefLab, Copenhagen, Denmark; www.reflab.dk). At present, the histamine release test is not recommended as part of the standard investigation programme, but can be useful when other tests are doubtful, inconclusive or not possible.

Flow cytometric analysis of in vitro-activated basophils: In flow cytometric analysis of *in vitro*-activated basophils, the up-regulation of certain membrane markers (e.g. CD63 and CD203c) is measured after challenge with the incriminated allergen (64).

The method does not discriminate between IgE- and non-IgE-mediated reactions. The application of passive sensitisation to the method may allow this. There is, as yet, insufficient experience with this test to recommend it as part of the standard investigation programme for anaesthesia allergy.

Drug provocation. The ultimate method of determination of whether or not a patient tolerates a drug is full-dose drug provocation. In the field of anaesthesia allergy, this has only been carried out on a larger scale with local anaesthetics (65, 66), mild analgesics (67–69) and antibiotics (69–71), probably because of the often very potent pharmacological effects (respiratory depression, paralysis, etc.) of anaesthetic drugs. Before drug provocation is performed, results of skintesting and lgE antibody analysis (if possible) must be available. It is recommended that drug provocation should be carried out according to the European Network for Drug Allergy and European Academy of Allergy and Clinical Immunology position paper (72) using a placebo-controlled incremental dosage regimen. The route of administration is preferably the same as in the original reaction (except for the spinal and epidural route). For drugs with potent pharmacological effects, the final provocation dose could be reduced to one-tenth of the therapeutic dose, thereby minimising unwanted pharmacological effects of the drug. By doing so, it should be borne in mind that a non-IgE-mediated and perhaps dose-related hypersensitivity reaction might be overlooked.

As drug provocation is a potentially high-risk procedure, informed consent from the patient is necessary, as well as electrocardiogram (ECG), intravenous access, full resuscitation back-up and back-up for handling any unwanted pharmacological effects of the drug.

In patients with suspected allergy to local anaesthetics, subcutaneous provocation is the method of choice in order to verify tolerance (33).

At present, only a few specialist centres are carrying out drug provocation for a large number of substances, and the method is not widely recommended.

Advice to patients

The purpose of follow-up is to identify the drug or substance responsible and the mechanism behind the reaction, in order to make subsequent anaesthesia as safe as possible. Knowledge that competent and standardised specialist investigations have been carried out will reassure both the patient and future anaesthetic personnel.

When all investigations have been completed, all tests should be interpreted in the light of the information about the clinical reaction. The patient should be warned against any substance which has tested positive, and a warning card/bracelet should be issued. In some countries, e.g. Australia and Denmark (32, 56), a detailed letter is given to the patient, even when the test results are negative. This letter contains information on the reaction, which drugs were given, the results of follow-up investigations and advice for future anaesthetics. The letter is given to the patient, the referring anaesthesiologist and the patient's general practitioner, and, with this information, it is hoped that the patient will be ensured safe subsequent anaesthesia.

Management of patients with previous anaphylactic reactions during anaesthesia (Fig. 1)

In an ideal world, all patients suffering an anaphylactic reaction during anaesthesia would have complete allergo-anaesthetic follow-up prior to subsequent anaesthesia. Unfortunately, the practical reality is different and sometimes patients require anaesthesia for emergency surgery, at times when little or no information about a previous reaction is available. In addition, many countries do not have a formalised set-up to investigate these patients.

Before conducting anaesthesia, it is necessary to make a risk evaluation considering whether: (i) the reaction was anaphylactic; (ii) the reaction has been investigated; and (iii) more information is needed.

It is important to stress, however, that such a risk evaluation must be carried out in the time available and should never delay urgent surgery or surgery for, for example, malignancy. In addition, the risks involved in other aspects of anaesthesia (e.g. difficult airway, risk of aspiration, etc.) should be taken into account when deciding on the strategy for anaesthetic management of a patient with a previous allergic reaction.

If the patient reports an allergy to certain substances, these should be avoided. Patients with an atopic constitution (i.e. documented IgE-mediated allergy to common allergens, such as pollen, fur of animals or dust mites) and those exposed to latex through the workplace may be at increased risk of reactions to latex (5).

If surgery can be managed with local or regional anaesthesia (and a local anaesthetic is not the incriminated substance), this is preferable, as true allergy to local anaesthetics is very rare (73). If

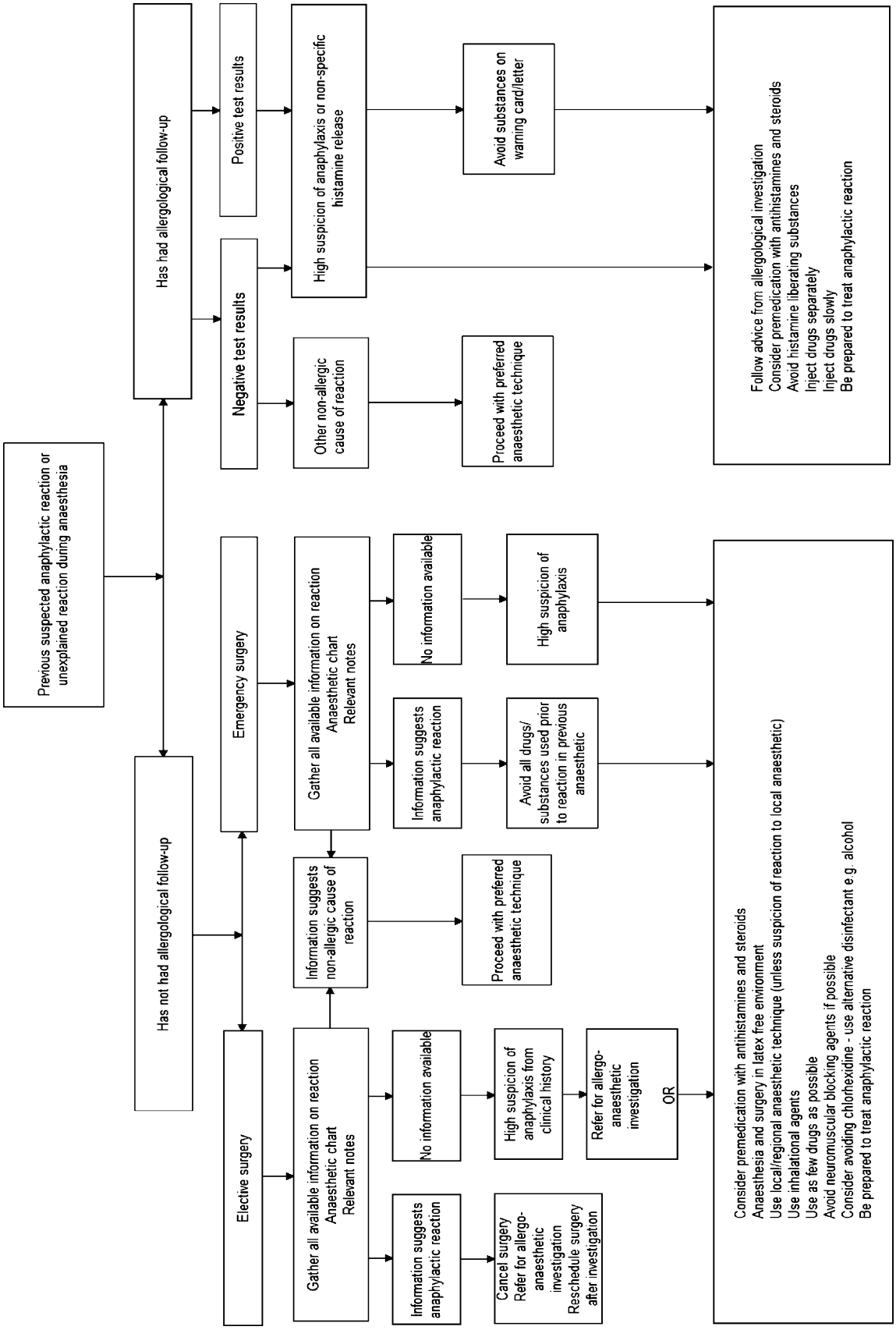

Fig. 1. SSAI Guideline on anaesthetic management of a patient with a previous suspected anaphylactic reaction during anaesthesia.

general anaesthesia is necessary, volatile anaesthetics should be used if possible, as allergy to these has never been described.

If a reaction to a NMBA is suspected, it is important to try to avoid other NMBAs as cross-reactions are reported to be common within this group (23, 61). As all patients have been exposed to latex and disinfectants during previous surgery and anaesthesia, a latex-free environment and alternative disinfectants should be considered.

If the anaesthetic chart from the reaction is available, all drugs and substances administered to the patient prior to the reaction should be avoided if possible. Patients who have had previous severe allergic reactions during anaesthesia are at increased risk of a recurrence during subsequent anaesthesia, and the anaesthetist should be prepared to diagnose and treat anaphylaxis promptly.

Pre-medication with antihistamines and steroids will probably not prevent anaphylactic shock (73, 74), but can reduce/prevent reactions caused by non-specific histamine release. These reactions can also be prevented by avoiding histamine-liberating drugs altogether, or by injecting drugs slowly and one by one.

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Appendix 1

Definitions in anaphylaxis

[According to Position Papers of the European Academy of Allergology and Clinical Immunology and the World Allergy Organization (9, 10).]

Hypersensitivity causes objectively reproducible symptoms or signs, initiated by exposure to a defined stimulus at a dose tolerated by normal subjects.

Allergy is a hypersensitivity reaction initiated by immunological mechanisms. The reaction is mediated by endogenous mediators, such as histamine and bradykinin, or by activation of complement. The clinical picture may be antibody- or cell-mediated; in the old terminology by Gell and Coombs, called Type I (IgE-mediated) or Type IV (lymphocyte-mediated).

Atopy is a personal and/or familial tendency, usually in childhood or adolescence, to become sensitised and produce IgE antibodies in response to ordinary exposure to allergens, usually proteins. As a consequence, these individuals can develop typical symptoms of asthma, rhinoconjunctivitis or eczema.

Anaphylaxis is a severe, life-threatening, generalised or systemic hypersensitivity reaction. If the anaphylaxis is caused by an allergic mechanism, it is termed allergic anaphylaxis, and, if not, non-allergic anaphylaxis (in the old nomenclature,

denoted as anaphylactoid). Independent of mechanism, the clinical picture gradually develops from one or more rather local symptoms, i.e. diffuse erythema, itching, urticaria, to a generalised reaction, including angioedema, bronchospasm, hypotension and, eventually, circulatory collapse. In allergic anaphylaxis, the patient is sensitised when exposed, which means that antibodies or specific lymphocytes have been formed during previous exposures. Non-allergic anaphylaxis is caused by a direct effect on the inflammatory system causing a severe general reaction, often as a response to a drug.

Allergen is an antigenic substance that stimulates the immune system and causes an allergic reaction. Typical allergens are proteins from pollen, food and epithelia from animals.

Hapten is an allergen with low molecular weight, which must bind to a carrier in order to cause an allergic reaction. Allergic reactions towards drugs administered during general anaesthesia, e.g. neuromuscular blocking agents and opioids, seem to generate an allergic response in this way. The allergic epitope, i.e. the structure that reacts with the antibody, may be the hapten itself or the hapten–carrier complex.

Appendix 2

Drugs and substances commonly used during anaesthesia

Antibiotics.

Incidence. All types of antibiotics have the potential to cause anaphylaxis. Reactions occur most commonly to penicillins, with an incidence of 1/1000 treatments (75). Up to 15% of anaphylactic reactions during anaesthesia have been reported to be caused by antibiotics in France (24) and Denmark (L. H. Garvey, personal observation). Many patients report an allergy to penicillin, which, on further questioning, can be dismissed as the symptoms are not allergic. Direct questioning on allergic symptoms, such as rash, itching or anaphylactic shock, is thus important.

Mechanism and cross-reactions. Anaphylaxis may occur at first exposure, and some drugs can cross-react. Penicillins cross-react with β-lactam antibiotics, including amidinopenicillins, cephalosporins and carbapenems. However, the risk of anaphylaxis has probably been overestimated previously, and therefore cephalosporins may be considered for patients with penicillin allergy (76, 77).

Diagnostic possibilities. Testing for penicillins is carried out by allergologists in most countries, and comprises IgE antibody measurement, skin testing and provocation. Skin testing with other antibiotics is possible, but experience is lacking. IgE antibodies have been demonstrated against amoxicilloyl, ampicilloyl, penicilloyl G, penicilloyl V, cefaclor, erythromycin, penicillin minor determinants, β-lactams, tetracyclines, cephalosporins and quinolones, but not all are commercially available (75).

Aspirin and non-steroidal anti-inflammatory drugs (NSAIDs).

Incidence. The prevalence of reactions towards aspirin and NSAIDs is about 1% in the general population. In patients with non-allergic asthma and nasal polyposis, the incidence is higher (78). Anaphylaxis to these substances occurs only rarely in connection with anaesthesia.

Mechanism and cross-reactions. Reactions towards aspirin and NSAIDs are non-allergic. However, a few cases of IgE-mediated reactions to pyrazolones have been described (79, 80). Cross-reactions occur between aspirin and most of the NSAIDs. Cross-reactions with paracetamol in aspirin-sensitive patients have been reported when high doses are used ($>$ 1 g) (81). The use of selective cyclo-oxygenase-2 (COX-2) inhibitors may be safe for aspirin/NSAID-intolerant asthmatic patients, but more experience is needed.

Diagnostic possibilities. Aspirin and NSAIDs do not initiate IgE antibody production and thus skin testing cannot be used. Oral provocation testing is diagnostic and is performed in some centres.

Chlorhexidine.

Incidence. Chlorhexidine is a widely used disinfectant in many countries, including Denmark, where 12% of anaphylactic reactions during anaesthesia are caused by chlorhexidine (L. H. Garvey, personal observation). In most other countries, the incidence is unknown, or underestimated, as reactions are often overlooked and chlorhexidine is not suspected as an allergen. Health care workers are also exposed to chlorhexidine, but allergy seems to be rare (29, 82).

Mechanism and cross-reactions. Reactions towards chlorhexidine are IgE-mediated.

Diagnostic possibilities. Skin testing (prick test and intradermal test) and measurement of IgE antibodies against chlorhexidine can be used (55). When

investigating patients following an anaphylactic reaction in connection with anaesthesia and surgery, chlorhexidine should be included (29).

Dextran.

Incidence. Compared with human serum albumin, the pooled incidence rate ratio for anaphylactic reactions to dextran is 2.32 (95% confidence interval, 1.21–4.45) (83). Severe anaphylactic reactions to dextrans after pre-treatment with low-molecular-weight dextran (Promiten®) occur in 1/70,000 treatments (84).

Mechanism and cross-reactions. IgG antibodies to dextran can be measured by ImmunoCAP (Phadia AB, Uppsala, Sweden) or enzyme-linked immunosorbent assay (ELISA) (85). By contrast with IgE antibodies in classical anaphylaxis, IgG antibodies are consumed when reacting with infused dextran. Cross-reactions with certain bacterial antigens may exist, implying that allergy to dextran may occur without previous exposure to intravenous dextran solutions.

Diagnostic possibilities. Skin testing is negative, as IgE is not involved in the reaction. *In vitro* diagnostic methods can be used. Analyses should preferably be performed on a serum sample taken either before the reaction or a few weeks after, but within a few months of the reaction (85). Drug provocation is also useful in some specialist centres, but, as for all other drug provocation, this should only be carried out in specialist centres with experience in drug provocation (M. Kroigaard, personal observation).

Gelatins.

Incidence. The risk of anaphylactic reactions is significantly higher for gelatins than for other colloids. Compared with human serum albumin, the pooled incidence rate ratio for anaphylactic reactions for gelatins is 12.4 (95% confidence interval, 6.4–24.0) (83). In France, gelatins are widely used and cause up to 4% of anaphylactic reactions during anaesthesia (24).

Mechanism and cross-reactions. Reactions to gelatins are most often non-allergic, but IgE-mediated reactions do occur (75). IgE-mediated reactions caused by contaminating proteins from the original source, for instance pig or cattle, have also been reported.

Diagnostic possibilities. Skin testing and IgE antibody tests may be positive in IgE-mediated reactions. Analysis of IgE against contaminating proteins may also be performed.

Hydroxyethylstarch (HAES).

Incidence. Compared with human serum albumin, the pooled incidence rate ratio for anaphylactic reactions for HAES is 4.51 (95 confidence interval, 2.06–9.89) (83). Severe reactions are reported in 0.006% of exposures (75, 86).

Mechanism and cross-reactions. The frequency of IgE antibody formation against HAES seems to be low (87), but has been reported (88).

Diagnostic possibilities. Skin testing may be used, but experience is minimal.

Iodinated contrast media.

Incidence. Several preparations of iodinated contrast media exist, and are of either high or low osmolality and either ionic or non-ionic. The different preparations have variable iodine concentration and different potential to cause anaphylactic reactions. Severe reactions are seen more frequently with high-osmolality ionic (0.04–0.22%) than with low-osmolality non-ionic (0.004–0.04%) iodinated contrast media. Mortality has been reported to be 1/170,000 (89, 90).

Mechanism and cross-reactions. The pathophysiology of acute adverse reactions to iodinated contrast media is multifactorial (91). Reactions can emerge through two pathways: the immune pathway involving IgE antibodies, and the non-specific toxic leakage pathway. The immune pathway is triggered by very small amounts of antigen, whereas non-specific toxicity is directly related to dose (92).

Diagnostic possibilities. Skin testing and drug provocation testing can be used. The experience is minimal.

Ketamine.

Incidence. Anaphylactic reactions related to ketamine are extremely rare (23).

Mechanism and cross-reactions. Information is limited. A direct effect on mast cells has been suggested (93).

Diagnostic possibilities. Skin testing may be performed. No tests for IgE antibodies are available.

Natural rubber latex.

Incidence. The incidence of allergy to natural rubber latex has increased over the last three decades. It is well established that an atopic disposition and

regular exposure to latex increase the risk of developing latex allergy in both patients and health care workers. The incidence of latex as a cause of anaphylaxis during anaesthesia differs between countries. In the 1999–2000 survey from France, latex caused 16.7% of reactions (24). The incidence in Denmark is 12% (L. H. Garvey, personal observation), and less than 5% of the anaphylactic reactions during anaesthesia in Norway are caused by natural rubber latex (1).

Mechanism and cross-reactions. Either IgE-mediated anaphylaxis to the latex proteins or contact allergy to the chemicals added in the manufacturing process causing eczema. IgE antibodies can be directed against many different proteins in natural rubber latex and cross-reactions are seen with, for example, tropical fruits, nuts and potatoes depending on the protein in question.

Diagnostic possibilities. Skin testing, measurement of IgE antibodies and provocation/exposure tests can be used for IgE-mediated anaphylaxis. Patch testing with rubber additives is used for contact allergy.

Local anaesthetics.

Incidence. The incidence of anaphylactic reactions to local anaesthetics is unknown, but is reported to be very low (65, 75). Most alleged reactions are caused by vasovagal reactions, toxic reactions from inadvertent intravenous administration or symptoms caused by added adrenaline.

Mechanism and cross-reactions. IgE-mediated reactions are very rare and have decreased in frequency with the decreasing use of the ester group of local anaesthetics. Cross-reactions were common in the ester group, but are rarely seen in the amide group (75).

Diagnostic possibilities. Most diagnostic protocols apply a step-by-step strategy starting with skin tests (skin prick, intradermal or patch tests) and proceeding to subcutaneous provocation. It is important to test the suspected local anaesthetic and to include a suitable alternative for tolerance testing. IgE measurement is currently not available for local anaesthetics.

Midazolam.

Incidence. Extremely rare (75).

Mechanism and cross-reactions. A direct effect on mast cells has been described (94). The imidazole ring may act as a potential trigger of the immune system (94). Reliable data on cross-reactions are missing.

Diagnostic possibilities. No tests for IgE antibodies are available. Skin tests may be used but experience is limited.

Neuromuscular blocking agents (NMBAs).

Incidence. NMBAs are exclusively used in connection with general anaesthesia, and the incidence of anaphylactic reactions to this group of drugs differs greatly between countries. The incidence is high in France, Norway and the UK (1/5000 to 1/10,000). In the rest of the world, the incidence is low (1/50,000 to 1/150,000) (1).

Mechanism and cross-reactions. IgE-mediated allergy. The quaternary ammonium ion is identified as the allergenic epitope (95), and is shared by all NMBAs, morphine, pholcodine and other morphine/codeine analogues (96). There is a high degree of cross-reactivity amongst NMBAs ($>$ 70%) (24).

Diagnostic possibilities. Skin prick testing is the gold standard, and has a high sensitivity and specificity. Special attention is needed if intradermal testing is performed, as false positives are seen when drug concentrations that are too high are used (27). IgE antibody measurement can be carried out for suxamethonium, but is not commercially available for the remaining drugs in the group. Alternatively, *in vitro* provocation tests, such as leucocyte histamine release tests and basophil stimulation tests, can be used (63, 64).

Opioids.

Incidence. The incidence of anaphylactic reactions to opioids is low.

Mechanism and cross-reactions. Reactions are probably caused by a direct effect on mast cells resulting in histamine release. Morphine, codeine and meperidine stimulate mast cells in the skin. Fentanyl, alfentanil and sufentanil have no local effect on mast cells. Morphine contains one quaternary ammonium ion and, in addition, another single allergenic determinant, not cross-reacting with the quaternary ammonium ion, has recently been identified (30). Morphine, meperidine, codeine and methadone cross-react, whereas the cross-reactivity of fentanyl is more uncertain (97).

Diagnostic possibilities. IgE antibodies against some opioids have been identified, but they are

usually monovalent with regard to the allergenic epitopes and thus should not provoke IgE-mediated reactions.

Propofol.

Incidence. Anaphylactic reactions to propofol are rare. In a French study, 2.3% of reactions occurring during anaesthesia were caused by propofol (24).

Mechanism and cross-reactions. Reactions to propofol are probably not IgE-mediated, but may be the result of a direct effect on mast cells initiating a release of histamine. Propofol is dissolved in a lipid vehicle (soybean, egg lecithin, glycerol). The lipid vehicle is purified making it protein free. According to the producer, there is no evidence of any specific reactions to the emulsion (Astra Zeneca, personal communication).

Diagnostic possibilities. Skin testing has been advocated by some authors. No IgE antibody tests are available.

Thiopental.

Incidence. The risk of an anaphylactic reaction to thiopental is estimated at between 1/23,000 and 1/29,000 administrations (98, 99). Previous exposure and female gender (gender ratio female: male, 3: 1) are acknowledged as risk factors.

Mechanism and cross-reactions. The mechanism is mainly non-allergic anaphylaxis, possibly as a result of direct stimulation of mast cells initiating a release of histamine. However, IgE antibodies towards thiopental have been described (100).

Diagnostic possibilities. Reagents to detect IgE antibodies are available. Skin testing can be used.